CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204819Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	**NDA**
Application Number(s)	**204819**
Priority or Standard	**Priority**
Submit Date(s)	**February 8, 2013**
Received Date(s)	**February 8, 2013**
PDUFA Goal Date	**October 8, 2013**
Division / Office	**DCRP/ODE-1**
Reviewer Name(s)	**Preston M. Dunnmon, MD, FACP, FACC**
Review Completion Date	**July 7, 2013**
Established Name	**Riociguat**
(Proposed) Trade Name	**Adempas**
Therapeutic Class	**Direct soluble guanylate cyclase (sGC) stimulator**
Applicant	**Bayer HealthCare**
Formulation(s)	**0.5-mg, 1.0-mg, 1.5-mg, 2.0-mg and 2.5-mg film-coated immediate-release tablets**
Dosing Regimen	**Initiate treatment at 1 mg 3 times daily (TID), 6 to 8 hours apart with or without food, initiate treatment at 1 mg 3 times daily (TID), 6 to 8 hours apart with or without food, Maintain riociguat at the maximum tolerated dose. The highest dose of riociguat is 2.5 mg, TID (Dose reduction can be considered at any time).**
Indication(s)	**Chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4) to improve exercise capacity and WHO functional class** **Pulmonary arterial hypertension (PAH, WHO Group I) to improve exercise capacity, improve WHO functional class,**

	and to delay clinical worsening
Intended Population(s)	**Adults with persistent/recurrent CTEPH (WHO Group IV) after surgical treatment with inoperable CTEPH** **Adults with PAH (WHO Group I)**

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommendation for regulatory action: Approve with modified dosing algorithm to start at 0.5 mg TID, increasing dose no sooner than every two weeks by 0.5 mg TID to a maximum dose of 1.5 mg TID in PAH.

For CTEPH, recommend same dosing strategy, referencing the clinical pharmacology analysis of the flat exposure-response curve in the CHEST-1 data. However, would add statement to this label that for patients with a baseline SBP >110 mmHg who do not experience an adequate clinical response at 1.5 mg TID, up-titration by 0.5 mg TID no sooner than every two weeks to a maximum dose of 2.5 mg TID has been safety tested in large clinical trials, though there is no clinical trial evidence of benefit from these higher doses, and there appears to be an increased incidence of drug-induced hypotension for those with baseline SBPs <110 mmHg.

1.2 Risk Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Summary of evidence**: • Pulmonary Artery Hypertension (Dana Point, 2008) **WHO Group 1 (PAH) – idiopathic, familial, associated with other diseases (collagen vascular disease), congenital heart disease, diet therapies or other drugs** WHO Group II – Left Heart Dz WHO Group III – Lung Dz (COPD, ILD, sleep disorders, high altitude, developmental lung abnormalities **WHO Group IV – chronic thrombotic/embolic disease (CTEPH)** WHO Group V - miscellaneous • Clinical manifestations include poor exercise tolerance, shortness of breath, marked elevation of pulmonary artery pressures due to vasoconstriction of and fibromuscular obstruction within pulmonary arteries • Symptoms include debilitating shortness of breath, exercise intolerance, chest pain,	**Conclusions (implications for decision):** Life threatening condition in patients with no remaining medical options other than lung transplantation

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	• Natural history – average survival 4-5 years after diagnosis in adults	
Unmet Medical Need	**Summary of evidence**: • There are no approved therapies for CTEPH. • Available PAH therapies include ERA, PDE5-i, and Prostanoids that target vasoconstriction • When drug therapy fails, the only remaining option is lung transplantation	**Conclusions (implications for decision):** On average, the prognosis of PAH patients is worse than that of many patients who are diagnosed with cancer. Lung transplantation is a suboptimal option for many patients due to limited supply of donor organs, cost, and complexity of post-operative care. Riociguat, if approved, would be the first non-surgical therapy approved for the treatment of CTEPH in the United States. According to the results of CHEST-1, less than 1/3 of CTEPH patients are not surgical candidates, leaving the rest with no approved therapeutic options at all. Even for those patients who undergo surgical pulmonary thromboembolectomy/endarterectomy, elevated pulmonary pressures may persist or recur, leaving these patients without medical options as well.
Clinical Benefit	**Summary of evidence**: The 6MWD has been the accepted endpoint measure on which prior PAH drugs have been approved in adults. Bayer completed two pivotal trials in support of the riociguat NDA – one in patients with CTEPH (CHEST-1) and another in patients with PAH (PATENT-1) in which the placebo-corrected change from baseline 6MWD was utilized as the primary efficacy variable. Adding to the robustness of the evidence for benefit were secondary analyses of time to clinical worsening (TTCW), hemodynamics, chemical biomarkers, and five different measures of functionality and/or quality of life. A summary table of the results for each of these pivotal trials is shown in the table below:	**Conclusions (implications for decision):** The combination of two positive pivotal trials with coordinate and positive results across multiple measures of clinical benefit in two different populations of pulmonary hypertension patients is a robust data set supporting the benefit of riociguat and its mechanism of action in the therapy of both PAH and CTEPH patients. The benefit-risk balance is probably optimized at the lower dose of 1.5 mg TID.

<table>
<tr><th>Decision Factor</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<tr><th>Parameter</th><th>p-value PATENT-1 (PAH)</th><th>p-value CHEST-1 (CTEPH)</th></tr>
<tr><td>6MWD</td><td><0.0001</td><td><0.0001</td></tr>
<tr><td>PVR</td><td><0.0001</td><td><0.0001</td></tr>
<tr><td>NT-proBNP</td><td><0.0001</td><td><0.0001</td></tr>
<tr><td>WHO FC</td><td>0.0033</td><td>0.0026</td></tr>
<tr><td>TTWC</td><td>0.0285*</td><td>0.2180**</td></tr>
<tr><td>Borg</td><td>0.0022</td><td>0.0035</td></tr>
<tr><td>EQ-5D</td><td>0.0663</td><td><0.0001</td></tr>
<tr><td>LPH</td><td>0.0019</td><td>0.1220</td></tr>
</table>
</td><td></td></tr>
<tr><td>Risk</td><td>Summary of evidence:

Hypotension. Riociguat causes dose-dependent decreases in blood pressure, both systolic and diastolic.

Events of renal failure. Serious TEAEs of renal failure (renal failure, renal failure acute, renal failure chronic, renal impairment) were observed in 10 subjects (1.3%) in the pooled riociguat group in the main studies in Pool 3 (all riociguat studies), and in 1 subject (0.3%) in the pooled placebo group. I suspect a secondary effect of blood pressure reduction may play a mechanistic role in the occurrence of these infrequent events.

Bleeding. There were a total of 10 treatment emergent serious hemorrhages across both pivotal studies, all of which occurred in riociguat-IDT-treated patients.</td><td>Conclusions (implications for decision):

Hypotension may have the worse consequences in real world use, especially among patients with underlying CV disease. I recommend more cautious dose escalation than the trials employed.

Bleeding risk is probably an unavoidable consequence of vasodilator therapy.</td></tr>
<tr><td>Risk Management</td><td>Summary of evidence:

The sponsor has proposed a REMS.</td><td>Conclusions (implications for decision):

The reviewer agrees with modifying the proposed REMS to align with other known teratogens use to treat pulmonary hypertension.</td></tr>
</table>

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The sponsor-proposed REMS should be modified to align with other teratogens that are used to treat pulmonary hypertension (in progress).

1.4 Recommendations for Postmarket Requirements and Commitments

I agree with the DRUP consultant that due to the severity of PAH and the somewhat limited treatment options in children, the nonclinical bone findings should not preclude pediatric studies. Were pediatric studies to be successful, this mechanistic pathway could once again be a therapeutic target in pediatric patients (it has been limited with the recent labeling changes to PDE5i therapy in children). If these studies proceed forward, the DRUP consultant states/suggests the following:

- Adolescents are less likely to experience any such bone effects, thus it would be appropriate to assess skeletal effects in adolescents prior to studies in younger children.

- 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.

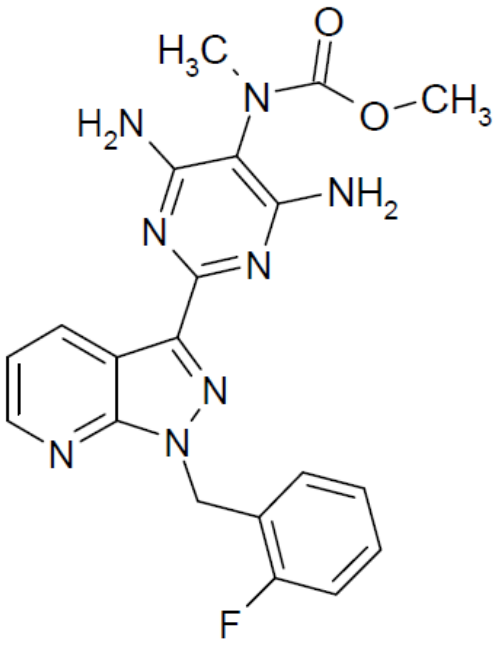
- It may be appropriate to investigate the possible development of hyperostosis with long term use. In particular, lateral spine X-rays (perhaps even PA/lateral chest X-rays) could readily detect calcification of the anterior spinal ligament in patients in the ongoing extension studies, at least in those with any complaints of back pain or stiffness. However, such calcifications are common in the general population of older adults so such findings may be difficult to interpret without a control group or baseline imaging.

- 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.

2 Introduction and Regulatory Background

2.1 Product Information

- Established (trade) names: Riociguat (Adempas)
- Chemical name: Methyl N-{4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}-N-methylcarbamate
- Chemical class. Riociguat is a small molecule agonist of sGC with the following molecular structure:



- Pharmacologic class. . Riociguat is a small-molecule agonist of soluble guanylate cyclase (sGC), which is the receptor for nitric oxide (NO). Stimulation of sGC results in the production of intracellular cGMP, which influences vascular tone, proliferation, fibrosis, and inflammation. Riociguat is purported to have a dual mode of action: it sensitizes sGC to endogenous NO by stabilizing NO-sGC binding, and it directly stimulates sGC via a different binding site, independently of NO.

- Proposed indications, dosing regimens, age groups.

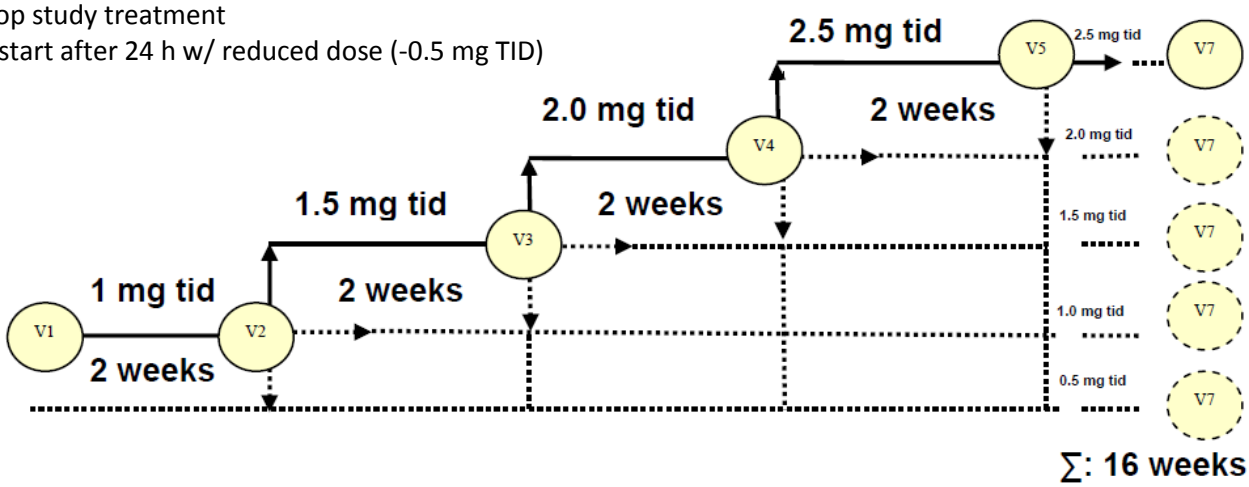
  - For the treatment of adult patients with inoperable CTEPH, and persistent or recurrent CTEPH after surgical treatment to improve exercise capacity

  - For the treatment for the treatment of adult patients with PAH to improve exercise capacity. Efficacy was shown in patients on riociguat monotherapy or in combination with endothelin receptor antagonists or prostanoids.

The sponsor proposes a single dosing algorithm for both indications that starts at 1.0 mg TID, then escalates dose every 2 weeks by 0.5 mg TID until the maximum dose of 2.5 mg TID is achieved at week 6 of dosing. This approach was taken due to high inter-patient variability of PK. The proposed dosing algorithm is based on blood pressure ranges with very tight tolerances for making decrease/maintain/increase dosing decisions, as shown in the figure below:

Figure 1: Proposed riociguat dosing scheme for adults

- Trough SBP ≥95 mmHg, increase dose (+0.5 mg TID)
- Trough SBP 90 to 94 mmHg, maintain dose
- Trough SBP <90 mmHg without symptoms of hypotension, reduce dose (-0.5 mg TID)
- Trough SBP <90 mmHg with clinical symptoms of hypotension such as dizziness or pre-syncope,
  - stop study treatment
  - restart after 24 h w/ reduced dose (-0.5 mg TID)



- Brief Product description. The drug product proposed for marketing is an immediate release, film-coated tablet with 5 different dose strengths: 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg. For oral use. Each IR tablet contains the active ingredient riociguat and the excipients lactose, microcrystalline cellulose, crospovidone, magnesium stearate, hypromellose and sodium lauryl sulphate. Additionally, the IR tablets are film-coated with hydroxypropyl cellulose, hypromellose, propylene glycol, iron oxide (red and/or yellow), and titanium dioxide.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved therapies for CTEPH in the United States. For this reason, the CHEST-1 trial data drove the decision to grant the sponsor a priority review.

There are other PAH therapies available in the US that fall into three categories: endothelin receptor antagonists (ERA), phosphodiesterase inhibitors (PDE5-i), and prostacyclin analogues (PRA). The drugs available in the US in these three categories are listed in the following table (amber background – ERAs, green background – PDE5 inhibitors, and blue background-PRAs):

Table 1: Available therapies in the US for the treatment of PAH

Drug	Starting –Max Doses
Ambrisentan – PO	**5 – 10 mg QD**
Bosentan – PO	**62.5 – 125 mg BID**
Sildenafil – PO	**20 mg TID (Q4-6H)**
Tadalafil – PO	**40 mg QD**
Epoprostenol – IV	**2 – 40 ng/kg/min**
Iloprost - Inhaled	**15 mcg/day (6 X 2.5) - 45 mcg (9 X 5)**
Treprostinol – IV **Treprostinol – SQ**	**1.25 – 100 ng/kg/min (Little experience > 40 ng/kg/min**
Treprostinol - Inhaled	**3 - 9 breaths (18 mcg – 54 mcg) QID**

Of note, the use of sildenafil is not recommended in children because an increase in mortality with increasing Revatio dose was observed in a long-term trial in pediatric patients with PAH. The safety and effectiveness of tadalafil in pediatric patients have

not been established. Thus, there is a lack of data supporting the use of the entire class of PDEi drugs in children, a fact that has relevance to the sponsor's request for a pediatric waiver for the PAH indication for riociguat.

2.3 Availability of Proposed Active Ingredient in the United States

Riociguat is a first-in-class NME that is not currently marketed in the US or in any other country. At the time of the NDA submission, the ATC code had not yet been assigned, but the application had been submitted to WHO.

2.4 Important Safety Issues with Consideration to Related Drugs

Riociguat belongs to a novel class of sGC stimulators that has been developed for the treatment of cardiovascular diseases, especially pulmonary hypertension (PH). The sponsor states that no other structurally related sGC stimulators are currently under development for this indication. Vasodilators in general have the potential to induce hypotension. This is also the case for riociguat.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sequence of communications between the sponsor and the review division with respect to this development program is summarized below:

Table 2: Regulatory activity related to this NDA

Date	Regulatory Activity
Feb 22, 2007	Pre-IND Meeting
May 29, 2008	End of Phase 2 (EOP2) Meeting
Oct 9, 2009	Type C meeting: Pulmonary hypertension associated with left systolic ventricular disease
Dec 14, 2011	Advice/Information Request Letter
Jul 26, 2012	Advice/Information Request Letter
Nov 01, 2012	Pre-NDA Meeting Preliminary Comments*
Dec 19, 2012	Teleconference to follow-up with ONDQA and DMEPA on items from the Division's pre-NDA preliminary responses

*Pre-NDA meeting scheduled for November 2, 2012 was cancelled by the Division.

Of relevance to the CHEST-1 and PATENT-1 trials by the sponsor, the following advice was given by the agency during the May 29, 2008 EOP2 meeting regarding the sponsor's proposed design of their proposed pivotal trials:

- **You must explore more than one dose in your pivotal trials or provide other data showing how dosage relates to clinical benefits (i.e., not just hemodynamic effects.)**
- **We suggest that you study more than one target dose in a parallel design.**

  Discussion during the meeting: The Division explained that the sponsor's proposal to perform a forced titration study where all patients receive the same dose and dose escalations every 14 days cannot help determine the dose response curve. If the sponsor needs to titrate the dose for reasons of patient safety, then the trial should include multiple treatment arms (to avoid confounding the effects of dose and time). In PAH trials, short-term titrations can be problematic since effects on exercise may take weeks to become evident (e.g., hysteresis) even though changes in PVR can occur almost immediately after administering the drug. The sponsor proposes to study a dose range, 1.0 to 2.5 mg, based on changes in hemodynamic effects in earlier studies; however, the difference between doses is quite narrow and the Division recommended studying a broader dose range. The Division emphasized that even a notion of unblinding (whether true or inferred) would affect how the Division views the integrity of a trial and that the sponsor should also be interpreting such findings cautiously – this is related to a patient in an open label study with a documented 100 meter improvement in 6MWD (sponsor's slide).

- **We recommend that your long-term safety study (PATENT-2) be controlled. Sildenafil is an appropriate active control.**

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

Unfortunately, the Division's advice on these design elements was only partially incorporated in into the clinical development program for riociguat – active therapy was confined to a single trial arm in CHEST-1 in which dose was escalated to the maximal tolerated level. A "capped dose" arm at 1.5 mg TID was incorporated into PATENT-1 but was small and underpowered for some of the secondary endpoints. Flat exposure-response relationships with respect to 6MWD in both trials, as well as dose-related occurrence of hypotension {defined as a systolic blood pressure (SBP) < 90 mmHg or a hypotension adverse event} in PATENT-1 somewhat complicate the benefit-risk determination for this product.

In addition to the meetings noted above, there were multiple communications between the Division and Bayer regarding our concern over potential riociguat-induced bone

toxicity, and specifically the impact that might have on the decision to waive pediatric study requirements under PREA for the PAH indication. Those communications are reviewed in detail in the toxicology review, but summarized for convenience in the following table that is excerpted from that review:

Table 3: DCRP communications with sponsor regarding potential bone toxicity

Date of communication	Filed in DARRTS
March 27, 2007. Teleconference with sponsor regarding questions from 30-day safety meeting, including bone	March 27, 2007
Internal meeting May 19, 2008. Preliminary responses, EOP2 meeting. Concerns for bone and endocrine effects noted.	May 22, 2008
EOP2 Meeting minutes May 29, 2008. Concerns for bone and endocrine effects noted.	June 14, 2008
Internal meeting October 2, 2009. Preliminary responses for Type C meeting: Clinical bone metabolism study discussed with recommendations for clinical monitoring.	October 8, 2009
Meeting with sponsor. October 9, 2009. Clinical bone study and nonclinical bone data discussed.	October 19, 2009
December 4, 2009. Email to sponsor. Clinical bone monitoring discussed.	December 4, 2009
June 14, 2011 telecon with sponsor regarding the nonclinical bone findings and implications for an osteoporotic population.	June 20, 2011
Advice/information email to sponsor. Necessity of juvenile animal studies prior to pursuing pediatric studies.	December 14, 2011

2.6 Other Relevant Background Information

This NME, first-in-class product for the proposed indications is neither approved nor marketed in any jurisdiction world-wide.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality is this NDA submission is outstanding. It is rigorously organized, exceptionally well internally cross-referenced with electronic linkages, and remarkably thorough. Information was easy to find and data sets were accessible and functional. The sponsor's responsiveness to information requests from the Division was exemplary. All presentations to and outputs from the oversight committees from both pivotal trials

were submitted to the NDA at the Division's request and all were reviewed. There was a truly herculean effort put forth to optimize the data integrity and process standardization within both trials, but particularly for the CTEPH trial with respect to the determination of the operability of patients for their thromboembolic pulmonary disease.

3.2 Compliance with Good Clinical Practices

All clinical studies that were submitted to support this NDA were compliant with GCP, incorporating an informed consent that was reviewed and approved by the IEC/IRB before its use. The conduct of the phase III studies was supervised by external Steering Committees (SC), and the safety of these trials was monitored Data Monitoring Committees (DMC).

There were no site-specific concerns that drove site selection for OSI inspections. Routine OSI audits of four trial sites were requested by the review division. Sites were selected for auditing based on review of the data for sites that may have driven safety and/or efficacy results. This data review was done by two methods: manual review by the clinical and statistical reviewers, and automated site analyses using the FDA site selection tool version 2.1. The final sites selected for auditing are shown in the table below:

Table 4: Sites selected for routine OSI inspections

Name of CI/Address/Contact Information	**Protocol No/ Site No./ No. of Subjects**	**No. of INDs in CDER's Database**	**Previous Inspectional History**
Zhicheng Jing Shanghai Pulmonary Hospital, Tongji University Department of Pulmonary Circulation, No. 507 Zhengmin Road, 200433 Shanghai	Study# 11348 (CHEST-1) **7 Subjects** Study # 12934 (PATENT- 1) **21 Subjects**	None	

Chen Wang Respiratory Diseases Institute, Beijing Chaoyang Hospital Pulmonology Dept. Baijianchuang Road 8#, Chaoyang District 100020 Beijing 19	Study# 11348 (CHEST-1) **21 Subjects** Study # 12934 (PATENT- 1) **18 Subjects**	None	
Andrea Maria D'Armini IRCCS Policlinico San Matteo Cardiochirurgia Dip. Chirurgia Generale e Trapianti d'Organo Piazzale Golgi, 19 27100 Pavia, Italy **(Alternate Site)** **Ardeschir Ghofrani** Universitätsklinikum Giessen und Marburg Standort Giessen, Medizinische Klinik II Ambulanz für Pulmonale Hypertonie / Klinische Studien Klinikstrasse 33, 35392 Gießen Hessen	Study# 11348 (CHEST-1) **18 Subjects** Study# 11348 (CHEST-1) **9 Subjects** Study# 12394 (PATENT-1) **16 Subjects**	None None	

Results from these inspections are pending at the time of the writing of this review.

3.3 Financial Disclosures

As per agreement with the Division (FDA Letter dated November 1, 2012), financial disclosure information was provided for the pivotal efficacy trials PATENT-1 (Study 12934) 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. This reviewer 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.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See CMC review.

4.2 Clinical Microbiology

None.

4.3 Preclinical Pharmacology/Toxicology

Key findings and recommendations from the pharm-tox review include the following:

- Studies submitted for the active metabolite (M1 or BAY60-4552) indicate similar pharmacologic activity with approximately 10 fold lower potency. The sponsor attributes adverse renal effects to the metabolite.

- Toxicities for riociguat include teratogenicity, effects on bone metabolism, potential renal effects, and variable effects on serum glucose, thyroid hormones and the liver. The effects on serum glucose, liver and thyroid may be individual phenomena or collectively may be a manifestation of decreased gastrointestinal efficiency secondary to smooth muscle relaxation.

- With respect to metabolic and/or hepatic effects, the following were noted from the animal studies:

    - Reduced T3 relative to the control group was reported in the rat 26 week study and the dog 52 week study. There were no apparent thyroid effects in shorter term dog studies.

    - Decreased cholesterol, decreased protein, foamy/enlarged hepatic macrophages, increased transaminases/bili, biliary hyperplasia with cysts, increased hepatic glycogen

- Renal affects were felt potentially attributable to the M1 metabolite. Three different studies with direct administration of BAY60-4552 demonstrated the following histological changes, some of them marked, mostly at the high doses: epithelial degeneration tubular degeneration, ductal cortical tubular hypertrophy/hyperplasia, mononuclear cell infiltration, interstitial fibrosis, degenerative lesions in the cortical tubules, and inflammation of the pelvis.

- With respect to bone effects, the following were noted/recommended:

    - The bone effects were identified by histopathological analysis and reported in mice and rats only, to include thickening of the hypertrophic zone of the femoral/tibial growth plates (physis), irregular resorption and thickness of the trabeculae of the primary spongiosa, and thickening of the chondral part of the growth plate, increased ratio of hematopoietic bone marrow to fat in the femoral epiphysis and sternum in both sexes, and hyperostosis in the femurs of both sexes.

    - Rat pups in the pilot juvenile animal study demonstrated disorganization of epiphyseal bone and thickening of the trabecular bone with a decrease in the morrow cavity area and marrow cells. In the definitive juvenile animal study, no histomorphological effects were reported for bone (highest dose below the LOAEL from the pilot study), but there was a marked decrease in the riociguat AUC from the beginning to the end of the dosing phase. There do not appear to be developmental effects as determined by the pre- and post-natal development (Segment III) study.

    - Histomorphological effects were also noted in several studies of BAY60-4552. The high dose (100 mg/kg) animals of both sexes given BAY60-4552 orally for 4 weeks showed histomorphological changes to the femur (thickening of the growth plate, disorganized trabecular bone, diffuse hyperostosis in the high dose animals).

    - Histomorphological effects on bone were not reported for the dog studies.

    - The bone toxicity is incompletely described with minimal examination of bones other than the sternum, femur and tibia in the standard approaches used for animal safety assessment studies. There are a number of safety assessment studies with apparent changes in serum calcium and phosphorous levels. Whether this is spurious, within normal variability, secondary to bone effects or involves a parathyroid effect, cannot be determined from the data in hand.

- There are multiple approved drugs with known skeletal system adverse effects (e.g. steroids, unfractionated heparin, antiepileptics, GnRH analogues, bisphosphonates, aromatase inhibitors, and methotrexate).

- The toxicology reviewer recommends a well-designed animal study that includes examination of bones such as mandible, nasal turbinates, calvarium, vertebrae, humerus, femur including the neck) and tibia and clinical chemistry parameters such as levels of vitamin D and metabolites, parathyroid hormones, and urinary calcium excretion to help to address the issue of exacerbation of osteoporosis, and that assessment of the mechanical properties of bone may be prudent. A clinical trial with monitoring and imaging of bones may also be of value.

- With respect to cardiac effects, the following were noted/recommended:

  - Cardiac morphologic damage was noted in dogs after administration of either BAY63-2521 or BAY60-4552. A summary of the cardiac morphologic changes for riociguat and its M1 metabolite are shown in two figures respectively (Hausner, toxicology reviewers, FDA):

Figure 2: Summary cardiac morphology changes, riociguat (FDA toxicology rev, Hausner, 2013)

Duration of study	Dose mg/kg	findings	AUC µg.hr/l BAY63-2521
13 weeks dog PH34778	≥0.3	Males: Endocarditis, perivascular edema of the myocardial arteries	483 (week 12)
	≥1	Males: medial hypertrophy of the myocardial arteries Females: perivascular edema + medial hypertrophy of the myocardial arteries	1721 (week 12)
	3	Females: endocarditis	3702 (week 12)
52 week dog A45725	2 (males) ≥0.3 (females)	1 HD (2 mg/kg) male unscheduled mortality day 279. Necropsy showed acute myocardial degeneration that was considered final circulatory decompensation. Cardiac vascular hypertrophy was seen in ¼ females in each of the drug-treated groups.	2980 (week 50) 828 (week 50)
2 year rat carcinogenicity PH36817	5, 10, 20 mg/kg	Thrombosis in heart, kidney,and other organs in males in all drug-treated groups. Not in females	≥1526

Figure 3: Summary cardiac morphology changes BAY 604552 (FDA toxicology rev, Hausner 2013)

BAY60-4552			AUC µg.hr/l
2 weeks dog PH34800	≥3	Coronary arteritis, necrosis, perivascular edema, Epicarditis, endocarditis	7351
	10	M +F: fibrosis of papillary muscle	13198
4 weeks dog PH34862	1.5	Females: papillary fibrosis	4771 (Day 25)
	≥1.5	Cardiac vascular inflammatory changes (both sexes)	4771
	5	Males: papillary fibrosis	9609 (Day 25)
13 weeks dog PH36085	≥1 3	Medial hypertrophy of the papillary muscle: females Medial hypertrophy of the papillary muscle:males	3633 9678
13 weeks rats PH35365	50 mg/kg 100 mg/kg	Males 8/10 medial hypertrophy cardiac blood vessels Females: 4/10 medial hypertrophy cardiac blood vessels	51428 82697
39 week dog PH35948	≥1	LOAEL for cardiac effects: hypertrophy of the arterial media of the left heart papillary muscles Hypertrophy of the ventricular septum(Females: ≥1 mg/kg ; Males: 3 mg/kg)	 2222 (week 39) 3755 (week 39)

- The sponsor identified a NOAEL for riociguat of 1 mg/kg in a 4-week oral dosing study. In the same study, doses of 3 mg/kg and 2 mg/kg given twice a day caused deterioration of body condition in the dogs with signs of trembling, ptyalism, vomiting, tenesmus, and unsteady gait. Mean blood pressure decreased profoundly in these animals (a change of 60 mm Hg relative to the control group), suggesting that the signs were due to hypotension, poor organ perfusion, and possibly cerebral ischemia.

- The 52 week dog study with riociguat reported that cardiac troponins I and T were measured days 9, 40, 89, 180, 271 and 362 and were "normal." The sponsor argued that cardiac changes happened acutely during the period of adaptation to the altered hemodynamics.

- With respect to repro-tox, the toxicology reviewer suggested modifications to the sponsor's proposed label to address the potential for teratogenicity as follows:

  - Use of admempas is contraindicated in females who are or may become pregnant. While there are no adequate and well-controlled studies in pregnant females, animal studies show that riociguat may cause fetal harm when administered during pregnancy. In rats administered riociguat orally (1, 5, 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested, which represents an exposure approximately 2.5 times that in humans at the MRHD of 2.5 mg three times a day based on AUC comparison. This dose also produced evidence of maternal toxicity (reduced body weight).

  - Incomplete ossification of the 4th sacral vertebrae was apparent from the lowest dose of 1 mg/kg/day, or an exposure approximately 0.15 that in

humans, without evidence of maternal toxicity. Post-implantation loss was statistically significantly increased from the mid-dose of 5mg/kg/day. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was seen starting at the middle dose of 1.5 mg/kg and an increase in resorptions was seen at 5 mg/kg/day, a dose which represents an exposure approximately 15 times that in humans at the MRHD. The highest dose tested also produced evidence of maternal toxicity (reduced body weight).

- Carcinogenicity studies of riociguat were conducted in mice and rats. In mice, oral administration of riociguat at 6, 12, 25 mg/kg/day in males and 8, 16 and 32 mg/kg/day in females for up to two years did not result in evidence of carcinogenic potential. Systemic exposure (AUC) at the highest dose was 1.6 times the human exposure at the MRHD. In male and female rats, oral administration of riociguat at 5, 10, 20 mg/kg/day for up to two years did not result in evidence of carcinogenic potential. Systemic exposure (AUC) of riociguat at the highest dose was 2 times the human exposure at the MRHD.

For discussions on these pre-clinical toxicology findings, including the extensive regulatory interactions that have occurred over the years between FDA and this sponsor regarding the potential for bone toxicity associated with chronic therapy with sGC stimulators, see the toxicology review for this NDA. Clinical correlates to the bone effects noted in the animal studies are discussed in section 7.7 of this review (additional submissions/safety issues), including the following information sources:

- Two separate information requests by FDA to Bayer to provide additional information and analyses of the animal bone findings during the course of this NDA review (Appendices A and B in section 9.4 of this review – Bone Toxicity Evaluations)

- Consultative review of the NDA bone data by internal bone metabolism experts here at FDA (Appendix C in section 9.4 of this review – Bone Toxicity Evaluations)

- Consultation of the maternal/fetal health division regarding the design of the sponsor's proposed REMS with respect to teratogenicity (specifically bone and cardiac)

Finally, the impact of the bone findings on this reviewer's recommendation for action regarding the sponsor's request for pediatric waivers for both the CTEPH and the PAH indications are discussed in section 7.6 of this review (Pediatrics and Assessment of Effects on Growth).

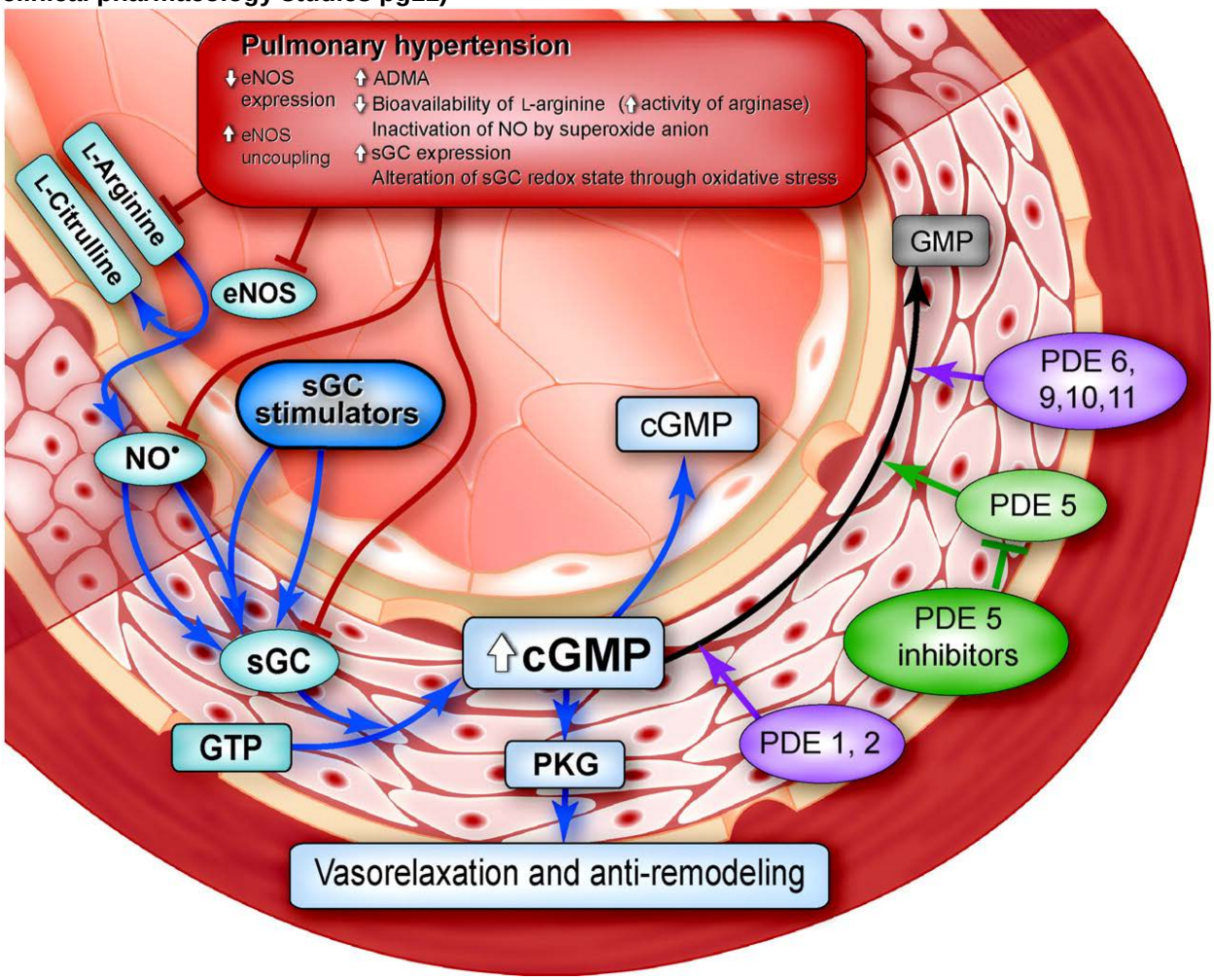
4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). When NO binds to sGC, the enzyme catalyzes synthesis of the signaling molecule cyclic guanosine monophosphate (cGMP). Intracellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Pulmonary hypertension is associated with endothelial dysfunction, impaired synthesis of nitric oxide and insufficient stimulation of the NO-sGC-cGMP pathway. Riociguat is thought to have a dual mode of action. It sensitizes sGC to endogenous NO by stabilizing the NOsGC binding. Riociguat also directly stimulates sGC via a different binding site, independently of NO.

Because of its vasodilatory properties, riociguat has been developed as a potential treatment for pulmonary hypertension. The main metabolite of riociguat, M1 (BAY 60-4552), exhibits pharmacological activity as a sGC stimulator. A schematic of the pharmacological targets in the NO/sGC/cGMP signaling pathway in PH are shown below:

Figure 4: Pharmacological targets in the NO-sGC-cGMP pathway (from sponsor's summary of clinical pharmacology studies pg11)



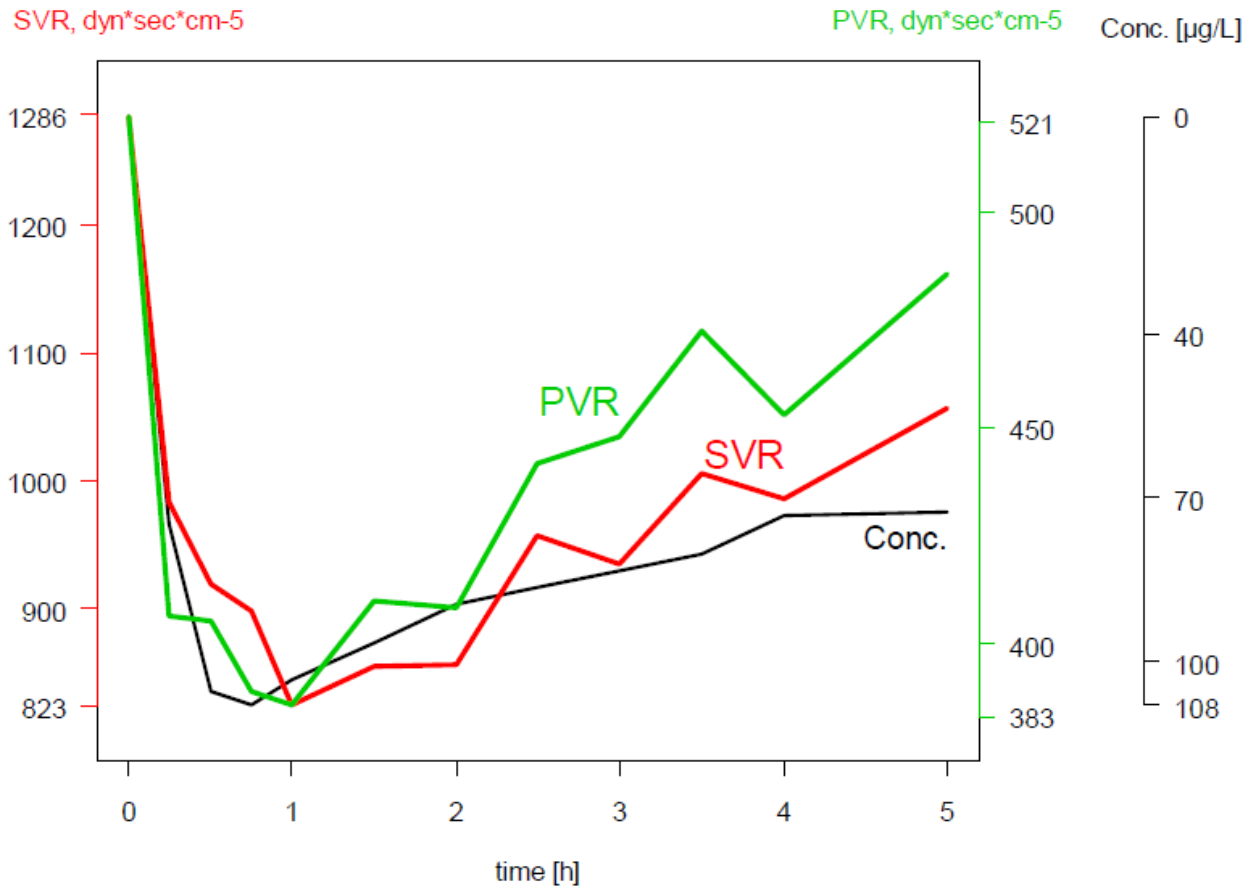
Note that sGC activation results in and increase in intracellular cGMP (increased synthesis). Likewise, PDE-5 inhibitors increase intracellular cGMP by preventing its degradation. Therefore, synergistic hemodynamic effects between NO donors (like nitroglycerin) and PDE-5 inhibitors (sildenafil and tadalafil) would be expected from a mechanistic point of view. Indeed, these interactions have been demonstrated in clinical testing (see the clinical pharmacology review for the riociguat NDA), and the sponsor warns against or proposes contraindications for their concomitant use with riociguat.

4.4.2 Pharmacodynamics

Hemodynamics

- Riociguat causes a dose dependent decrease in peripheral blood pressure in healthy subjects and subjects with PH.
- Riociguat causes a dose dependent increase in heart rate in healthy subjects and subjects with PH.
- Riociguat is a balanced vasodilator effecting a concentration-dependent reduction in pulmonary and systemic vascular resistances and pressures, as demonstrated in the following figure:

Figure 5: Correlation between mean PVR, SVR, and plasma concentration over time (N=10, PoC study 11874 FSR pg 67)



PD Interaction Studies

NO donors. Riociguat and NO delivered by nitroglycerin both act on sGC to increase intracellular cGMP, therefore, an additive effect is possible, and indeed, was demonstrated by the sponsor. In a Phase 1 study in healthy subjects, administration of a standard dose of 0.4 mg sublingual nitroglycerin 4 hours after a single oral tablet dose of 2.5 mg riociguat resulted in a pronounced PD interaction leading to significant hypotensive effects and syncope. (Study 14360 [PH-36542 in Module 5.3.4.1]). The sponsor's proposed label carries a contraindication for the concomitant use of any nitrates or NO donors in any form with riociguat.

Reviewer's comment: I agree with the sponsor's proposed label that NO donors in any form are contraindicated with riociguat therapy. This creates an issue for any patient with CAD who is prescribed or may need to use SL NTG. Since all of these patients are prescribed SL NTG in the event it is needed, it would seem that this is a contraindicated population. This is related to the discussion that patients with occult CAD, CVD, and PVD may tolerate the dose-responsive occurrence of hypotension associated with riociguat poorly (see reviewer's comments, vital signs, section 7.4.3).

Sildenafil. Riociguat and the PDE5 inhibitor sildenafil both act on the NO / sGC / cGMP signaling pathway. Thus, an additive effect on pulmonary and systemic circulation is possible and indeed has been demonstrated by the sponsor. In subjects with PAH stable for the last 6 weeks and treated with 20 mg sildenafil TID, sildenafil alone reduced pulmonary artery mean pressure (PAP_{mean}) and pulmonary vascular resistance (PVR), and led to pronounced and significant effects on the parameters of the systemic circulation like systolic and diastolic blood pressure, systemic vascular resistance (SVR) and cardiac output (CO). On top of sildenafil single doses of 0.5 mg and 1 mg riociguat had an additive but not significant effect on the parameters of the systemic circulation and a less additive effect on the parameters of the pulmonary circulation (Study 11917 [PH-36136 in Module 5.3.4.2]).

In a follow-up clinical trial (study 15096, PATENT-PLUS), IDT-dosed riociguat was added to a background of 20 mg TID of sildenafil in phase I of the study (blinded, placebo controlled). The plan was to assess the safety and efficacy data from Part I, then to progress to Part II where riociguat was to be added to any dose of sildenafil being used in clinical practice. In Study Part 1, 18 subjects were randomized in a 2:1 ratio to either the riociguat group or the placebo group (add-on therapy to the sildenafil background). During the main study, one patient withdrew due to a TEAE of "vision blurred" that was classified as drug related, and two patients experienced TEAEs of hypotension. All three of these events occurred in the riociguat treatment arm. However, after 17 out of 18 of these patients rolled over to the open label extension after 12 weeks of blinded therapy, an alarming withdrawal rate occurred in fairly short order, with 7 subjects (41%) suffering TEAEs of hypotension and one suffering frank

syncope (not one of the 7 patients with hypotension). Four of the subjects who experienced hypotension withdrew from the study, and 3 additional patients in the LTE study died (causes of death including cardiac arrest, decompensation of chronic right heart failure, and fall complicated by subdural hematoma).

As a consequence of the LTE dropout rate in Part 1 of PATENT-PLUS, study Part 2 was not initiated. Given the mechanistic interaction of riociguat and the PDE inhibitors (both increase intracellular cGMP, the former by increased production, the latter by inhibition of breakdown), the proposed label from the sponsor warns against concomitant use of PDE5 inhibitors with riociguat.

Reviewers comment: it is curious that nitrates and NO donors of any kind are contraindicated, but there is only a warning regarding concomitant use of PDE inhibitors in the sponsor's proposed label.

Warfarin. In a Phase 1 study in healthy subjects, concomitant administration of 2.5 mg riociguat TID at steady state did not influence prothrombin time and factor VII % activity compared to concomitant administration of placebo. Thus, no PD interaction between riociguat and warfarin (Coumadin) was detected (Study 11918 [PH-35468 in Module 5.3.3.4] and [PH-36263 in Module 5.3.2.3]).

Aspirin. Increasing cGMP in platelets by stimulation of sGC via riociguat has an anti-aggregatory effect *in vitro*. Thus, riociguat may have the potential to increase the anti-aggregatory effect of Aspirin. In a Phase 1 study in healthy subjects, no additive effect or interaction of 2.5 mg riociguat on top of 500 mg Aspirin on bleeding time, platelet aggregation measured *ex vivo* after stimulation with collagen and arachidonic acid, or on thromboxane B2 in serum could be demonstrated. Thus, no PD interaction between riociguat and Aspirin was detected (Study 14204 [PH-36360 in Module 5.3.3.4]).

4.4.3 Pharmacokinetics

Riociguat is a low solubility, high permeability compound (Class 2 Biopharm Classification System). It is a basic molecule (pk_a 4.3), so highly soluble in aqueous acidic media, but solubility in pure water is low. It is a substrate for P-gp and BCRP. Bioavailability of riociguat administered as a 1.0 mg tablet dose was almost complete at 94% reflecting unrestrained absorption and lack of first-pass extraction of this low-clearance drug.

Riociguat is rapidly absorbed after oral administration of 0.25 to 5.0 mg as an oral solution with C_{max} after approximately 0.5 to 1.5 h (Study 11258 [PH-34400 in Module 5.3.3.1]). Peak concentrations of the micronized IR tablets were seen with similar timing, with C_{max} after approximately 0.5 to 1.5 h. AUC was similar between the two

formulations as well. Absence of a food effect on absorption has been shown for the 2.5 mg tablet. At tablet doses from 0.5 to 2.5 mg investigated in a 5-way crossover design under fasting conditions riociguat PK behaved dose-proportionally (Study 13009 [PH-36258 in Module 5.3.1.2]).

Riociguat in the human is mainly distributed into plasma; the human plasma-to-blood partition coefficient is 1.5. Plasma protein binding for riociguat in humans is high at approximately 95% *in vitro*, with serum albumin and α1-acidic glycoprotein being the main binding components. The binding of riociguat to plasma proteins is fully reversible. No concentration-dependency up to more than 10-fold the maximum therapeutic concentration for the 2.5 mg dose and no gender difference in fraction unbound was detected [Module 2.6.4.4.1].

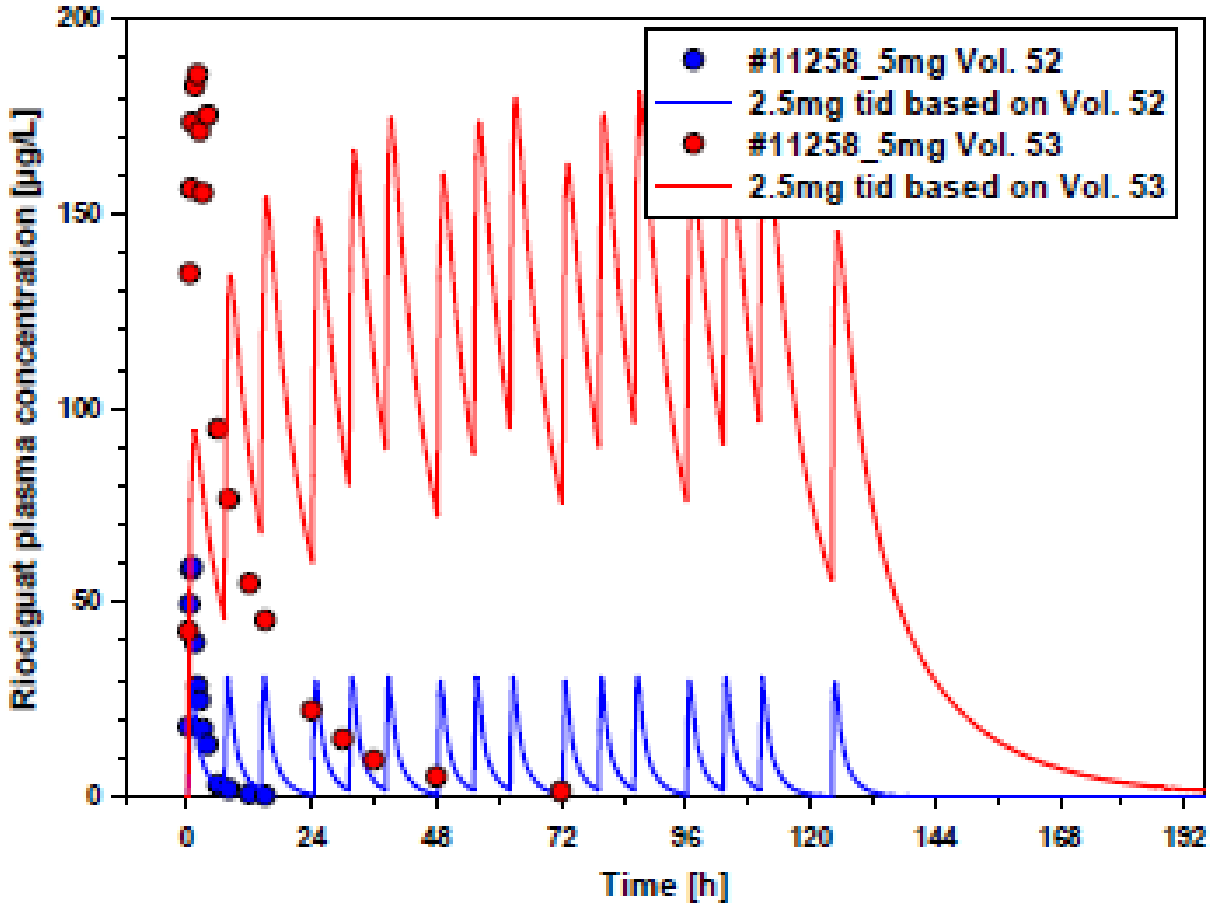
Due to its high plasma protein binding riociguat is not expected to be dialyzable.

Displacement studies in human plasma revealed that the unbound fraction of riociguat remains unchanged *in vitro* after co-incubation with ibuprofen, warfarin, nifedipine, digitoxin, atorvastatin, furosemide, sildenafil, and bosentan. There was a 1.5-fold increase of the unbound fraction after addition of 200 mg/L salicylic acid (approximately corresponding to the C_{max} of single oral doses of 4 - 5 g of acetylsalicylic acid [ASS]) [Section 4.1 of Module 2.6.4]. In a phase 1 study employing riociguat 2.5 mg co-administered with Aspirin500 mg, no relevant pharmacokinetic interaction was observed (Study 14204 [PH-36360 in Module 5.3.3.4]).

The volume of distribution at steady-state (Vss) was determined in the absolute bioavailability Study 11910 [PH-36361 in Module 5.3.1.1] to be approximately 30 L (0.38 L/kg) for riociguat, indicating its low affinity to tissues. Riociguat penetration across the blood-brain-barrier and the placental barrier was of low and moderate extent in the respective rat studies [Module 2.6.4.4.2]. The estimated amount of radioactivity excreted with milk of lactating rats was 2.2% of the dose within 32 h after administration [Module 2.6.4.6.4].

CYP1A1significantly contributed to the N-demethylation of riociguat as demonstrated with microsomes from human liver and lung tissue in the presence of CYP1A1 inhibitors like α-naphthoflavone, ketoconazole and quercetin [Module 2.6.4.5.1.2]. Induction of CYP1A1 in the liver and lungs of smokers resulted in a 2-3-fold difference of riociguat clearance between smokers and non-smokers. Thus, smokers demonstrate substantially lower riociguat exposure, as demonstrated by simulations of plasma concentrations in a smoker and a non-smoker following multiple-dosing of 2.5 mg TID from study 11258 (based on single-dose data of 5 mg), as shown in the figure below:

Figure 6: Simulation of riociguat plasma concentrations following multiple-dosing of 2.5 mg TID for subject #53 (non-smoker, low clearance, long half-life) and subject #52 (smoker, higher clearance, short half-life), based on single-dose data of 5 mg



This effect has been seen in all studies where smokers have been included, including the clinical phase 2/3 trials. Of note, in the pivotal CHEST-1 trial (11348), there were only 6/173 current smokes in the IDT treatment arm, and in the pivotal PATENT-1 trial (12934) only 17/254 subjects were current smokers in the IDT treatment arm. No beneficial treatment effect in current smokers subgroup in the PAH trial was demonstrated (actually had a negative 58m placebo subtracted treatment effect).

The M1 metabolite (BAY 60-4552) stimulates sGC with 3-10 fold lower potency than the parent molecule, and M4 is pharmacologically inactive.

Riociguat is eliminated via three routes in man: 27 to 71% of the dose was subject to oxidative biotransformation (as metabolites M1, M3 and M4). 13% (up to 44%) was excreted as unchanged drug in feces, and 6% (up to 19%) was excreted as unchanged drug in urine via glomerular filtration (Study 11911 [PH-35338 in Module 4.2.2.4]). The quantitative contribution to these elimination/ clearance pathways considerably varies

between individuals, mainly dependent on the individual metabolic, specifically CYP1A1, activity status.

Elimination of riociguat in healthy subjects is associated with a mean terminal half-life of 6.8 h at high inter-individual variability (CV%: 74%) (Pooled analysis of PK data [PH-36936 in Module 5.3.5.3]). In elderly healthy subjects mean half-lives are prolonged to 12 h (Study 11914 [PH-35666 in Module 5.3.3.3]). Due to the underlying disease (PH) affecting riociguat clearance, riociguat terminal half-life in patients is about 12 h on average (PK/PD Study 12653 [PH-36006 in Module 5.3.3.5]).

Variability in riociguat exposure (AUC) in PH patients is high with inter-individual variability (coefficient of variation) of approximately 60% across all doses (PK/PD Study 13817 [PH-36960 in Module 5.3.3.5]). The intra-individual variability is considerably lower with 35% for riociguat trough plasma concentration (C_{trough}). PH patients showed about 3 times higher AUC/D than healthy subjects after single dose administration of riociguat oral solution, most likely as a function of disease-inherent impaired elimination/excretion. The difference was statistically significant (Study 11874 [PH-34730 in Module 5.3.4.2] and Supplemental statistical analysis [PH-36988 in Module 5.3.5.3]). Subjects aged 65 years and older show prolonged riociguat half-lives (by approximately 30%) and increases in riociguat exposure (by approximately 40%). Likewise, exploratory across-study analysis of all Phase 1 trials showed that AUC/D and Cmax/D of riociguat were approximately 35% respectively 40% higher at body weights below 60 kg (Pooled analysis of PK data [PH-36936 in Module 5.3.5.3]). AUC and t1/2 (terminal half-life) values were similar for men and women. Cmax values were on average 35% higher in women than in men ($p<0.05$). This difference was explained at least partly by body weight, as body weight-normalized Cmax, i.e. Cmax, norm values, were on average only 20% higher in women.

The mean half-life of riociguat was prolonged in all subjects with renal impairment (9.5 to 11.4 hours) compared to results in healthy subjects (6.2 hours). Likewise, the mean half-life of M1 (BAY 60-4552) was also longer in all subjects with renal impairment (22.6 - 31.0 hours) compared to results in healthy subjects (13.9 hours). The impact of renal insufficiency on riociguat exposure, by severity of renal impairment, is shown in the table below:

Table 5: Riociguat exposure in renal impairment (dose and weight normalized AUC [AUC_{norm}]; all subjects valid for PK, summary of clinical pharm studies table 1-3 pg 21)

Intrinsic factors	Ratio	Point estimate	90% confidence interval lower	upper
Renal Function (groups acc. to CL_{CR} at baseline)	50 - 80 / >80 mL/min	1.4276	0.8714	2.3388
	30 - <50 / >80 mL/min	2.0429	1.2570	3.3201
	<30 / >80 mL/min	1.4402	0.8862	2.3407

CL_{CR} = creatinine clearance
Source: Study 15678 [PH-36803 in Module 5.3.3.3; Table 14.4 / 4.2]

Mean exposure to riociguat (AUC_{norm}) was significantly increased by approximately 50% (total) to 70% (unbound) in Child Pugh B subjects compared to their matched healthy controls, as shown in the table below:

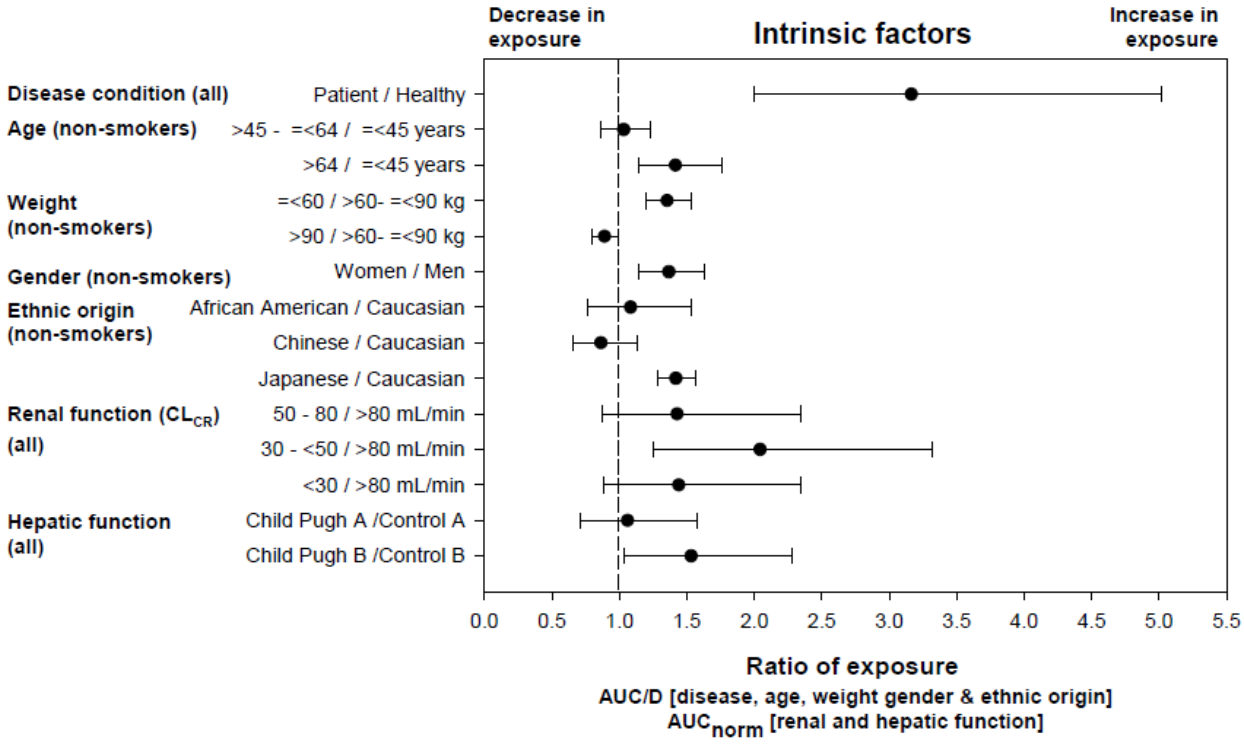
Table 6: Riociguat exposure in hepatic impairment (dose and weight normalized AUC [AUC_{norm}]; all subjects valid for PK, summary of clinical pharm studies table 1-4 pg 22)

Intrinsic factors	Ratio	Point estimate	90% confidence interval lower	upper
Hepatic Function	Child Pugh A /Control A	1.0612	0.7138	1.5775
	Child Pugh B /Control B	1.5313	1.0301	2.2764

Source: Study 15679 [PH-36804 in Module 5.3.3.3; Table 14.4 / 4]

A summary of the impact of extrinsic factors on riociguat exposure is shown in the forest plot below:

Figure 7: Impact of intrinsic factors on riociguat exposure (Pooled analysis of PK data, summary of clinical pharm fig 1-2 pg 23)



Source: Pooled analysis of PK data [PH-36936 in Module 5.3.5.3], Study 15678 [PH-36803 in Module 5.3.3.3], Study 15679 [PH-36804 in Module 5.3.3.3], Supplemental statistical analyses [PH-36988 in Module 5.3.5.3]

Drug-Drug Interactions

The sponsor has noted the following findings from extensive investigation of drug-drug interactions for riociguat:

- Pre- and co-treatment with the **proton pump inhibitor omeprazole** 40 mg once daily (od) reduced riociguat bioavailability with a mean Cmax decrease of 35% and a corresponding AUC decrease of 26% (Study 11262 [PH-35196 in Module 5.3.3.4]).

- Co-treatment with an **antacid** (10 mL of aluminum hydroxide/magnesium hydroxide) reduced riociguat bioavailability with a mean Cmax decrease of 56% and a mean AUC decrease of 34% (Study 11890 [PH-35362 in Module 5.3.3.4]).

- Co-treatment with the **H2-antagonist ranitidine** (150 mg od) reduced riociguat bioavailability with a mean Cmax decrease of approximately 15% and a mean

AUC decrease of approximately 10% (Supplemental statistical analyses [PH-36988 in Module 5.3.5.3]).

- Co-administration of **acetylsalicylic acid** (500 mg) or **warfarin** (25 mg), respectively, did not affect riociguat PK (Study 14204 [PH-36360 in Module 5.3.3.4]; Study 11918 [PH-36263 in Module 5.3.2.3]

- Riociguat and its main human metabolite M1 (BAY 60-4552) are neither inducers (CYP1A2, CYP3A4) nor inhibitors (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2, and 3A4) of any major CYP isoforms or human UGTs or SULTs (sulfotransferases) *in vitro* at therapeutic plasma concentrations (Module 2.6.4.5.1.3, Module 2.6.4.5.1.4, Module 2.6.4.5.1.5, Module 2.6.4.5.1.6).

- No clinically relevant drug-drug interactions due to inhibition of transporters such as P-gp or BCRP, or organic anion transporting polypeptides OATP1B1, OATP1B3, or organic anion transporters OAT1, OAT3, or organic cation transporters OCTs by riociguat are expected (Module 2.6.4.8.4 to Module 2.6.4.8.6). Furthermore, metabolite M1 (BAY 60-4552) is not an inhibitor of P-gp, BCRP and OCTs at relevant therapeutic concentrations (Module 2.6.4.8.16 to Module 2.6.4.8.18).

- Lack of mutual PK interaction between riociguat and the co-administered **CYP3A4 substrates midazolam and sildenafil** could be demonstrated *in vivo* (Study 14982 [PH-36597 in Module 5.3.3.4]; Study 11917 [PH-36136 in Module 5.3.4.2]).

- Riociguat and M1 (BAY 60-4552) revealed an inhibitory potency on CYP1A1 *in vitro* with an inhibition constant (Ki) value of 0.6 µM, each. Clinically relevant drug-drug interactions with co-medications which are significantly cleared by CYP1A1-mediated biotransformation (such as erlotinib or granisetron) cannot be ruled out (Module 2.6.4.5.1.3).

- Due to the involvement of CYP1A1, CYP3A4, CYP2C8 and CYP2J2 in riociguat biotransformation and P-gp/BCRP in its active excretion processes, riociguat was classified as susceptible to PK interaction when co-medicated with inhibitors or inducers of these enzymes and/or transporter proteins.

- To evaluate the CYP-mediated drug-drug interaction potential for riociguat as victim, a series of 87 drugs from various compound classes (e.g., anticancer drugs, analgesics, antiviral drugs, antibiotics, antifungal azoles, etc.) were part of a broad *in vitro* screening with common co-medications tested regarding their potential to affect riociguat oxidative metabolism *in vitro* applying human liver microsomes or human recombinant CYP1A1 (A50207 in Module 4.2.2.6):

- N-demethylation, i.e. metabolite M1 (BAY 60-4552) formation, in human liver microsomes was considerably inhibited by HIV (human immunodeficiency virus) protease inhibitors (ritonavir, atazanavir > indinavir, with half maximal inhibitory concentration [IC50] values of 5.3 to 11.7µM) and antifungal azoles (ketoconazole > clotrimazole, miconazole, IC50 values of 0.6 to 5.7 µM) (Module 2.6.4.7.1).

- Pronounced inhibition of recombinant human CYP1A1 – an important CYP isoenzyme in riociguat metabolism, especially in smokers – was observed by the antifungal azoles ketoconazole, clotrimazole and miconazole (IC50 values of 0.3 to 0.6 µM), as well as carvedilol, ebastine, quercetin (IC50 values of 0.6 to 2.5 µM) and tyrosine kinase inhibitors like erlotinib, gefitinib, imatinib, sorafenib and sunitinib (IC50 values of 0.2 to 4.2 µM).

- Mechanism-guided clinical *in vivo* drug-drug interaction studies within the clinical-pharmacological program confirmed these results:

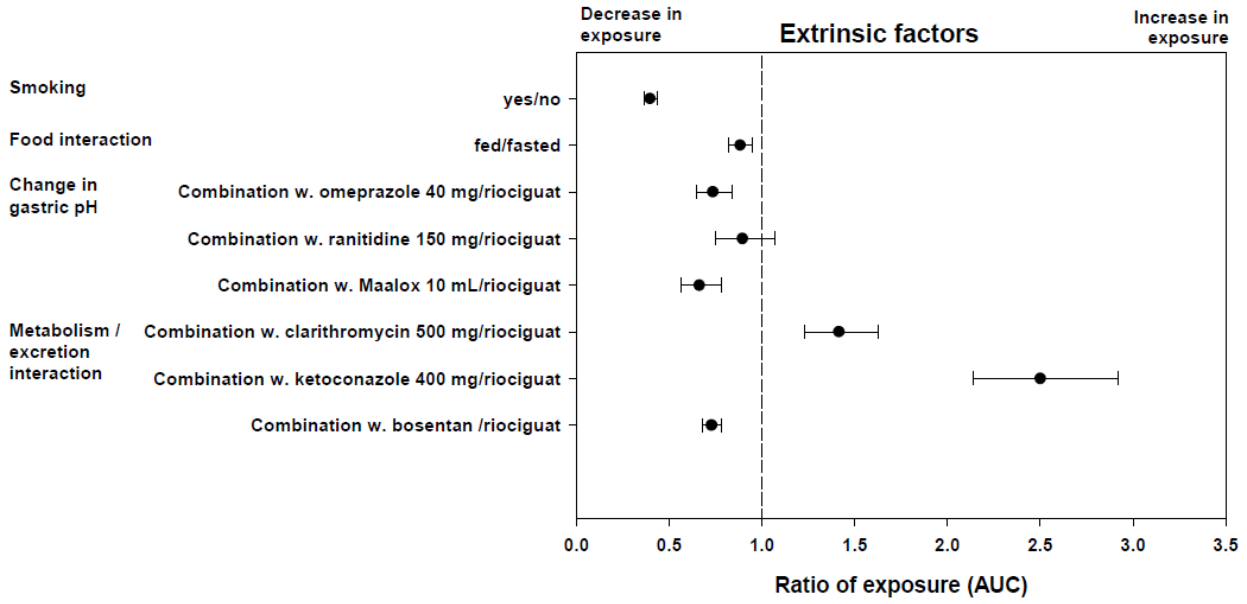
  - Co-administration of **clarithromycin** (500 mg bid [twice daily]), classified as strong and selective CYP3A4 and weak-to-moderate P-gp inhibitor,(2) moderately increased riociguat exposure with a mean AUC increase by 41% and with no significant change in Cmax. M1 (BAY 60-4552) mean AUC increased by 19% without significant change in Cmax (Study 13284 [PH-36280 in Module 5.3.3.4]).

  - **Ketoconazole** is classified as strong CYP3A4 and P-gp inhibitor according to the FDA guidance. *In vitro*, ketoconazole could be established as a potent 'multi-pathway CYP and P-gp/BCRP inhibitor' for riociguat metabolism and excretion (Section 3.4.2.2.1). As expected from these *in vitro* data, concomitant administration of 400 mg od ketoconazole led to a 150% (range up to 370%) increase in riociguat mean AUC and a 46% increase in mean Cmax. Mean terminal half-life increased from 7.3 to 9.2 hours and mean apparent (total) body clearance decreased from 6.1 to 2.4 L/h. M1 (BAY 60-4552) mean Cmax decreased by 49% and mean AUC by 24%. Mean terminal half-life of M1 (BAY 60-4552) increased slightly from 16.2 hours to 18.3 hours (Study 11261 [PH-35000 in Module 5.3.3.4]).

  - **Bosentan**, a common PAH-specific co-medication and reported to be a moderate inducer of CYP3A4 led to a decrease of riociguat steady-state plasma concentrations in PH patients by 27% on average (PK/PD Study 13817 [PH-36960 in Module 5.3.3.5]).

The following figure summarizes the impact of extrinsic factors on riociguat exposures as shown from *in vivo* data:

Figure 8: Impact of extrinsic factors on riociguat exposure (pooled analysis of PK data, summary of clinical-pharm fig 1-3 pg 28)



With respect to the overall PK/PD of riociguat, the sponsor concludes: A close and direct relationship between riociguat hemodynamic activity related to its mode of action and riociguat exposure is established. Riociguat has predictable PK and PD in PAH and CTEPH patients, although with considerable inter-individual (at moderate intra-individual) variability in its exposure and consequently hemodynamic effects which was coped with by an individualized dosing approach.

Dose/Exposure-Response relationship for efficacy

For both the CTEPH and the PAH trial populations (from CHEST-1 and PATENT-1 respectively), the E-R relationship for the placebo corrected 6MWD change from baseline was flat, as seen in the following figures for the PAH phase III trial and for the CTEPH phase III trial, respectively:

Figure 9: Change in 6MWD separated by 1.5 mg and 2.5 mg doses, pentiles (left panel) and more quantiles of expsure for 2.5 mg dose (right panel) in PATENT-1 (FDA Clinical Pharmacology Review, Dhananjay 2013)

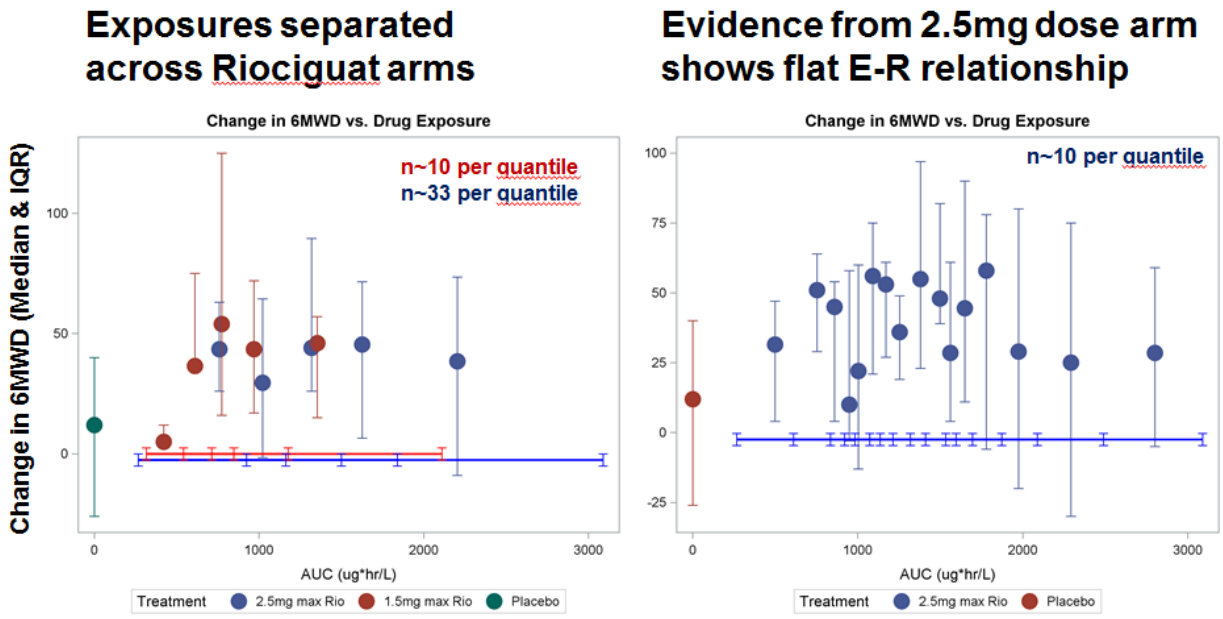
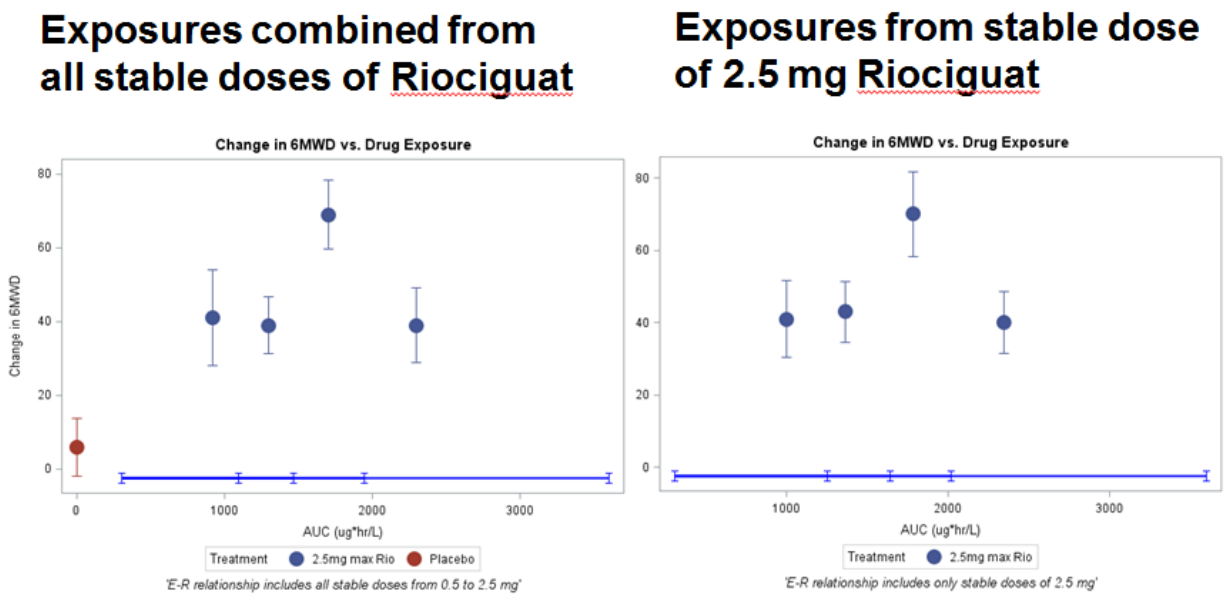


Figure 10: Change from baseline in 6MWD separated by quartiles of exposure in 2.5 mg dose from CHEST-1, with efficacy data corresponding to all stable doses at week 16 in left panel, and efficacy data only for patients on 2.5 mg TID at week 16 in right panel



Dose-Safety relationship (hypotension)

In the PAH trial, a small third arm receiving a capped dose of 1.5 mg TID was included (N=64) but formal testing versus placebo not planned. However, there was a higher event rate of both SBP < 90 mm hg and Hypotension adverse events in the IDT ARM as shown from the following table:

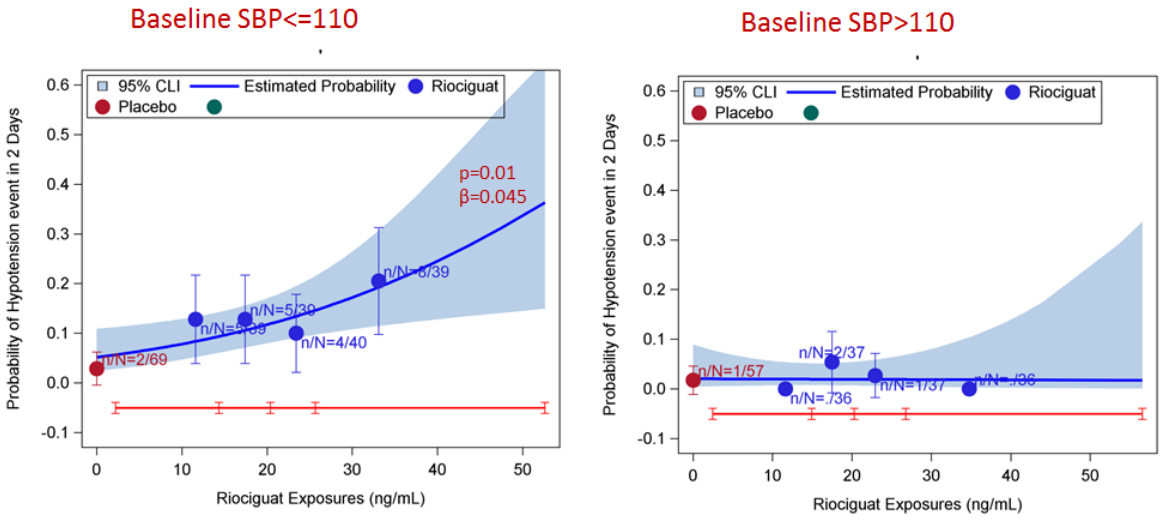
Figure 11: PATENT-1 SBP<90 mmHg and hypotension AEs by dose arm (Dhananjay, FDA clin-pharm review pg 14)

Hypotension SBP <90	Placebo	1.5 mg Fixed Dose Arm	2.5 mg Ind. Titration Dose Arm		
		1.5 mg	1.5 mg	2 mg	2.5 mg
Events (n)	12	1	3	10	13
Patients (N)	126	52	245	222	189
Exposure in Weeks	12	10	2	2	6
Events per 100 person-year	**41**	**10**	**32**	**117**	**60**

Hypotension AE	Placebo	1.5 mg Fixed Dose Arm	2.5 mg Ind. Titration Dose Arm		
		1.5 mg	1.5 mg	2 mg	2.5 mg
Events (n)	3	2	4	6	6
Patients (N)	126	52	245	222	189
Exposure in Weeks	12	10	2	2	6
Events per 100 person-year	**10**	**20**	**42**	**70**	**28**

The clinical pharmacology reviewer has noted that the occurrence of drug-induced SBPs <90 mmHg were exposure related and front loaded, the 45% occurring on day 1 or day 2 of taking the 1 mg TID dose, and almost all of these events occurred in patients with baseline SBP of ≤110 mmHg, as is seen in the following figure:

Figure 12: Hypotension events (SBP <90 mmHg) are front occurring within 2 days of starting treatment, most in patients with baseline SBP ≤ 110 mmHg (FDA Clinical Pharmacology review, Dhananjay 2013))



Reviewer's note: The clinical pharmacology reviewer suggests that starting the up-titration with 0.5 mg TID may ameliorate these episodes of drug-induced hypotension, and I agree. However, given the flat E-R responses that have been demonstrated for efficacy, I favor capping PAH dosing at 1.5 mg TID based on the clinical efficacy data from the capped dose arm of PATENT-1.

There was no capped dose arm in CHEST-1 to demonstrate equivalent clinical efficacy of the lower dose, however, the E-R relationship for efficacy is also flat per the clinical pharmacology analysis for CHEST-1 in figure 9 above, suggesting that the 1.5 mg TID dose is sufficient in that population as well. In contradistinction to the PAH trial, It is noted that SBP events <90 were similar between the placebo and the IDT arm, which interestingly has occurred in the setting of higher baseline SBP's in CHEST-1. This was undoubtedly related to the fact that the CTEPH population in CHEST-1 was substantially older, with 40% being over the age of 65 years. Therefore, it is reasonable to label the CTEPH indication one of two ways:

1. either cap it's dosing at 1.5 mg TID for simplicity to match the PAH indication, with the notation in the label that doses as high as 2.5 mg TID were tested in CHEST-1 but did not show improved efficacy, or

2. Labeling the dose escalation as the sponsor did it in the trial, but limiting the dose to 1.5 mg TID for patients with a baseline SBP ≤ 110 mmHg.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Figure 13: Phase I and Phase II studies of historical interest to this development program

Type of Study Clinical Phase	Study No. (Report No.)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Numbers of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status Type of Report	Location of Study Report
PK I	11258 (PH-34400)	Safety and Tolerability, Pharmacokinetics	Randomized, Single-blind/ Parallel-group Placebo-control	Riociguat 0.25, 0.5, 1.0, 2.5 or 5.0 mg solution 0.05% 2.5 mg IR tablet	58 treated	Healthy subjects	Complete; Full	Module 5.3.3.1
PK I	11260 (PH-34881)	Safety and Tolerability, Pharmacokinetics, Pharmacodynamics	Randomized, Single-blind/ Cross-over/ Placebo-control	Riociguat 0.5, 1.0, 1.5 or 2.5 mg tid IR-tablets over 10 days	60 treated	Healthy subjects	Complete; Full	Module 5.3.3.1
PD/PK II	11874 (PH-34730)	POC SD invasive hemodynamics in patients with PH Safety, tolerability, pharmacokinetics and the impact on pulmonary- and systemic-hemodynamics and gas exchange	Non-randomized, non-blinded, Incremental -dose escalation of 2 single doses/ single-dose, solution	Riociguat 0.5/1.0/1.0 mg increments, solution; single dose; Riociguat 1.0, 2.5 mg solution, single dose	19	Patients with PH	Complete; Full	Module 5.3.4.2
PK II	11917 (PH-36136)	Interaction with Sildenafil Safety and Tolerability, Pharmacokinetics	Non-randomized, non-blinded	20 mg Sildenafil tid; Riociguat 0.5, 1.0 mg IR tablet SD	7	Patients with PAH and stable treatment of sildenafil 20 mg tid	Complete; Full	Module 5.3.4.2
II	15096 (A57218)	Safety and efficacy of combined treatment with sildenafil and riociguat	Randomized, double-blind, placebo-controlled, multicenter Placebo-control	Riociguat 0.5 mg tid 1.0 mg tid 1.5 mg tid 2.0 mg tid 2.5 mg tid individual dose titration oral administration pre-treatment with sildenafil 20 mg tid	18	PAH	Interim cut-off complete	Module 5.3.5.1

Figure 14: Phase II and Phase III studies pertinent to the claimed indications

Study number Primary indication	Study Design	Riociguat regimen and treatment duration	Comparator	ITT population	Riociguat dosage: number of subjects
Phase II trials PAH and CTEPH					
12166 (report PH-35772) Treatment of PAH and CTEPH	Multicenter, non-randomized, non-blinded, non-controlled, dose-titration	12 weeks 0.5, 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration	None	N = 72 [e]	IDT at end of study 3.0 mg [a]: 1 2.5 mg: 51 2.0 mg: 7 1.5 mg: 8 1.0 mg: 4 0.5 mg: 1
12166 (report A61224) Long-term extension study in treatment of PAH and CTEPH	Multicenter, non-randomized, non-blinded, non-controlled, dose-titration	Interim analysis after up to 4.5 years of treatment 0.5 , 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration	None	N = 68 [f]	IDT up to 2.5 mg IDT [b] 7.5 mg TID [c]: 51 6.0 mg TID: 4 4.5 mg TID: 7 3.0 mg TID: 6
Phase III trials CTEPH					
11348 (report A62508) Treatment of CTEPH	Multicenter, double-blind, randomized, placebo-controlled	16 weeks 0.5 , 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration	Placebo	N = 261	Arm 1 IDT up to 2.5 mg TID: 173 Arm 2 Placebo: 88
11349 (report A62509) Long-term extension study in treatment of CTEPH	Multicenter, multinational, open label, one-arm extension	8 weeks titration, following main study until drug approval 0.5 , 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration	None	N = 194 [f] (cut-off date 03 May 2012)	IDT up to 2.5 mg TID: 194 (Former riociguat = 129 subjects Former placebo = 65 subjects)
12934 (report A62510) Treatment of PAH	Multicenter, double-blind, randomized, placebo-controlled, 3-arms, dose-titration	12 weeks 0.5 , 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration 1.0 to 1.5 mg capped dose titration	Placebo	N = 443	Arm 1 IDT up to 2.5 mg TID: 254 Arm 2 1.5 mg TID (capped) [d]: 63 Arm 3 Placebo: 126
12935 (report A62511) Long-term extension study in treatment of PAH	Multicenter, multinational, open label, one-arm extension	8 weeks titration, following main study until drug approval 0.5 , 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration	None	N = 363 [f] (cut-off date 16 Apr 2012)	IDT up to 2.5 mg TID: 363 (Former riociguat 1.5 mg = 52 Former riociguat IDT = 215 Former placebo = 96)

a Single dose
b N > 68 because the numbers include a few subjects who had received other doses for short periods of time.
c Including 1 subject who overdosed with 3 mg TID for 32 days, and 4 subjects who overdosed for part of the 12-week phase; details are presented in the study report (PH-35772).
d In study 12934 PATENT-1, the 1.0 - 1.5 mg riociguat capped dose arm is inaccurately referred to as the "1.5 mg *fixed dose*" arm in the statistical tables of the study report. For details, see Section 2.4.1.1.
e Subjects valid for PK/PD analysis
f All subjects entering the long-term extension study (study 12166 LTE) or long-term safety and efficacy analysis set (studies 11349 and 12935)
Abbreviations: IDT = individual dose titration; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension;
TID = *ter in die* (3 times a day);
Source: ■ PH-35772 (Study 12166 in Module 5.3.5.2), Section 11.1 and Table 14.1/9, ■ A61224 (Study 12166-LTE in Module 5.3.5.2) Table 14.2./1, ■ A62508 (Study 11348 in Module 5.3.5.1) Table 14.1/1, ■ A62509 (Study 11349 in Module 5.3.5.2) Table 14.1/1, ■ A62510 (Study 12934 in Module 5.3.5.1) Table 14.1/1, ■ A62511 (Study 12935 in Module 5.3.5.2) Table 14.1/1

5.2 Review Strategy

Riociguat is a first-in-class vasodilator and an NME that has been developed for the treatment of pulmonary hypertension. This NDA is somewhat unique in that the two pivotal trials that are submitted for review have been performed in two separate patient populations as follows:

- CHEST-1 (trial 11348) enrolled patients with pulmonary hypertension secondary to chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4). There are no approved therapies for this indication. Therefore, this trial in this population drove the decision to grant a priority review.

- PATENT-1 (trial 12934) enrolled patients with pulmonary arterial hypertension (PAH, WHO Group1 – FC II-III idiopathic, heritable, or connective tissue induced PAH) for whom other vasodilator therapies are approved and available, though riociguat, if approved will be the first vasodilator in its mechanistic class to be approved for the treatment of these patients.

Because the etiology of the pulmonary hypertension in these two populations is mechanistically unique, the efficacy for these two populations is considered individually in section 6: the CHEST-1/CTEPH efficacy is demonstrated in section 6.1, and then the PATENT-1/PAH efficacy is reviewed in section 6.2 in the identical format as section 6.1.

It is this reviewers concern that not all patients require the highest doses of riociguat that were tested in the individual dose titration (IDT) arms of both CHEST-1 and PATENT-1. This conclusion is not only based on the efficacy results from PATENT-1 where two dosing strategies were tested (IDT to 2.5 mg TID and capped dosing at 1.5 mg TID), but also results from the sponsor's early multi-dose trial in healthy normal human subjects (trial 11260) and the original proof of concept hemodynamic trial (trial 11874). Therefore, results from trials 11260 and 11874 will be presented in section 5.3.

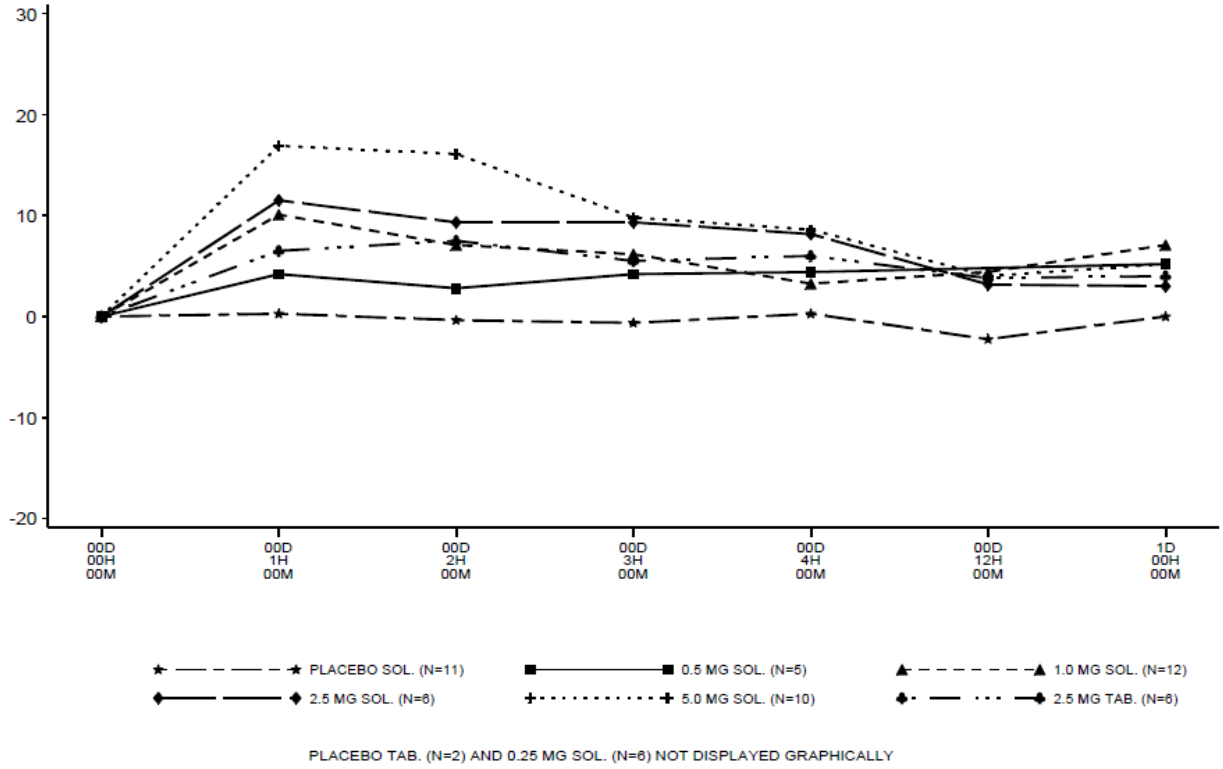
The sponsor conducted trial 12166 as a phase II study to evaluate the individual dose titration dosing strategy that was ultimately tested in both pivotal trials as a strategy for dealing with wide inter-patient variability of pharmacokinetics. This trial was non-randomized, non-blinded, and non-controlled, so was limited in its ability to define the minimal effective dose or the dose above which no further clinical benefit was obtained. Study 12166 did, however, provide longer term follow-up for safety purposes. Its results will also be presented in section 5.3 as well.

5.3 Discussion of Individual Studies/Clinical Trials

Riociguat has a history of well-documented effects on cardiovascular PD parameters, namely HR and BP effects. I will briefly summarize the findings of three such studies below, in that they are relevant to the major safety concern in the PH pivotal trials.

Trial 11258. This was a single ascending dose PK trial in 8 healthy normal male subjects per group demonstrated clearly the dose-responsive nature of riociguat's HR effects as shown in the figure below of change from baseline of mean heart rates in each dose group:

Figure 15: Study 11258 mean HR change from BL by dose (PK/PD/safety set, N=58, FSR pg 162)



Note that at one hour post dose (solution), the mean HR increase in the 1.0 and 2.5 mg groups was approximately 10 BPM and the mean increase in the 5.0 mg arm was approximately 18 BPM. However, these means mask what was occurring in the individual patients, for which the following figures for the 1.0 mg, 2.5 mg, and 5.0 mg doses are instructive:

Figure 16: Study 11258 HR change from BL, 1.0 mg oral dose

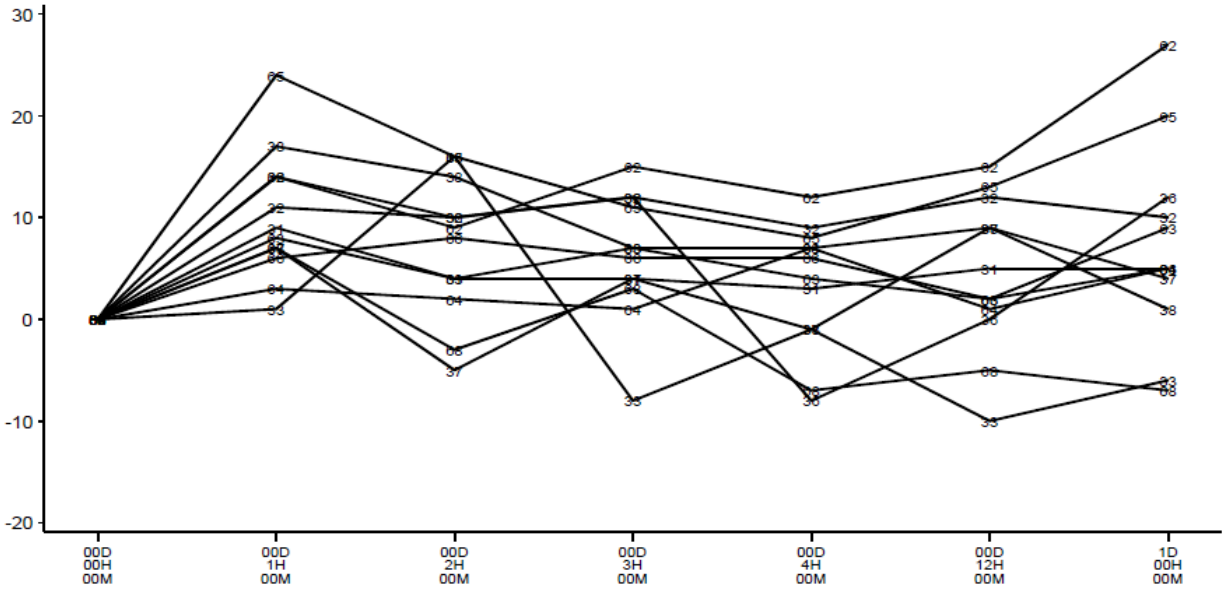


Figure 17: Study 11258 HR change from BL, 2.5 mg oral dose

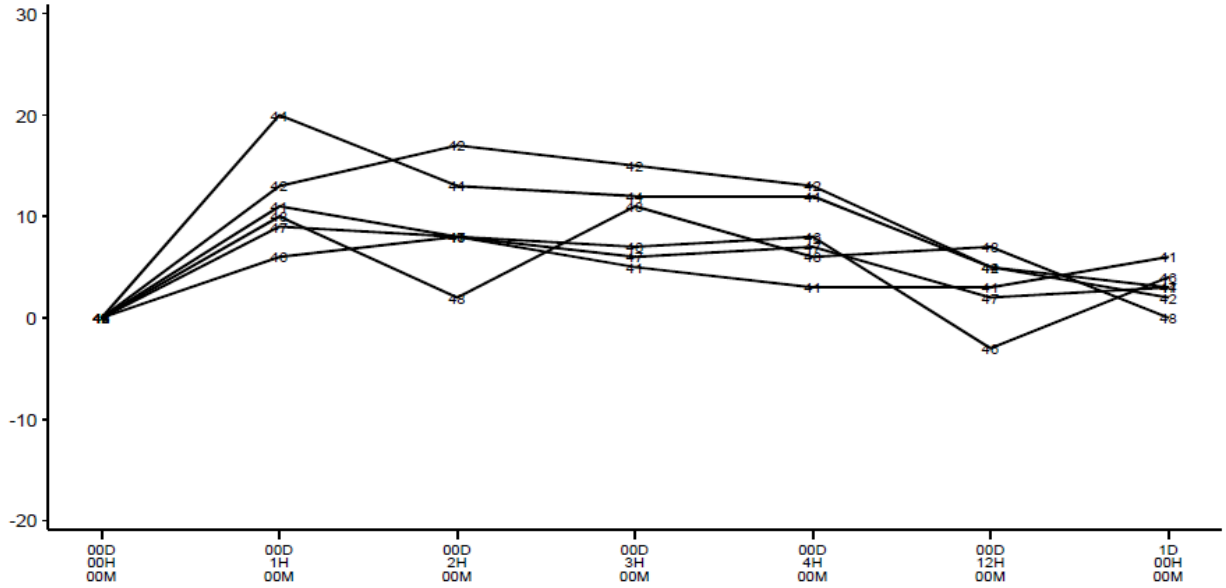
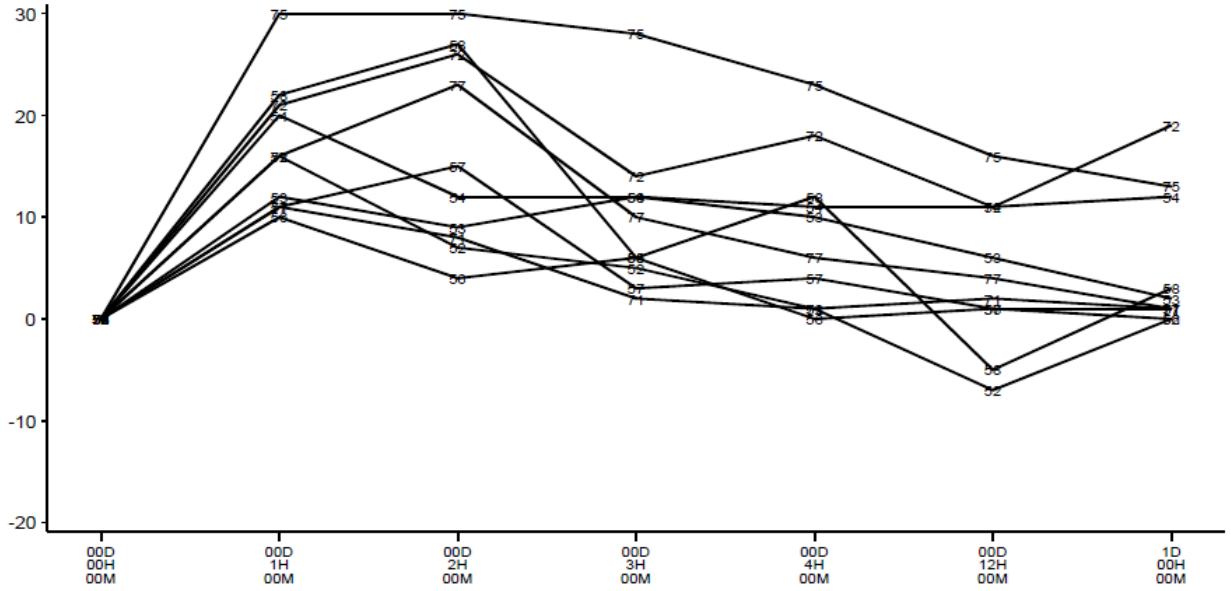


Figure 18: Study 11258 HR change from BL, 5.0 mg oral dose



In describing these changes the sponsor wrote the following in the FSR for 11258:

> *Mean heart rate increased dose-dependently and reached peak values 1 to 2 h after administration of 1, 2.5, and 5 mg solution. Mean changes 1 to 2 h postbaselineranged from 12.0 (2.5 mg solution) to 16.6 BPM (5 mg solution) and were less pronounced after administration of the 2.5 mg tablet. Individual maximum increases in heart rate were 26 BPM (2.5 mg solution) and 28 BPM (5 mg solution) 2 h after drug administration and 38 BPM (2.5 mg solution) and 47 BPM (5 mg solution) 6 h after drug administration.*

Likewise, for diastolic blood pressure, the findings were cordinate, with the sponsor describing a dose-responsive decrease as follows:

> *A decrease in diastolic blood pressure 1 h after drug application was observed for the 2.5 mg and 5.0 mg dose. Mean diastolic blood pressure decreased dose-dependently. Mean changes 0.5 to 2 h post-baseline ranged from +2.8 mmHg (0.25 mg solution) to -7.7 mmHg (5 mg solution). Individual maximum decreases in diastolic blood pressure ranged from 3 mmHg (0.25 mg solution) and 20 mmHg (2.5 mg solution) 0.5 to 2 h post-baseline. The maximum individual decrease with the 5 mg dose was 12 mmHg; changes with placebo ranged between -4 and -10 mmHg during this observation period.*

Of note, systolic blood pressure drops were less impressive, decribed by the sponsor as follows:

Mean systolic blood pressure decreased slightly without a pronounced dosedependency. Mean changes 0.5 to 2 h post-baseline ranged from -3.0 mmHg (0.25 mg solution) to -5.3 mmHg (2.5 mg tablet). Individual maximum decreases in systolic blood pressure ranged from 3 mmHg (0.25 mg solution) to 17 mmHg (2.5 mg tablet) 0.5 to 2 h post-baseline. The maximum individual decrease with the 5 mg dose was 11 mmHg; changes with placebo ranged between 0 and -5 mmHg during this observation period.

Trial 11260. This as a Multiple dose basic phase I dose escalation study, placebo-controlled, 2 fold crossover, randomized, single-blind, to investigate safety, tolerability and pharmacokinetics of BAY 63-2521 after oral dosing of 0.5 mg, 1.0 mg, 1.5 mg or 2.5 mg TID IR-tablets over 10 days in 12 healthy male subjects per dose step. The dose responsive nature of the drug-induced decrease in mean BP with the expected reflex tachycardia is dmonstrated after single doses of drug as well as following 10 days of in the the following two figures:

Figure 19: Study 11260 mean placebo-adjusted HR change from BL (FSR pg B-6)

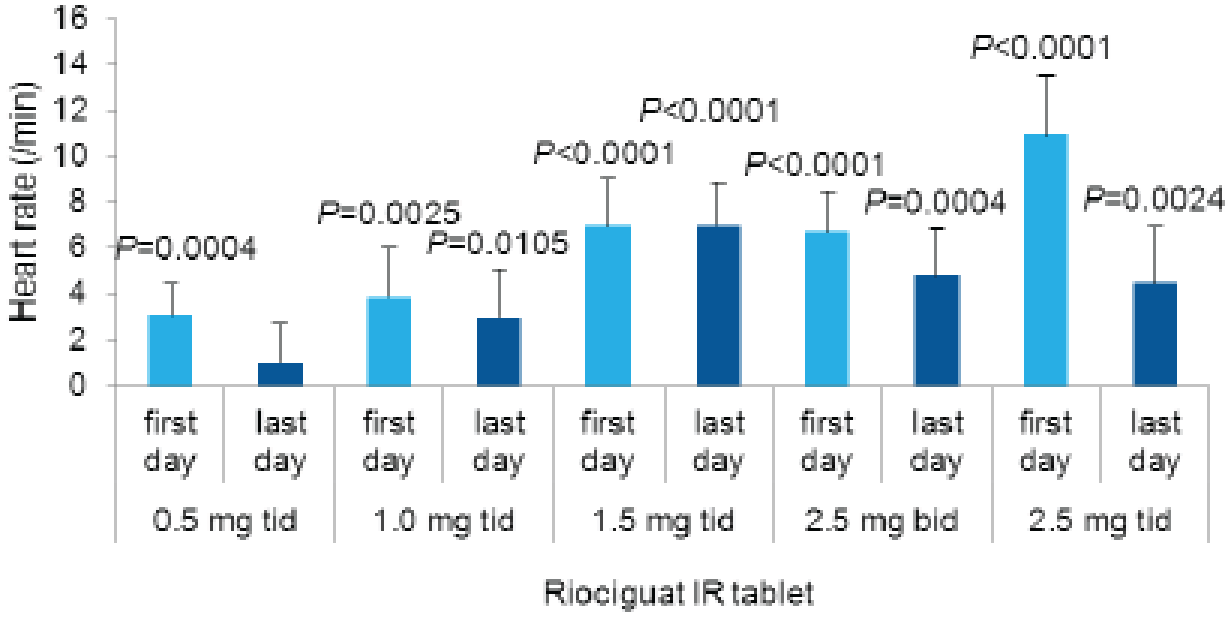
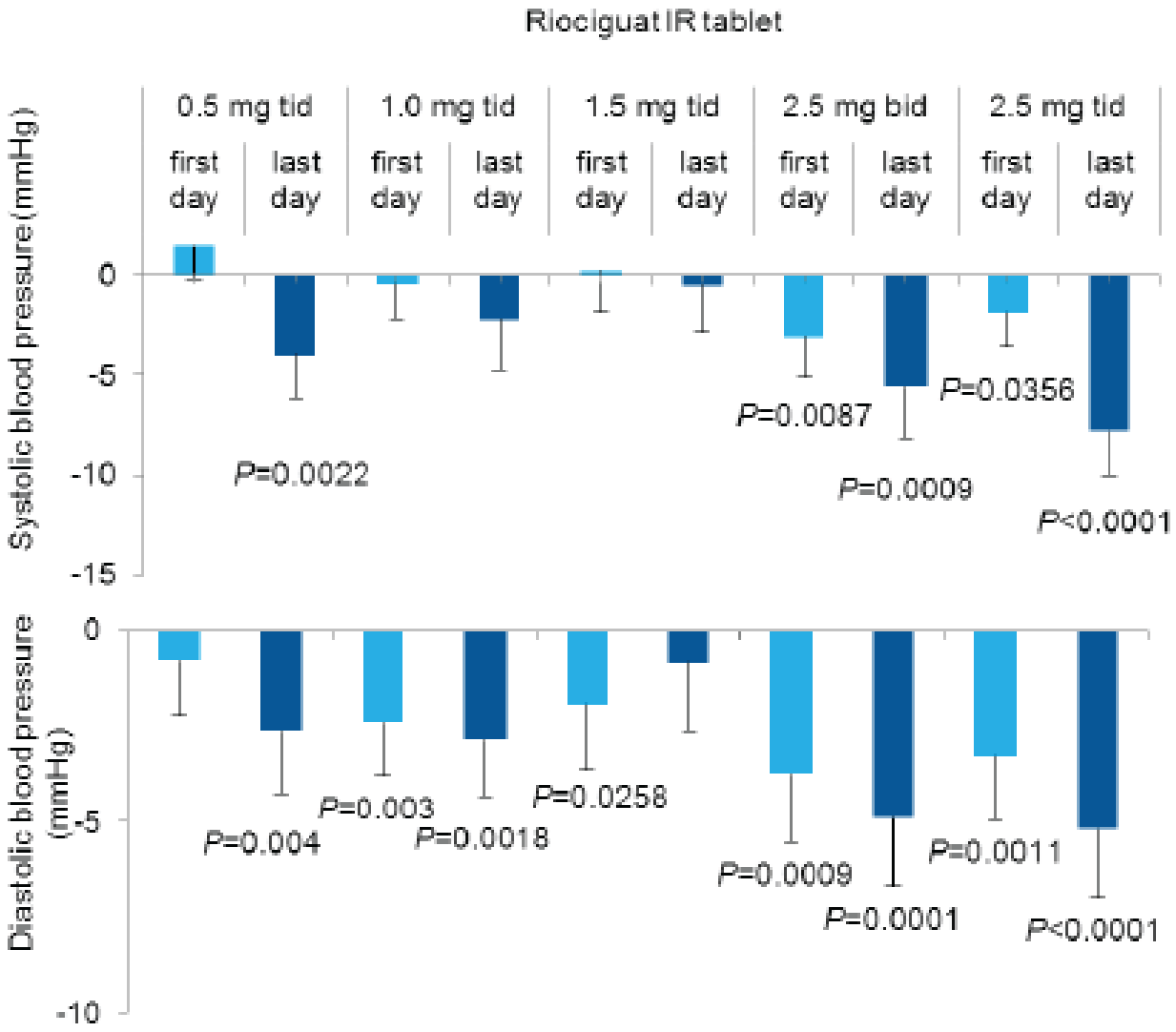
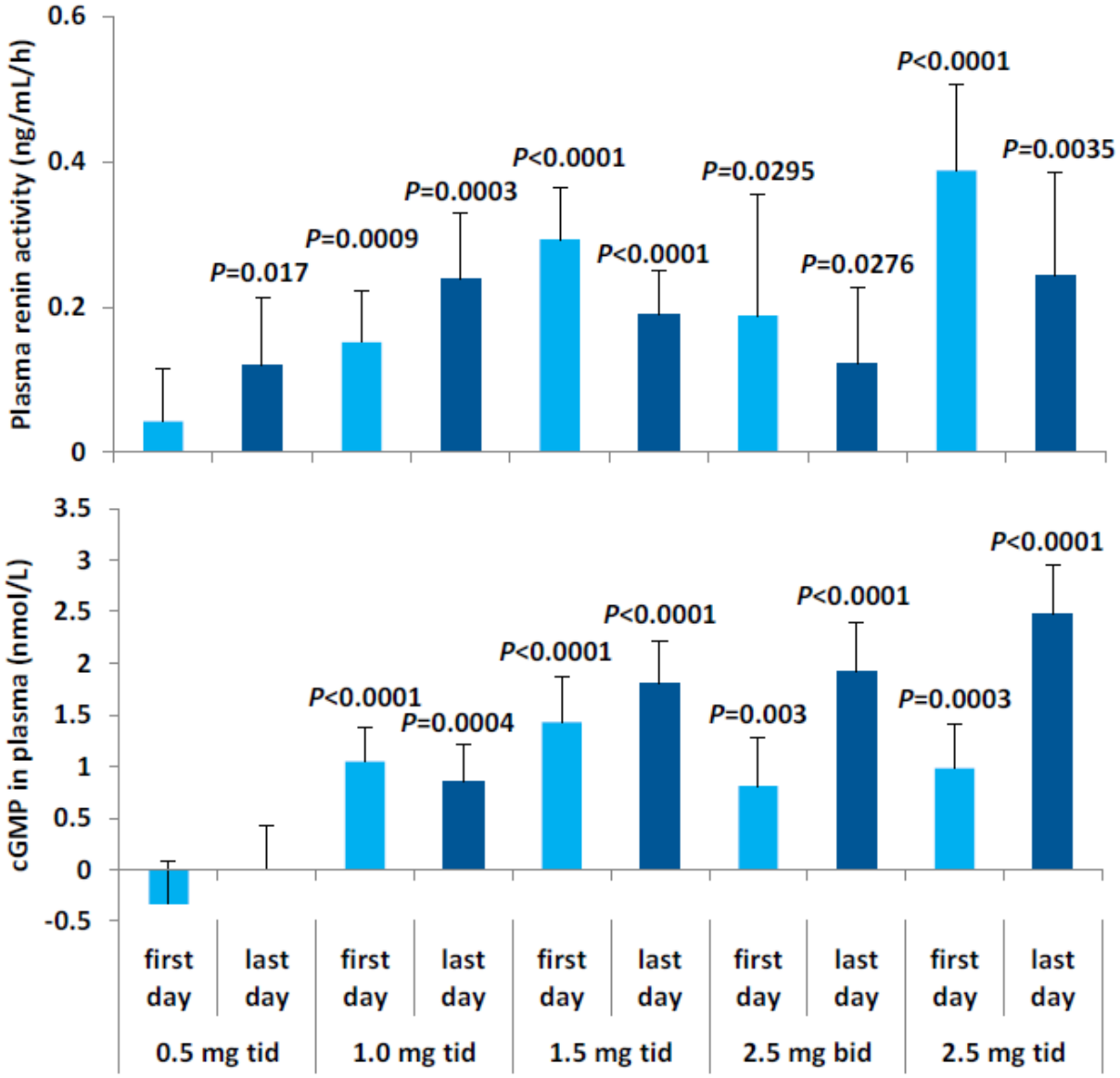


Figure 20: Study 11260 mean placebo-adjusted SBP and DBP change from BL (FSR pg B-7)



It appears as though the reflex increase in HR tends to abate with time, though the pressure differneces persisted. There also appeared to be a dose-responsive increase in serum biomarkers overall (plasma renin activity and plasma cGMP), though these trends were more variable, as shown in the following figure:

Figure 21: Study 11260 mean placebo-adjusted PRA and cGMP change from BL (FSR pg B-8)



Study 11874 – phase I proof of concept in patients suspected of having PH

This was a two-part hemodynamic study in patients suspected of having PH to test incremental doses of riociguat (oral solution). The original plan was to incrementally increase the dose of riociguat in each patient in Part A as follows:

- Group 1: 0.5 mg + 1 mg + 1 mg (=2.5 mg)
- Group 2: 1 mg + 2 mg + 2 mg (=5 mg)
- with 60-min intervals between the application of the single doses

Based on the anticipated results in Part A, a formal SAD design was planned for part B, starting with 2.5 mg and ascending to a maximum of 10 mg in four separate dose groups (the 10 mg dose would be twice the maximal dose that had been previously tested in human volunteers at that time).

The plan changed, however, based on results with the 5 mg dose in a patient in Part A of the study. Specifically, the following occurred:

- In Study Part A, Subject 011874-003 receiving BAY 63-2521 1 mg – 2 mg – 2 mg experienced a drop in blood pressure from baseline 140/57 mmHg to 106/40 mmHg 15 min after drug application, 90/36 mmHg 2 h 30 min after drug application, and 88/36 mmHg 5 h after drug application. Blood pressure was 97/41 mmHg after 6 h.

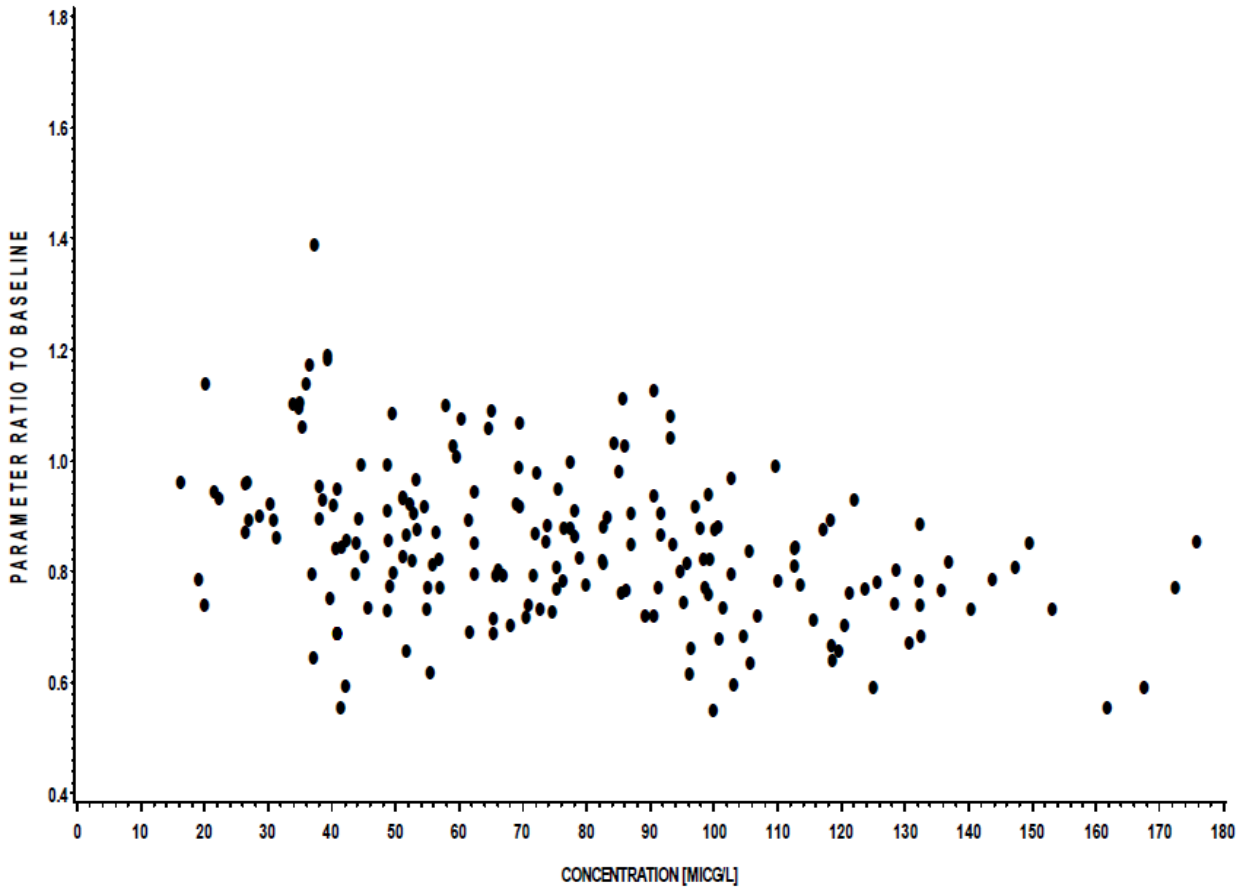
Following this occurrence, no further dose escalation was performed. 2.5 mg was used as the maximal dose in Part B, which also tested a second group of patients at 1.0 mg. The rationale for assuming that 1.0 mg would be the minimally effective starting dose (first-effect level) in PH patients was that 0.5 mg doses had not shown effects on either HR or systemic blood pressure in prior dose-escalation studies of healthy subjects. This rationale did not consider, however, that riociguat exposure in PH patients is approximately 3-fold higher than it is in healthy subjects (this may not have been known at the time).

The summary hemodynamics results of Part B, as well as the scatterplot of concentration versus PVR ratios are shown in the following table and figure, respectively:

Table 7: **Study 11874 Part B – LS-means for peak effects of PAP, SBP, PVR, SVR, and CI following riociguat (PK/PD set n=15, FSR table 11-4 pg 2-45)**

Parameter BAY 63-2521 dose group	Unit	Point estimator (LS-mean)	95% confidence interval	*P* value of F statistic
2.5 mg				
Mean pulmonary arterial pressure (PAP)	mmHg	-5.10	[-7.12; -3.08]	0.0001
Systolic systemic blood pressure (SBP)	mmHg	-28.60	[-36.21; -20.99]	<0.0001
Pulmonary vascular resistance (PVR)	dyn*s*cm^{-5}	-168.12	[-273.87; -62.36]	0.0046
Systemic vascular resistance (SVR)	dyn*s*cm^{-5}	-545.90	[-724.19; -367.62]	<0.0001
Cardiac index (CI)	L/min/m^2	0.95	[0.72; 1.18]	<0.0001
1 mg				
Mean pulmonary arterial pressure (PAP)	mmHg	-6.80	[-9.66; -3.94]	0.0001
Systolic systemic blood pressure (SBP)	mmHg	-24.00	[-34.76; -13.24]	0.0003
Pulmonary vascular resistance (PVR)	dyn*s*cm^{-5}	-296.45	[-463.67; -129.23]	0.0022
Systemic vascular resistance (SVR)	dyn*s*cm^{-5}	-689.95	[-942.08; -437.82]	0.0001
Cardiac index (CI)	L/min/m^2	0.65	[0.33; 0.98]	0.0008

Figure 22: Study 11874 scatterplot of PVR ratios to baseline vs. riociguat concentrations (PK/PD set n=19, FSR figure 11-4 pg 2-48)



From these data, the sponsor acknowledged/concluded the following:

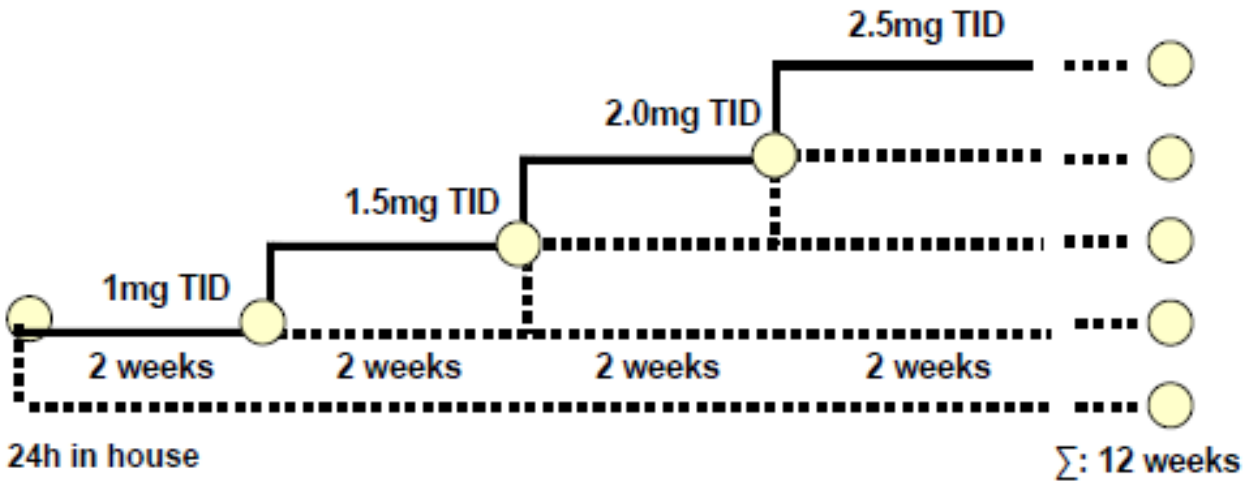
- 2.5 mg was the maximal dose for Part B because of hypotension induced by the 5.0 mg dose in Part A
- For Part B, 1 mg was chosen in order to establish first-effect level because the 0.5 mg dose was the no-effect level in healthy subjects
- No clinically relevant differences between the 2.5 and 1 mg dose groups. PVR and SVR reductions were more pronounced with 1mg (296 vs. 168 and 690 vs. 546 dyn*s*cm^{-5}, respectively)
- BAY 63-2521 plasma concentrations were significantly correlated with the reductions in PAP, SBP, PVR, and SVR and the increase in CI
- There was no pulmonary selectivity: hemodynamic pulmonary and systemic effects are parallel
- There was no deterioration in gas exchange due to pulmonary vasodilation (data not shown).

Phase II study 12166 (core study)

Study 12166 was a 12 week, non-randomized, non-blinded, non-controlled, multicenter, PK/PD-hemodynamic-safety study of both CTEPH and PAH patients with a planned 4.5 years of follow-up in its extension phase. Enrollment included 76 hemodynamically stable NYHA class II/III patients, 66 of whom where therapy naïve, and 10 of whom were being treated with an endothelin receptor antagonist (ERA). This was the first study utilizing the IDT dosing strategy which was justified by the sponsor based on the following arguments:

- Riociguat was investigated in a multiple-dose study in healthy subjects with a dose range of 0.5 to 2.5 mg 3 times a day (TID) (Study 11260) and in subjects with PH in a single ascending dose design from 0.5 to 5 mg (Study 11874) – the sponsor stated that in both studies, these doses where shown to be safe, well-tolerated, and efficacious with respect to hemodynamic measurements
- "Individual titration seems necessary due to the pronounced inter-individual variability of C_{max} and AUC
- The phase II study is therefore designed to demonstrate the feasibility and safety of an the IDT dosing scheme according to peripheral systolic blood pressure (SBP) as preparation for a sustainable dose-titration scheme to be evaluated in phase III.

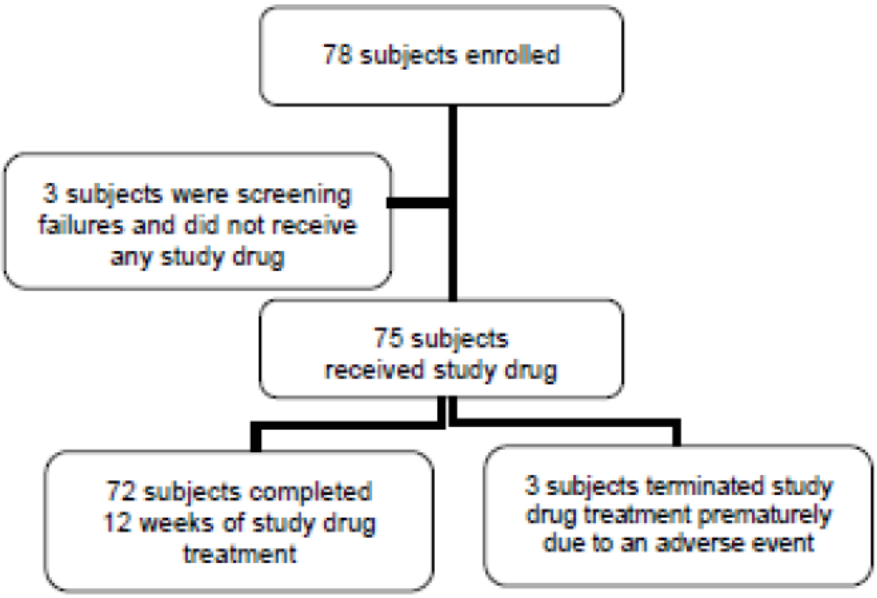
With this reasoning, the following dosing strategy was embarked upon in which patients were escalated to the highest tolerated dose (based on SBP) to a maximum of 2.5 mg TID:



The up-titration rules for this dosing strategy were as follows, based on SBP:

- For trough SBP >100 mmHg, increase dose (+0.5 mg TID)
- For trough SBP 90 to 100 mmHg, maintain dose
- For trough SBP <90 mmHg without symptoms of hypotension, reduce dose (-0.5 mg TID)
- For trough SBP <90 mmHg with clinical symptoms of hypotension such as dizziness or pre-syncope:
    - Stop study treatment
    - Restart after 24 h w/ reduced dose (-0.5 mg TID).

In the event that 1 mg TID was not tolerated, the dose could be reduced to a minimum dose of 0.5 mg TID (changed per protocol amendment 6). The disposition of the 78 patients enrolled in the core phase of the trial was as follows:



Of note, the majority of patients tolerated the 2.5mg TID dose, but a sizable minority (32%) did not, as shown in the following table of final doses at the end of study in the safety population:

Trial (N/n)	1.5 mg	3.0 mg	4.5 mg	6 mg	7.5 mg	9 mg
(75/75)	1 (1%)	6 (8%)	8 (11%)	8 (11%)	51 (68%)	1 (1%)

It is relevant that five patients in this study experienced drug overdoses, and for 4 of 5 of these patients, no hypotension was reported, but the manner in which hyoptensive events were ascertained is not described. The outcomes of these patients are described in that study as follows:

Subject	Dose taken	TEAE
01-008	22.5 mg/d for 14 days	Flushing
03-006	22.5 mg/d for 15 days	Dizziness
04-009	9 mg/d for 32 days	None
06-001	9 mg/d for 13 days	None
13-002	25 mg/d for 2 days	Hypotension

50 patients in this study participated in the optional follow-up Swan-Ganz hemodynamics on study day 84. The trends in pulmonary and systemic responses with respect to pressures and resistances were consistent between the PAH and the CTEPH patients, as shown in the table below:

	RA_m mm Hg	PA_m mm Hg	PCWP mm Hg	HR bpm	SBP mm Hg	DBP mm Hg	PVRI dyn*s*c $m^{-5}m^2$	SVRI dyn*s*c $m^{-5}m^2$	CI L/min/m^2
PAH N=30	0.65 n=20 p=.65	-6.85 n=20 p=.01	1.90 n=20 p=.10	3.32 n=19 p=.27	-8.33 n=18 p=.04	-4.67 n=18 p=.15	-[b]87 n=19 p=.0001	-846 n=16 p=.03	0.51 n=19 p=.0038
CTEPH N=20	0.03 n=30 p=.97	-4.33 n=30 p=.0005	0.67 n=30 p=.37	-0.67 n=30 p=.74	-7.00 n=29 p=.07	-8.76 n=29 p=.0034	-479 n=29 p=<.0001	-673 n=28 p=.0009	0.46 n=29 p=<.0001

6MWD results at day 84 in the population valid for PK and PD assessment (n=72) was impressive and consistent across the diagnostic groups, as shown in the following table:

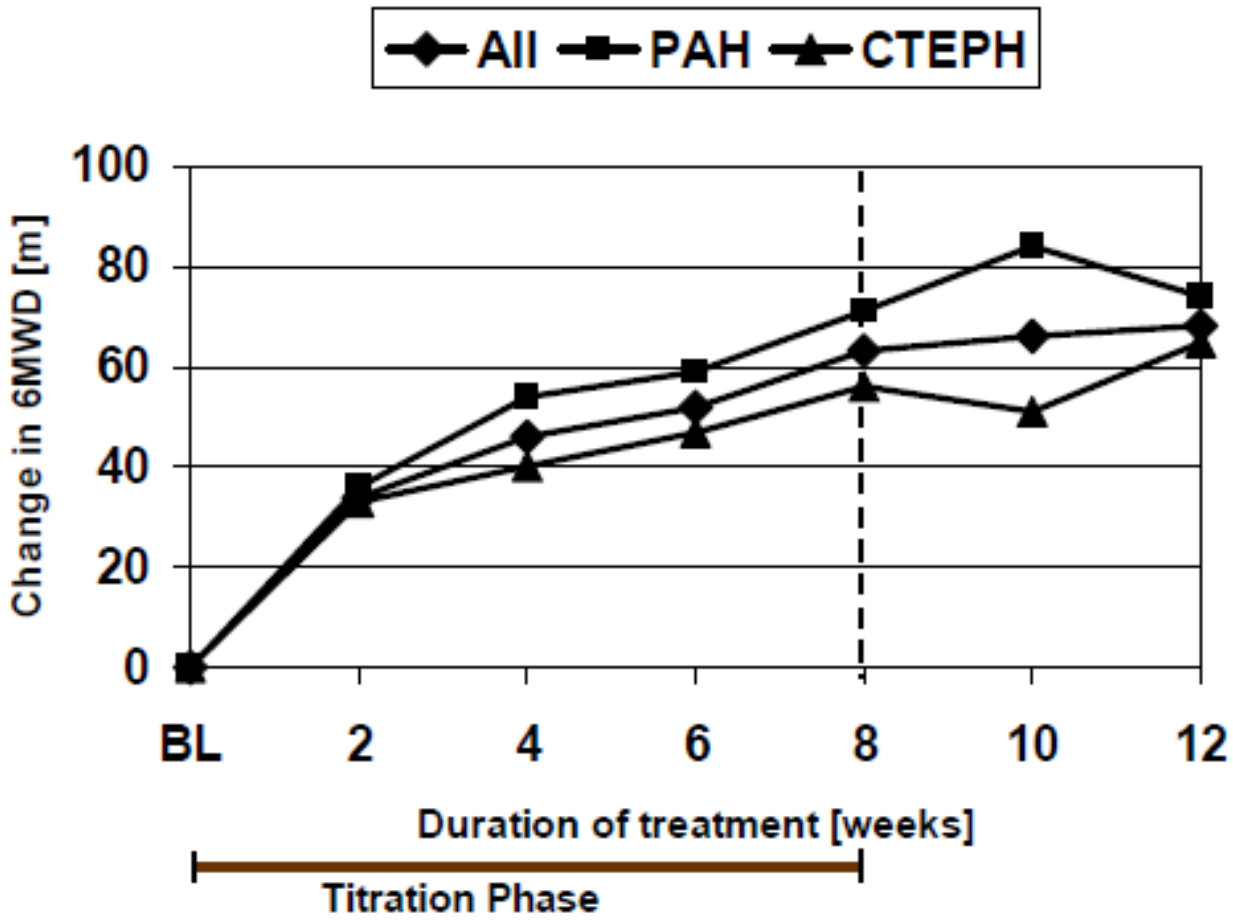
Table 8: Study 12166 change from baseline 6MWD (LS-mean, PD/PK population, N=72)

Primary diagnosis	Parameter	Unit	n	Point estimator (LS-mean)	Lower 95% confidence limit	Upper 95% confidence limit	*P* value of F-statistic
PAH	Distance at the end of 6MWT	m	31	73.5	42.7	104.3	<0.0001
CTEPH	Distance at the end of 6MWT	m	39	64.3	44.2	84.4	<0.0001
Total	Distance at the end of 6MWT	m	70	68.4	51.2	85.6	<0.0001

Abbreviations: PAH = pulmonary arterial hypertension; CTEPH = chronic thromboembolic pulmonary hypertension
Source: Table 14.2/14

It is notable that improvement began with the 1.0 mg dose during the up-titration and leveled off after the maximal dose was reached at week 8, as shown in the figure below:

Figure 23: Study 12166 change in 6MWD (m) over time (PK/PD pop, N=72)



Reviewer's comment: Given the hemodynamic findings presented above from PoC SAD-study 11874 showing no difference in the hemodynamic effects of single doses of 1.0 mg versus 2.5 mg of riociguat, it is not clear that continuation of the 1.0 mg dose with sequential 6MWD testing over the first eight weeks would not have produced the same incremental efficacy benefit as a consequence of progressive drug effect, training effect, or both. This issue will be examined in FDA's detailed analysis of the capped dose arm of the PATENT-1 trial (see below, section 6.2).

Coordinate with the 6MWD improvement demonstrated in this study are improvements in echocardiographic indicies of right ventricular function, as shown in the table below of changes from baseline at day 84 (from spoonsor's study 12166 FSR, pg. 2-85):

Table 9: Study 12166 change from baseline in echocardiographic indices of RV performance at day 84 (PK/PD pop, N=72)

Primary diagnosis	Parameter	Unit	n	Point estimator (LS-mean)	Lower 95% confidence limit	Upper 95% confidence limit	*P* value of F-statistic
PAH	Tei index	N/A	15	-0.1887	-0.3791	0.0018	0.0519
	PASP	mmHg	21	-5.2619	-12.4849	1.9611	0.1442
	TAPSE	cm	23	0.1883	-0.0476	0.4241	0.1120
CTEPH	Tei index	N/A	20	-0.1665	-0.2740	-0.0590	**0.0043**
	PASP	mmHg	32	-7.9375	-14.2081	-1.6669	**0.0147**
	TAPSE	cm	36	0.3319	0.1788	0.4851	**<0.0001**
Total	Tei index	N/A	35	-0.1760	-0.2721	-0.0799	**0.0007**
	PASP	mmHg	53	-6.8774	-11.4807	-2.2740	**0.0041**
	TAPSE	cm	59	0.2759	0.1479	0.4040	**<0.0001**

Abbreviations: PAH = pulmonary arterial hypertension; CTEPH = chronic thrombembolic pulmonary hypertension; PASP = systolic pulmonary artery pressure (echocardiography); TAPSE = tricuspid anular plane systolic excursion; Tei index = myocardial performance index (isovolumic contraction time plus isovolumic relaxation time divided by ejection time)

Numerical improvements were also observed on day 84 in WHO functional classification, Borg dyspnea score (median Borg dyspnea score decreased by 1 point), and NT-proBNP (nominally significant for the entire population but technical problems limited the validity of the NT-proBNP result). Troponin I remained below the level of detection in all subjects during the course of the study.

From the cohort of patients eligible for the PK/PD analysis, the sponsor concluded that in the cohort of subjects treated with background bosentan (n=6) as compared to the subjects not treated with bosentan (n=66):

- riociguat exposure was decreased by 60 – 70%
- this was most probably due to the known CYP3A4 enzyme-inducing effects of concomitant bosentan therapy
- BAY 60-4552 (M1 metabolite) exposure was increased by approximately 10-20%.

The most commonly reported treatment-emergent adverse events by MedDRA preferred term in the 12166 core study were dyspepsia (n=18 [24%]), headache (n=12 [16%]), hypotension (n=11 [15%]), peripheral edema (n=9 [12%]), and tachycardia (n=9 [12%]). Treatment-emergent adverse events with regard to heart rate and blood pressure included tachycardia/sinus tachycardia (n=11), hypotension (n=11; the dose of study drug was reduced for Subject 12166-13-002 with severe hypotension and for Subjects 12166-01-002 and 12166-04-013 with moderate hypotension), and syncope (n=4). There was a single patient that experienced a TEAE of bone pain that was mild

in severity and resulted in temporary interruption of therapy, but no rported bone fractures.

Phase II study 12166 (4.5 year follow-up)

Of the 75 subjects who received study drug in the 12166 core study, 68 participated in this extension study up to a treatment duration of 4.5 years (54 months) as of the cutoff date of 1 November 2011, at which point 47 were still participating.

Post-hoc analyses were performed with regard to the PD parameters 6-minute walk test, modified Borg dyspnea score, WHO functional class, and NT-proBNP. The analyses were performed in all subjects who had data available at all of the following time points: pre-study visit (Day -1), end of the main study (Day 84), and Month 9 (LTE Month 6), Month 15 (LTE Month 12), Month 27 (LTE Month 24), Month 39 (LTE Month 36), and Month 45 (LTE Month 42). The mean treatment duration during the long-term extension study was 36.5 months (PAH group 36.9 months, CTEPH group 36.2 months). Total exposure to BAY 63-2521 during long-term extension was 2481 patient months (PAH: 996 patient months; CTEPH: 1485 patient months).

Post-hoc analyses were performed in all subjects who had data available at all of the following time points: pre-study visit (Day -1), end of the main study (Day 84), and Month 9 (LTE Month 6), Month 15 (LTE Month 12), Month 27 (LTE Month 24), Month 39 (LTE Month 36), and Month 45 (LTE Month 42).The sponsor reports the following observtions from these analyses:

- Clinically relevant improvements in the 6-minute walk test had been observed within the first 12 weeks of treatment during the main study (mean increases in walking distance in all subjects: 81 m; subjects with PAH: 102 m, subjects with CTEPH: 69 m). These improvements were generally sustained during the long-term extension period up to 45 months (LTE Month 42) in the PAH as well as in the CTEPH subgroups. Inter-subject variability was high.
- Improvements in WHO functional class were shown after the first 12 weeks of treatment (end of main study) with 60.5% of the subjects in functional classes I and II compared to 23.3% at the pre-study visit. Between Month 9 (LTE Month 6) and Month 39 (LTE Month 36), the percentage of subjects with functional classes I and II ranged between 62.8 and 69.8% and was 53.5% at Month 45 (LTE Month 42).
- NT-proBNP concentrations decreased by a mean of about 1800 pg/mL comparing baseline vs. Week 12. NT-proBNP concentrations showed high fluctuations over time and inter-subject variability was high.
- At 47 months, the probability of survival was greater than 91% and the probability of event-free survival, i.e. survival without heart/lung transplantation, atrial septostomy, pulmonary endarterectomy or start of new pulmonary hypertension treatment was 45%. The median survival time without heart/lung transplantation,

atrial septostomy, pulmonary endarterectomy or start of new pulmonary hypertension treatment was 35.7 months.

- At 48 months, the probability of event-free survival, i.e. no new start of treatment for pulmonary hypertension, was >47% in all subjects (>54% and >38% in subjects with CTEPH and PAH, respectively).
- Geometric mean plasma concentrations of BAY 63-2521 and BAY 60-4552 corresponding to a 2.5 mg dose at scheduled extension visits remained in a relatively constant range over time 138 to 174 μg/L (BAY 63-2521) and 91 to 184 μg/L (BAY 60-4552). This shows that the exposure to BAY 63-2521 when subjects took a 2.5 mg dose during the extension study was stable over the treatment time.
- The variability of BAY 63-2521 plasma concentrations between subjects (geometric coefficients of variation) was high during the long-term extension ranging between 15 to 89% at the 2.5 mg dose level. A comparable variability (39 to 63%) was also observed for BAY 60-4552.
- Smokers tended to have lower plasma concentrations of BAY 63-2521 (smoking induces CYP1A1, an enzyme involved in the metabolism of BAY 63-2521) compared to non-smokers; similarly, subjects on concomitant therapy with bosentan – a known inducer of CYP3A4 – tended to have lower BAY 63-2521 concentrations.
- Mean changes in serum creatinine concentrations were minimal and showed no relevant differences between non-smokers and smokers.
- Mean changes from baseline in blood glucose concentrations appeared to decrease rather than increase. Mean changes in serum calcium concentrations were minimal and appeared to decrease rather than increase. Differences between male and female subjects did not appear to be relevant.
- The 68 subjects entering study 12166 LTE experienced decreases in mean SBP between 8 to 11 mmHg during the main study. In the following 12 months of the LTE, mean SBP decreased further, between 9 to 15 mmHg. Mean SBP decreased from 123 mmHg at baseline to 112 at month 42 (n=46) in the LTE.
- Serious adverse events SAEs were reported in 47 (69.1%) subjects. The most frequent SAEs were syncope (n=12 [17.6%]), right ventricular failure (n=8 [11.8%]), pulmonary arterial hypertension (n=7 [10.3%]), cardiac failure (n=6 [8.8%]), pulmonary hypertension (n=5 [7.4%]), atrial flutter (n=4 [5.9%]), and pneumonia (n=4 [5.9%]).
- 7 subjects reported AEs as the primary reason for discontinuation of study participation. Laboratory abnormalities were not reported as a reason for termination of study medication.
- Treatment-emergent AEs with an incidence ≥2 with regard to heart rate and blood pressure included syncope (n=12 [17.6%]), hypotension (n=12 [17.6%]), palpitations (n=5 [7.4%]), and tachycardia (n=3 [4.4%]). In 11 cases with hypotension and in 3 cases with syncope, the investigators considered the respective events as related to BAY 63-2521.

- Events of special interest included syncope, hypotension, and SBP <90 mmHg, which were reported in 28 subjects. Of these, 12 subjects experienced syncope, 13 hypotension as AE, and 16 subjects had objective measurements of SBP <90 mmHg. 18 subjects experienced only 1 of the 3 events and 10 subjects 2 or 3 events. In most cases, the total daily dose of BAY 63-2521 was kept unchanged.
- 7 subjects died due to the following reasons: "cardiac decompensation", "fatal decompensation of cor pulmonale", "worsening of pulmonary arterial hypertension", "sudden death", "progressive right heart failure", decompensated cor pulmonale", and "hepatocellular carcinoma". All cases were assessed as sequelae of the respective underlying disease and unrelated to study drug.
- There was a single TEAE of bone pain in the extension study (both hips and left hand) in a CTEPH patient that was mild in severity. There was a single serious TEAE of thoracic vertebral fracture (osteoporotic compression fracture 1 year and 10 months of study drug), a single serious TEAE of tibia fracture (fell off chair on day 145 of therapy), one non-serious TEAE of ankle fracture, one non-serious foot fracture, and one non-serious TEAE of tooth fracture.

6 Review of Efficacy

Efficacy Summary

Riociguat is an NCE, first-in-class, potent, balanced vasodilator, meaning that it very prominently reduces pulmonic and systemic vascular resistance. Riociguat stimulates soluble guanylate cyclase (sGC) which in turn raises intracellular cGMP which leads to vasodilation. NO stimulates sGC in vivo. PDE5-i prevent the breakdown of cGMP. Therefore, the observed synergies between NO donors like nitroglycerin and PDE5-i drugs like sildenafil in producing potentially dangerous falls in systolic blood pressure are not surprising.

At the EoP2 meeting, the sponsor proposed an "Individual Dose Titration" (IDT) strategy whereby each patient would be escalated to the maximal dose of riociguat based on systolic blood pressure (SBP) responses. While using the SBP as a guide to maximize pulmonary vascular unloading effects with a balanced vasodilator has some appeal, in reality, this approach was taken to compensate for wide intra-patient variability of the PK of this drug. The Division recommended against this approach at the EoP2 meeting, extolling the virtues of parallel fixed-dose testing in more than a single active therapy arm in the phase III trials. However, the IDT approach was chosen, and it was incorporated into two pivotal trials in two separate WHO pulmonary hypertension (PH) groups as follows:

- CHEST-1 enrolled adults with Chronic Thromboembolic Pulmonary Hypertension (CTEPH), WHO group IV

- PATENT-1 enrolled adults with Pulmonary Arterial Hypertension (PAH) secondary to familial, idiopathic, connective tissue disorder, portal-pulmonary hypertension, anorexigen, or congenital heart disease causes of PH.

The primary endpoint in both trials was the 6MWD test, with secondary endpoints including pulmonary vascular resistance changes, NT-pro-BNP, WHO functional class, time to clinical worsening, Borg scores, EQ-5D scores, and LPH scores.

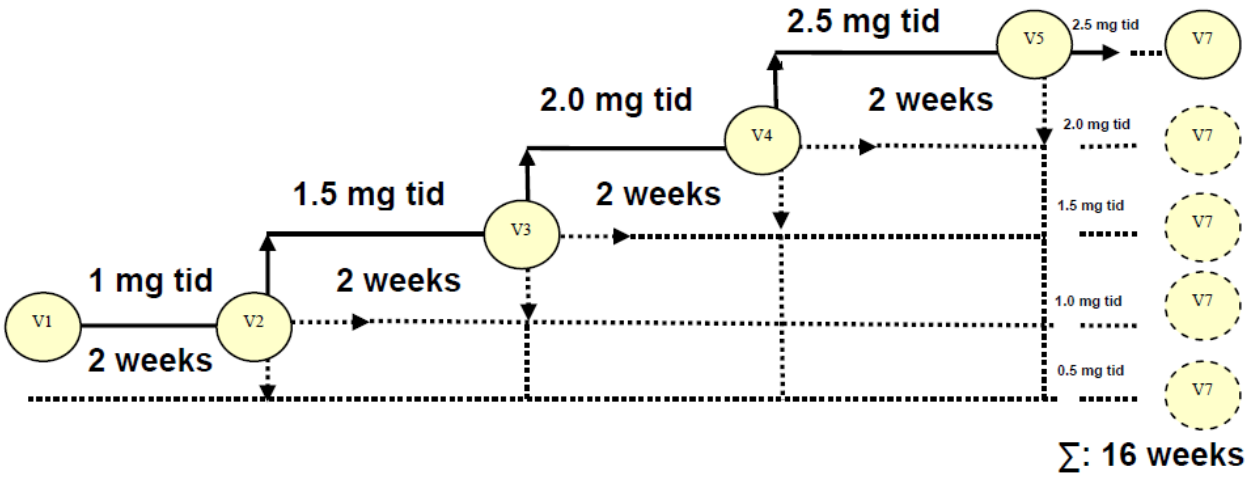
The results of these two trials are now submitted to support the approval of riociguat for the treatment of these two WHO pulmonary hypertension groups, and the efficacy results are both robust and impressive, particularly in that there are no approved therapies for the treatment of CTEPH. The following table shows first the results of the 6MWD primary endpoint for both trials, then moves on to the secondary endpoints in the order of the pre-specified hierarchical testing that was done by the sponsor:

Parameter	p-value PATENT-1	p-value CHEST-1
6MWD	<0.0001	<0.0001
PVR	<0.0001	<0.0001
NT-proBNP	<0.0001	<0.0001
WHO FC	0.0033	0.0026
TTWC	0.0285*	0.2180**
Borg	0.0022	0.0035
EQ-5D	0.0663	<0.0001
LPH	0.0019	0.1220

*ANCOVA – stratified Wilcoxon (non-parametric) p = 0.0046
**ANCOVA – stratified Wilcoxon (non-parametric) p = 0.1724

The efficacy results have been reproduced by FDA clinical pharmacology and biometrics. They are robust in that removal of any single site, country, or region does not alter the treatment effect. Subgroups analysis, as well as efficacy demonstrated in placebo patients who roll over to active therapy in the LTE trials provide internal consistency in both CHEST-1 and PATENT-1. Multiple sensitivity analyses using different methods for imputation of missing data demonstrate the similar clinical benefits to the primary analysis. The benefit persists regardless of the use of ANCOVA or stratified Wilcoxon testing.

However, the principle issue that is causing concern was, and remains, the dosing strategy that the sponsor chose to incorporate into the development program, that essentially created a single active therapy arm with multiple doses based on the titration scheme below:



Our concern is that the low SBP cutoffs and narrow windows for holding dosing constant may not be realistically reproducible in the medical system at large. These dosing rules to decrease/maintain/increase dose are given below:

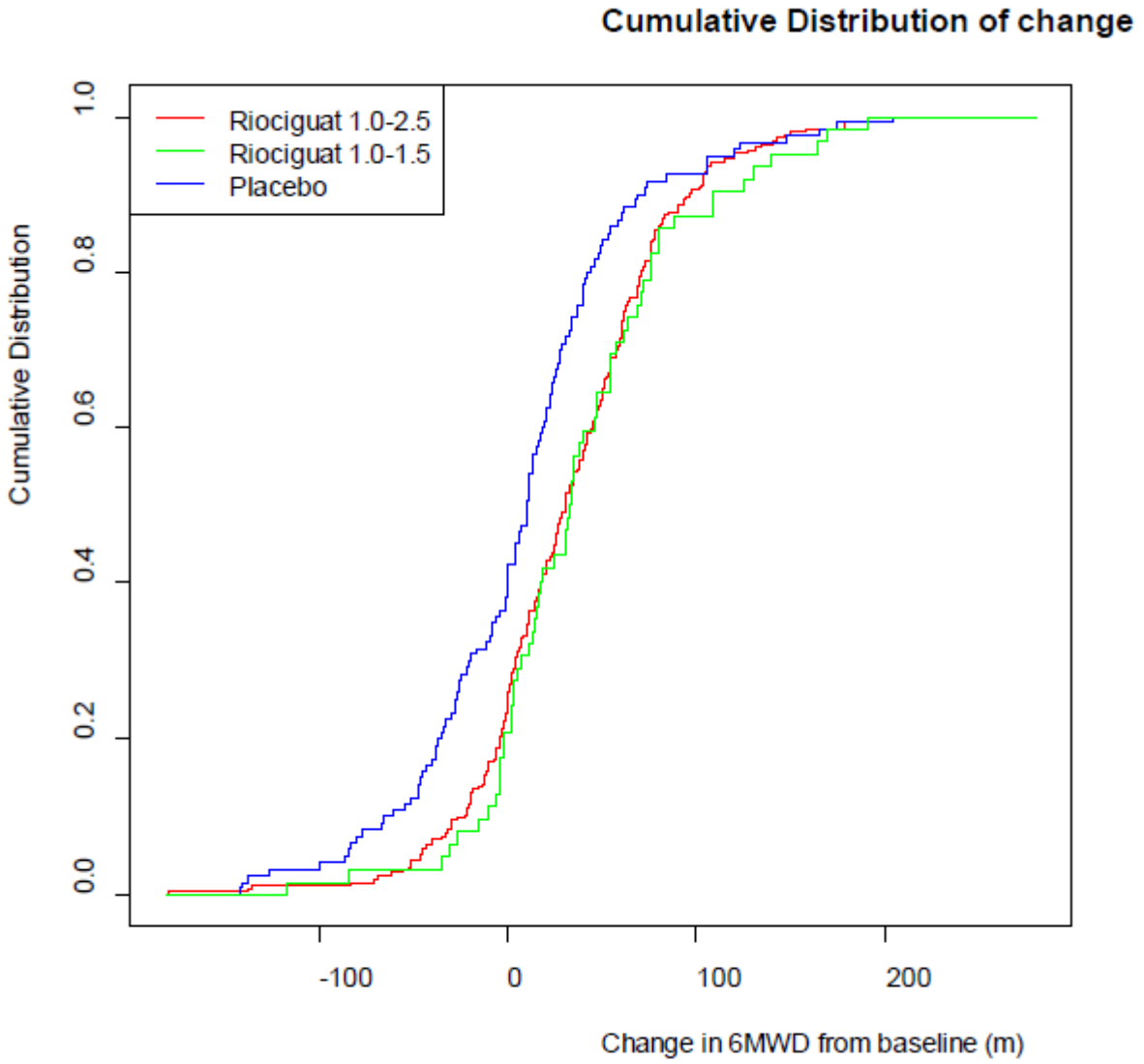
- Trough SBP ≥95 mmHg, increase dose (+0.5 mg TID)
- Trough SBP 90 to 94 mmHg, maintain dose
- Trough SBP <90 mmHg without symptoms of hypotension, reduce dose (-0.5 mg TID)
- Trough SBP <90 mmHg with clinical symptoms of hypotension such as dizziness or pre-syncope,
    - stop study treatment
    - restart after 24 h w/ reduced dose (-0.5 mg TID)

This reviewer continues to be concerned that this IDT dose range is too high because:

- In the phase II and phase III trials supporting this submission, between 1/4 and 1/3 of patients did not tolerate the 2.5 mg TID dose presumably based on SBP effects

- The exposure-response curves are flat for both trials, showing no incremental efficacy in either population at exposures above those achieved with 1.5 mg TID

- The small/exploratory parallel arm in the PAH trial that tested 1.5 mg TID as a capped/fixed dose demonstrated the same incremental benefit to patients in the 6MWD test as did the higher 2.5 TID target dose of the IDT arm, as shown from the FDA analysis of the cumulative distribution of change of the 6MWD as follows:



Cumulative distribution of change in 6MWD for three treatment groups in trial 12934 (FDA).

- Drug-induced hypotension with the agent is dose-dependent
- 40% of CTEPH patients in CHEST-1 were above ≥ age 65, putting them at risk for occult coronary artery disease, cerebral vascular disease, and peripheral vascular disease which may tolerate drug induced SBP <90 mmHg events poorly.
- Therefore, my recommendation is to approve riociguat for the treatment of the two indications in adults for which it was tested, but in a lower dose range: beginning at 0.5 mg TID, and escalating by 0.5 mg TID not sooner than every two weeks until a maximal dose of 1.5 mg TID is achieved.

6.1 Indication – CTEPH (WHO Group 4)

For the treatment of adult patients with chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group4) whose CTEPH is inoperable, or who suffer persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity and WHO functional class

6.1.1 Methods

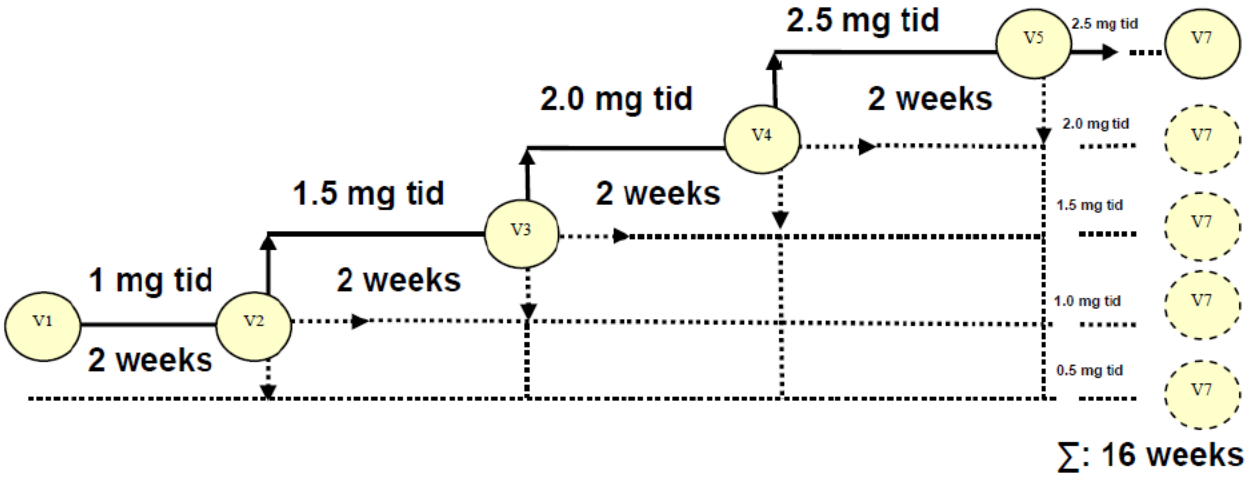
A single pivotal trial is submitted to support this indication (CHEST-1, trial 11348). Efficacy data presented in this section is therefore specific to that study only (no pooled data).

CHEST-1 was a randomized, double-blind, placebo-controlled, multicenter, multinational, 16 week trial to assess the efficacy and safety of oral riociguat in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or recurrent or persisting pulmonary hypertension (PH) after surgical treatment. Riociguat given at an individualized dose after dose titration (starting with 1 mg 3 times a day [TID] and if tolerated up-titrated in steps of 0.5 mg dose increases every 2 weeks up to 2.5 mg TID) was to be compared with placebo.

The up-titration IDT algorithm and its SBP dosing cut-off rules are as shown in the figure below:

Figure 24: CHEST-1 IDT dosing scheme

- Trough SBP ≥95 mmHg, increase dose (+0.5 mg TID)
- Trough SBP 90 to 94 mmHg, maintain dose
- Trough SBP <90 mmHg without symptoms of hypotension, reduce dose (-0.5 mg TID)
- Trough SBP <90 mmHg with clinical symptoms of hypotension such as dizziness or pre-syncope,
    - stop study treatment
    - restart after 24 h w/ reduced dose (-0.5 mg TID)



As occurred in the phase II study 12166, while the majority of patients were tolerated the up-titration to the highest dose (2.5 mg TID), 23% did not, as shown in the table below:

Table 10: CHEST-1 total daily riociguat dose at end of study (safety set)

Arm (N/n)	1.5 mg	3.0 mg	4.5 mg	6 mg	7.5 mg
IDT (173/160)	1 (0.6%)	6 (3.8%)	10 (6.3%)	20 (12%)	123 (77%)

The primary efficacy variable was the placebo-corrected change in 6MWD from baseline to week 16 (last observation until week 16) in subjects valid for ITT, with imputation of missing values for subjects who withdrew (without termination visit data) or died before 16 weeks. The riociguat 1.0-2.5 mg and placebo groups were compared using analysis of covariance (ANCOVA), with baseline 6MWD as a covariate and treatment group and region as main effects. The primary statistical method would be the stratified Wilcoxon test if the Shapiro-Wilk test for normality of residuals was statistically significant. Least squares (LS) mean and 95% confidence intervals (CIs) of the treatment difference were calculated based on the ANCOVA. Superiority of the riociguat 1.0-2.5 mg group over the placebo group was to be declared if the two-sided significance level was less than or equal to 0.05.

Key Chest-1 Inclusion Criteria

- Baseline 6-minute walking distance (6MWD) 150 m - 450 m
- CTEPH defined as:

- o inoperable (adjudicated by an experienced surgeon or a central adjudication committee) with RHC at least 90 days after start of full anticoagulation
  - PVR >300 dyn*sec*cm^{-5} measured (lowered from 480 dyn*sec*cm^{-5} by amendment 5)
  - mPAP >25 mmHg, or as persisting or recurrent PH after
- o Persisting/recurrent PH after pulmonary endarterectomy
  - PVR >300 dyn*sec*cm^{-5} by RHC ≥ 180 days after surgery)

Key CHEST-1 General Exclusions

- Patients with a relative difference (i.e. absolute difference/mean) of more than 15% between the eligibility- and the baseline 6MWD test
- For relative > 15%
  - o May perform a third test (including Borg Scale)
  - o Compared with the second test
  - o For relative difference between the second and the third test < 15% the patient can be randomized and the third 6MWD Test (including Borg Scale) will be considered as baseline test.

Key CHEST-1 Con-med Exclusions

- Pre-treatment with NO donors (e.g. Nitrates) within the last 90days before Visit 1
- Endothelin Receptor Antagonists
- Prostacyclin Analogues
- Specific (e.g. Sildenafil or Tadalafil) or unspecific Phosphodiesterase Inhibitors (e.g. dipyridamole, theophylline)
- In principle, must be therapy naïve with respect to PAH specific medications.
  - o If treated but suffering AEs or lack of efficacy PAH specific medication must have been stopped finally at least 30 days before performance of baseline right heart catheter
- Strong CYP3A4 inhibitors may “significantly increase (Riociguat) concentrations
- Maaloxan decreases bioavailability – take at least one hour after Rio
- Omeprazole lowers bioavailability
- Bosentan decreases Rio exposure (CYP3A4) – same positive effect on 6MWD
- Structured exercise/rehab not allowed during titration phase

Key CHEST-1 Pulmonary Exclusions

- PH other than subtypes 4.1 and 4.2 of the Venice Clinical Classification of Pulmonary Hypertension
- Mod to severe COPD (FEV1 < 60% pred)
- Severe restrictive lung dz (TLC < 70% pred)
- Congenital abnormalities of the lungs, thorax, and diaphragm

- SaO2 < 88% despite supplemental oxygen
- PaO2 < 55 mmHg despite supplemental oxygen
- PaCO2 > 45 mmHg

Key CHEST-1 CV Exclusions

- History of uncontrolled arterial hypertension within the last 90 days before Visit 1 and/or
    - Systolic blood pressure >180 mmHg and /or diastolic blood pressure >110
    - Systolic blood pressure <95 mmHg
- Resting heart rate in the awake patient <50 BPM or >105 BPM
- Atrial fibrillation / atrial flutter within the last 90 days
- Left heart failure with an ejection fraction less than 40% within the last 90 days
- pulmonary capillary wedge pressure >15 mmHg (if age is between 18 and 75 years at Visit 1) or >12 mmHg (if age is > 75 years at Visit 1)
- Hypertrophic obstructive cardiomyopathy
- Severe proven or suspected coronary artery disease (patients with Canadian Cardiovascular Society Angina Classification class 2-4, and/or requiring
- nitrates, and/or myocardial infarction within the last 90 days
- Clinical evidence of symptomatic atherosclerotic disease (e.g. peripheral artery disease with reduced walking distance, history of stroke with persistent neurological deficit etc.
- Congenital or acquired valvular or myocardial disease if clinically significant apart from tricuspid valvular insufficiency due to pulmonary hypertension
- thromboembolism despite sufficient (documented) oral anticoagulation

Key “Other Organ” Exclusions

- bilirubin >2 times upper limit normal
- ALT (Alanine-Amino-Transferase) or AST (Aspartate-Amino-Transferase) >3 times upper limit normal
- albumin < 32g/l, hepatic encephalopathy > grade 1
- glomerular filtration rate <30 mL/min by CG or MDRD

6.1.2 Demographics

The sample sizes by region for subjects participating in the CHEST-1 double-blind trial and its CHEST-2 LTE study are presented in the table below:

Table 11: CHEST-1 and CHEST-2 sample size by region (safety set, ISS table 7-5 pg 366)

	11348 CHEST-1				11349 CHEST-2	
Region Country	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)		TOTAL 194 (100%)	
Asia/Pacific	**18**	**(10.4%)**	**9**	**(10.2%)**	**21**	**(10.8%)**
Australia	2	(1.2%)	0	–	2	(1.0%)
Japan	11	(6.4%)	5	(5.7%)	13	(6.7%)
South Korea	3	(1.7%)	2	(2.3%)	5	(2.6%)
Taiwan	2	(1.2%)	2	(2.3%)	1	(0.5%)
China	**21**	**(12.1%)**	**11**	**(12.5%)**	**27**	**(13.9%)**
Europe	**104**	**(60.1%)**	**53**	**(60.2%)**	**111**	**(57.2%)**
Austria	1	(0.6%)	0	–	1	(0.5%)
Belgium	2	(1.2%)	1	(1.1%)	3	(1.5%)
Czech Republic	18	(10.4%)	6	(6.8%)	18	(9.3%)
Denmark	4	(2.3%)	3	(3.4%)	3	(1.5%)
France	7	(4.0%)	4	(4.5%)	7	(3.6%)
Germany	39	(22.5%)	18	(20.5%)	42	(21.6%)
Italy	13	(7.5%)	5	(5.7%)	13	(6.7%)
Netherlands	0	–	1	(1.1%)	0	-
Poland	5	(2.9%)	6	(6.8%)	10	(5.2%)
Portugal	1	(0.6%)	1	(1.1%)	1	(0.5%)
Russia	2	(1.2%)	1	(1.1%)	2	(1.0%)
Slovakia	1	(0.6%)	1	(1.1%)	2	(1.0%)
Spain	2	(1.2%)	2	(2.3%)	2	(1.0%)
Switzerland	3	(1.7%)	1	(1.1%)	2	(1.0%)
Turkey	4	(2.3%)	2	(2.3%)	3	(1.5%)
United Kingdom	2	(1.2%)	1	(1.1%)	2	(1.0%)
North America	**15**	**(8.7%)**	**9**	**(10.2%)**	**19**	**(9.8%)**
Canada	6	(3.5%)	3	(3.4%)	7	(3.6%)
USA	9	(5.2%)	6	(6.8%)	12	(6.2%)
Latin America [a]	**15**	**(8.7%)**	**6**	**(6.8%)**	**16**	**(8.2%)**
Argentina	1	(0.6%)	0	–	0	-
Brazil	8	(4.6%)	4	(4.5%)	10	(5.2%)
Mexico	6	(3.5%)	2	(2.3%)	6	(3.1%)

[a] Referred to as "South America" in the source.

With respect to individual patient demographics, the majority of subjects in CHEST-1 were white and female, with a mean age of 59 years and just over 40% being 65 years of age or older. The majority of patients had never smoked, and most drank little or no alcohol. BMI was similar between the groups. 30% had undergone prior surgery for CTEPH in the riociguat treatment group, as opposed to 22% in the placebo group. Most were treatment naïve, and most of those on prior medications had those medicines

stopped for participation in CHEST-1. Most were WHO FC III. Demographic details for CHEST-1 patients are shown in the tables 12 – 17 below:

Table 12: CHEST-1 demographics (safety set, from FSR table 8[-5] pg. 87)

Characteristic	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
Sex				
Male	55	(31.8%)	34	(38.6%)
Female	118	(68.2%)	54	(61.4%)
Race / Ethnicity				
White	120	(69.4%)	65	(73.9%)
Black or African American	7	(4.0%)	1	(1.1%)
Asian	37	(21.4%)	20	(22.7%)
Multiple races	1	(0.6%)	0	–
Hispanic or Latino	8	(4.6%)	2	(2.3%)
Age (years)				
N	173		88	
Mean (SD)	59.3 (13.9)		59.2 (12.7)	
Median (Min-Max)	62.0 (19-80)		61.0 (26-77)	
Age group				
Age <65 years	99	(57.2%)	52	(59.1%)
Age ≥65 years	74	(42.8%)	36	(40.9%)
Smoking history				
Never	113	(65.3%)	47	(53.4%)
Former	52	(30.1%)	34	(38.6%)
Current	6	(3.5%)	5	(5.7%)
Missing	2	(1.2%)	2	(2.3%)
Alcohol use				
Abstinent	90	(52.0%)	45	(51.1%)
Light	77	(44.5%)	39	(44.3%)
Moderate	5	(2.9%)	3	(3.4%)
Heavy	0	–	1	(1.1%)
Missing	1	(0.6%)	0	–
Weight (kg) at baseline				
N	173		88	
Mean (SD)	73.99 (18.47)		76.24 (16.33)	
Median (Min-Max)	73.60 (36.0-158)		76.50 (44.0-120)	
Body mass index (kg/m^2) at baseline				
N	173		88	
Mean (SD)	27.13 (5.75)		27.73 (5.30)	
Median (Min-Max)	26.64 (16.9-53.1)		26.52 (17.6-44.0)	

Note: Except where indicated, numbers denote number and percentage of subjects per treatment group. Percentages are calculated including missing values.

Table 13: CHEST-1 primary diagnoses (safety set, FSR table 8-7 pg 89)

	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
Inoperable CTEPH	121	(69.9%)	68	(77.3%)
Postoperative CTEPH	52	(30.1%)	20	(22.7%)

Table 14: CHEST-1 disease-specific characteristics at BL (safety set, FSR table 8-8 pg 90)

Characteristic	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
WHO functional class				
I	3	(1.7%)	0	–
II	55	(31.8%)	25	(28.4%)
III	107	(61.8%)	60	(68.2%)
IV	8	(4.6%)	2	(2.3%)
Missing	0	–	1	(1.1%)
6MWD category				
<320 m	60	(34.7%)	25	(28.4%)
≥320 m	113	(65.3%)	63	(71.6%)
6MWD category				
<380 m	109	(63.0%)	50	(56.8%)
≥380 m	64	(37.0%)	38	(43.2%)
PVR (dyn*s*cm^{-5})				
N	151		82	
Mean (SD)	790.7 (431.6)		779.3 (400.9)	
Median (Min-Max)	711.1 (195.2-3942.0)		691.4 (258.1-2046.8)	

Table 15: CHEST-1 specific PH con-meds (safety set, FSR table 8-13 pg 95)

Medication class/ category	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
Endothelin receptor antagonists				
Prior medication	5	(2.9%)	1	(1.1%)
Any concomitant medication	2	(1.2%)	0	–
Any new concomitant medication	1	(0.6%)	0	–
Prostacyclins (inc. analogues)				
Prior medication	17	(9.8%)	9	(10.2%)
Any concomitant medication	0	–	0	–
Any new concomitant medication	0	–	0	–
Phosphodiesterase Type 5 inhibitors				
Prior medication	3	(1.7%)	4	(4.5%)
Any concomitant medication	0	–	0	–
Any new concomitant medication	0	–	0	–

Table 16: CHEST-1 non-specific PH con-meds (safety set, FSR table 8-14 pg 96)

Medication class/ category	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
Calcium channel blockers				
Any concomitant medication	34	(19.7%)	17	(19.3%)
Any new concomitant medication	8	(4.6%)	4	(4.5%)
Digitalis glycosides				
Any concomitant medication	18	(10.4%)	8	(9.1%)
Any new concomitant medication	1	(0.6%)	1	(1.1%)
Oral anticoagulants				
Any concomitant medication	165	(95.4%)	85	(96.6%)
Any new concomitant medication	44	(25.4%)	33	(37.5%)
Loop or high ceiling diuretics				
Any concomitant medication	106	(61.3%)	54	(61.4%)
Any new concomitant medication	48	(27.7%)	19	(21.6%)
Thiazides or low ceiling diuretics				
Any concomitant medication	28	(16.2%)	11	(12.5%)
Any new concomitant medication	9	(5.2%)	3	(3.4%)

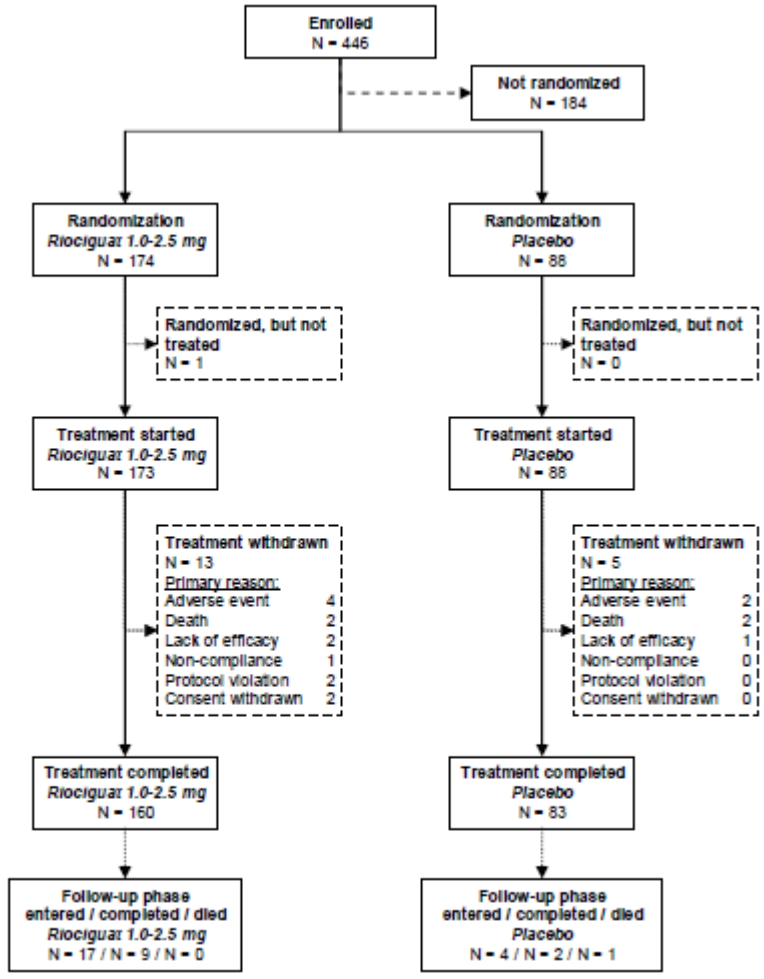
Table 17: CHEST-1 adjunctive therapies (safety set, FSR table 8-15 pg 97)

Type of therapy	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
Supplemental oxygen				
Prior therapy	37	(21.4%)	18	(20.5%)
Concomitant therapy	38	(22.0%)	19	(21.6%)
New concomitant therapy	10	(5.8%)	4	(4.5%)
Supportive physical training				
Prior therapy	0	–	0	–
Concomitant therapy	0	–	1	(1.1%)
New concomitant therapy	0	–	1	(1.1%)

6.1.3 Subject Disposition

The disposition of patients from CHEST-1 is shown in the following figure:

Figure 25. Disposition of subjects in trial 11348 (FSR pg 93)



Note: Subjects entered the safety follow-up phase only if they were prematurely withdrawn from the treatment phase (for reasons other than death) or if they completed the treatment phase but did not enter the extension study CHEST-2.

From this diagram, it is seen that with the exception of one patient that was randomized to riociguat but not treated, the ITT set is identical to the safety set. Because of this difference of one, I refer to the efficacy analysis set as the mITT set, whereas the sponsor refers to it as the ITT set. The number of patients who did not complete the study was small and relatively balanced between the arms considering the 2:1 randomization. Patients who entered the safety follow-up phase had a safety follow-up visit at day 30. The following table defines the various analysis sets of CHEST-1:

Table 18: CHEST-1 patients in analysis sets (from FSR table 8-4 pg. 85)

	Riociguat 1.0–2.5 mg	Placebo	Total
Enrolled			446
Randomized	174 (100%)	88 (100%)	262 (100%)
Valid for safety	173 (99.4%)	88 (100%)	261 (99.6%)
Valid for ITT	173 (99.4%)	88 (100%)	261 (99.6%)
Valid for per protocol	143 (82.2%)	75 (85.2%)	218 (83.2%)

Per FDA's request at the pre-NDA meeting, the sponsor was very clear on how missing data was treated with respect to imputation rules for calculating endpoints. For those patients who withdrew early due to death or a TTCW event with no termination visit, the following imputation rules were applied:

- 6MWD = 0
- Borg scale = 10 (worst scale on mod Borg)
- $EQ^{-5}D$ and LPH worst possible score
- WHO FC
  - TTCW event – worst possible score (IV)
  - Death – worst possible score +1 (V)

For all other withdrawals without termination visit data, LOCF of the most recent data (baseline if no post-baseline data) was utilized.

6.1.4 Analysis of Primary Endpoint(s)

The sponsor's analysis of the 6MWD primary endpoint for the CHEST -1 trial is as follows:

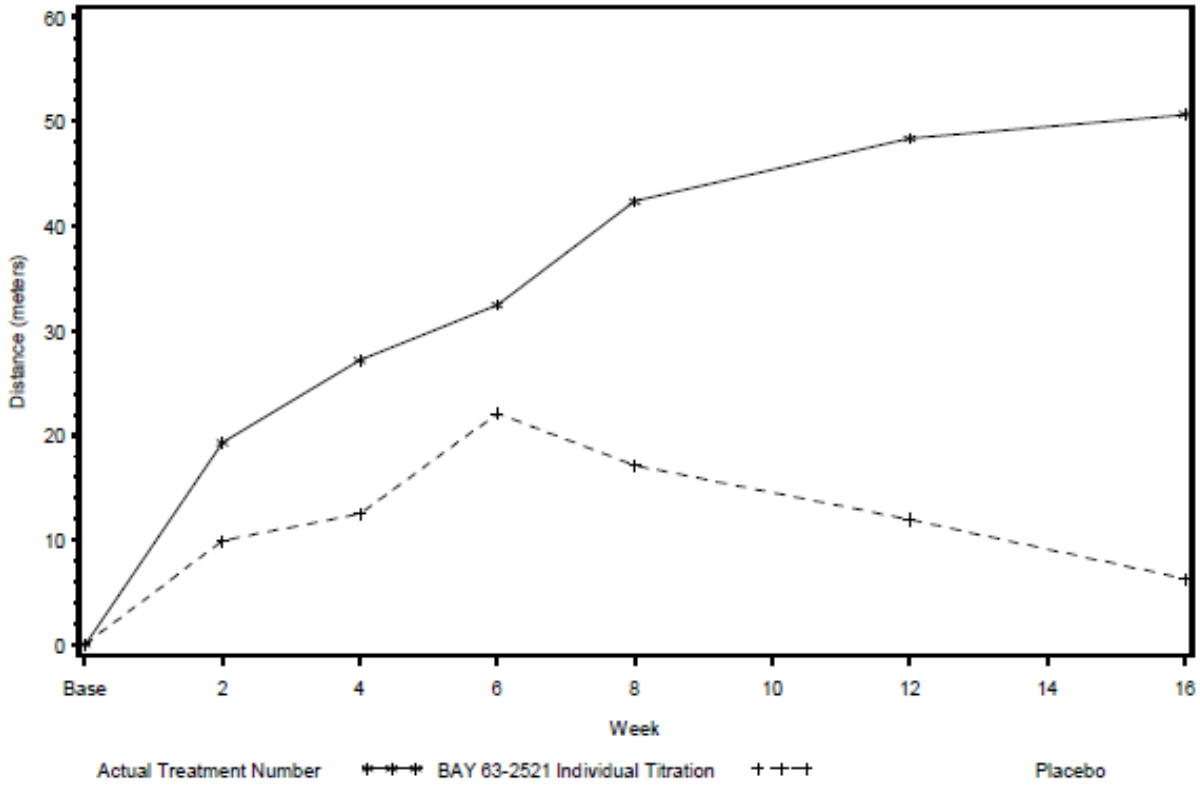
Table 19: CHEST-1 change in 6MWD (m) from BL to last visit (mITT set, FSR table 9.2 pg. 101)

Statistic	Riociguat 1.0–2.5 mg N=173	Placebo N=88
Baseline		
Mean (SD)	342.3 (81.9)	356.0 (74.7)
Median (Min-Max)	360.0 (150-557)	372.0 (152-474)
Change from baseline to last visit		
Mean (SD)	38.9 (79.3)	–5.5 (84.3)
Median (Min-Max)	42.0 (–376-335)	5.0 (–389-226)
Treatment comparison	**Riociguat 1.0-2.5 mg – placebo**	
LS mean difference	45.69	
95% CI	24.74 to 66.63	
p-value (ANCOVA)	<0.0001	
p-value (stratified Wilcoxon test)	<0.0001	

ANCOVA model with baseline value, treatment group, and region as fixed effects, stratified Wilcoxon test by region

The sponsor also provided the following graphical display of the six minute walk results by visit:

Figure 26: CHEST-1 mean 6MWD change from BL (mITT set, FSR fig. 9-1 pg. 102)



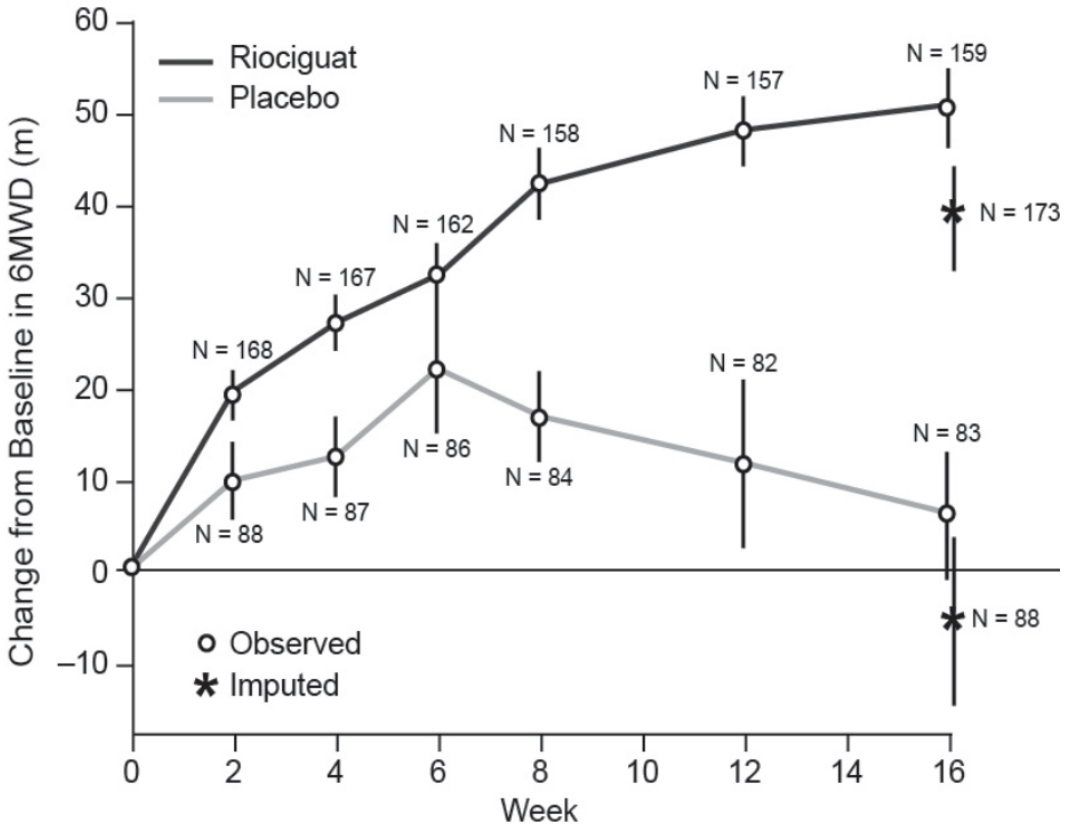
Number of subjects at each timepoint

	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16
Riociguat 1.0-2.5 mg	N=168	N=167	N=162	N=158	N=157	N=159
Placebo	N=88	N=87	N=86	N=84	N=82	N=83

Source: Figure 16.1.9.3/2

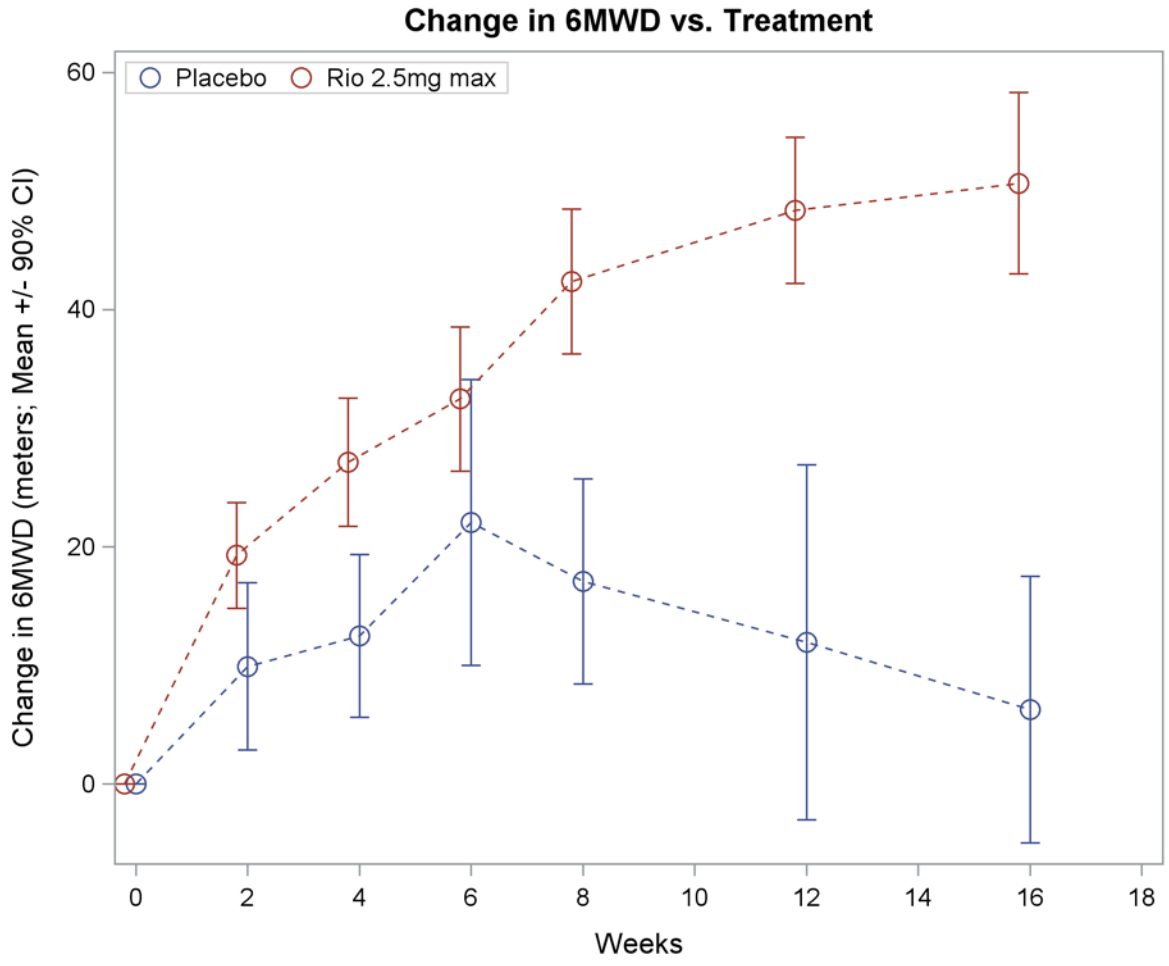
The proposed product label contains the following graphical display of by-visit results that includes standard error bars

Figure 27: CHEST-1 mean 6MWD change from BL with SEM (mITT set, proposed label)



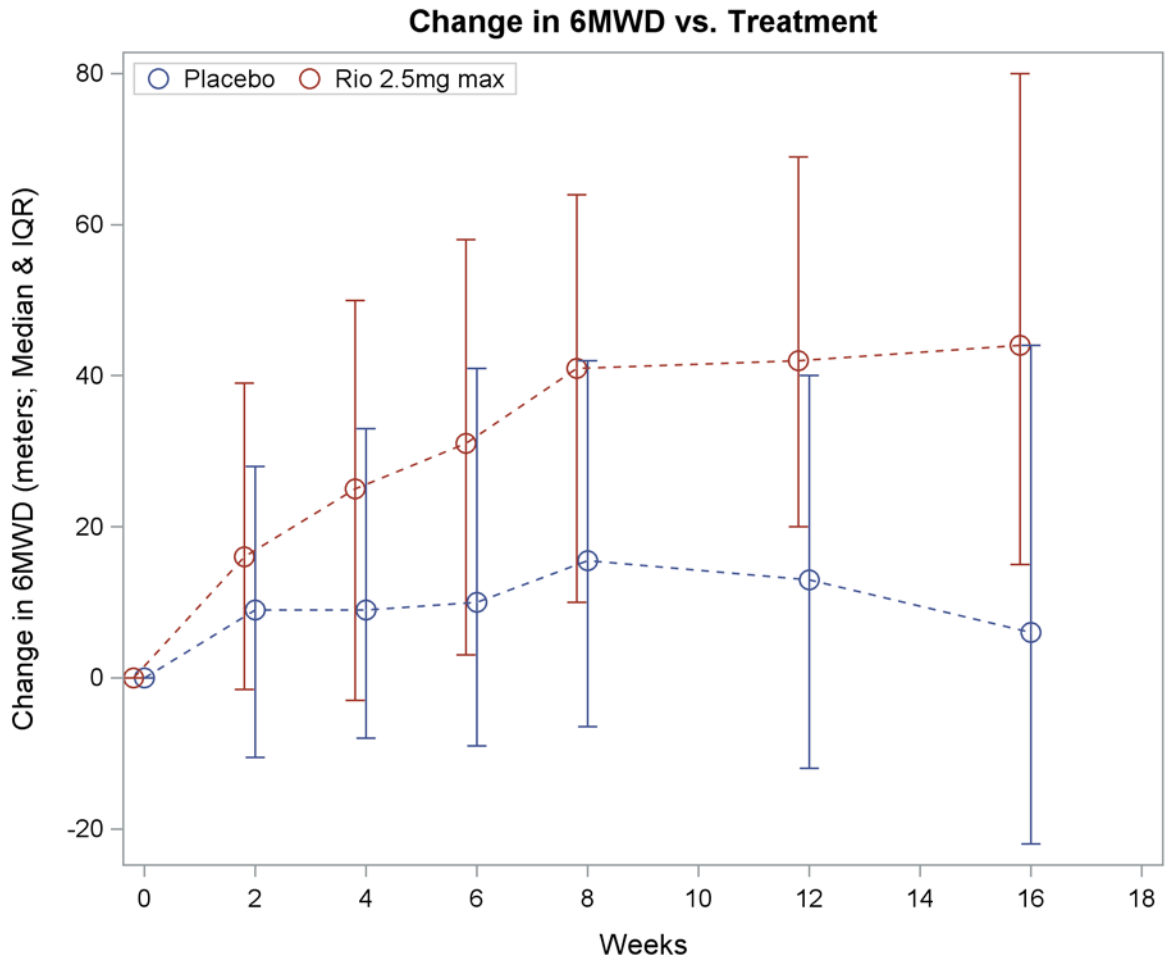
The primary analyses by the sponsor were reproduced/confirmed by FDA biometrics and FDA clinical pharmacology. The following figure displays FDA's un-adjusted reanalysis of the raw primary efficacy datasets from CHEST-1:

Figure 28: CHEST-1 un-adjusted analysis of efficacy sets by FDA (means with 95% CI)



Similar results were obtained using median values and interquartile ranges, as are shown in the following figure:

Figure 29: CHEST-1 un-adjusted analysis of efficacy sets by FDA (median values with IQR)



As would be expected, the sponsor's per protocol analysis demonstrated a larger treatment effect, as shown below:

Table 20: CHEST-1 6MWD change from BL to LV (PP set, FSR table 9-3 pg. 103)

Statistic	Riociguat 1.0–2.5 mg N=143	Placebo N=75
Baseline		
Mean (SD)	345.6 (82.6)	356.6 (73.6)
Median (Min-Max)	362.0 (150-557)	372.0 (170-474)
Change from baseline to last visit		
Mean (SD)	45.5 (71.2)	–5.9 (88.4)
Median (Min-Max)	43.0 (–305-335)	6.0 (–389-226)
Treatment comparison	**Riociguat 1.0-2.5 mg – placebo**	
LS mean difference	52.24	
95% CI	30.53 to 73.95	
p-value (ANCOVA)	<0.0001	
p-value (stratified Wilcoxon test)	<0.0001	

Multiple sensitivity analyses and imputation methods showed persistence of the overall treatment effect as follows:

Table 21: CHEST-1 6MWD (m) change from BL sensitivity analyses (mITT set, FSR table 9-4 pg. 104)

Analysis	Estimated treatment difference [a]	95% CI
Mixed model at Visit 7	44.40	27.94 to 60.85
Multiple imputation – Fixed penalty: Riociguat 1.0-2.5 mg –60 m and placebo –60 m	43.69	26.25 to 61.13
Multiple imputation – Decreasing slope: Riociguat 1.0-2.5 mg –20 m and placebo –20 m per visit	41.81	24.05 to 59.58
Multiple imputation – Fixed penalty: Riociguat 1.0-2.5 mg –60 m and placebo –0 m	40.07	22.94 to 57.21
Multiple imputation – Decreasing slope: Riociguat 1.0-2.5 mg –20 m and placebo –0 m per visit	38.71	21.27 to 56.15
Robust regression	40.31	25.86 to 54.75

Finally, as examined by FDA biometrics, there were no individual sites, countries, or regions that if removed would have neutralized the overall treatment effect (data not shown).

6.1.5 Analysis of Secondary Endpoints(s)

Time to Clinical Worsening (TTWC)

Clinical worsening (CW) was defined by the occurrence of any of the following clinical events:

- Death (all-cause mortality)
- Heart/lung transplantation
- Rescue pulmonary endarterectomy for persistent worsening of PH
- Hospitalization for persistent worsening of PH
- New PH therapy for worsened PH (ERA, PDE5i,Prost)
- Persistent decrease of more than 15 % from baseline or more than 30% compared to the last study related 6MWD due to worsening PH
    - Must be confirmed by second measure after 14 days
- Persistent worsening of functional class due to deterioration of Pulmonary Hypertension
    - deteriorate from class II or III to class IV
    - Must be confirmed by second measure after 14 days

Any subject suffering a clinical worsening event was withdrawn from the trial, and if no termination visit testing was performed, worst case imputation of final visit data used for the purpose of endpoint analyses (see above, imputation of missing data, page 76 of this review). The number of CW events was very small. The analyses of CW events from CHEST-1 are shown in the table below (p-values for TTCW):

Figure 30: CHEST-1 Clinical Worsening (mITT set, FSR table 9-11 pg 115)

Event	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
Any clinical worsening	4	(2.3%)	5	(5.7%)
Hospitalization due to PH	0	–	1	(1.1%)
Start of new PH treatment	2	(1.2%)	1	(1.1%)
Decrease in 6MWD due to PH	1	(0.6%)	2	(2.3%)
Persistent worsening of functional class due to PH	0	–	1	(1.1%)
Death	2	(1.2%)	3	(3.4%)
Treatment comparison	**Riociguat 1.0-2.5 mg – placebo**			
p-value (stratified log-rank test)	0.1724			
p-value (Mantel-Haenszel estimate)	0.2180			

The mean/median results for the remaining secondary endpoints are summarized in the following table:

Table 22: PATENT-1 mean/median change from BL to LV for secondary endpoints (mITT set)

	RIO IDT	Placebo
PVR (dyn*s*cm^{-5})	-225/-176	23.1/14.9
NT-proBNP (pg/mL)	-291/-185	76/41
Borg Scale	-0.83/-1.00	0.17/0.00
EQ^{-5}D-u	0.062/0.036	-0.082/0.000
EQ^{-5}D-v	10.5/10.0	-0.9/0.0
LPH-total	-6.72/-6.00	-2.09/-4.00
LPH-Physical	-3.84/-4.00	-2.20/-2.00
LPH-Emotional	-1.89/-1.25	-0.19/-1.00

P-values for these secondary efficacy endpoints, together with a determination of the significance of the finding in hierarchical testing, are shown in the table below:

Table 23: CHEST-1 secondary efficacy endpoints, hierarchical testing (mITT set, FSR table 9-6 pg. 108)

Variable	Treatment effect ANCOVA p-value	Shapiro-Wilk test p-value	Stratified Wilcoxon test p-value	Statistically significant	Statistically significant in hierarchical testing
6MWD (primary)	<0.0001	0.0001	**<0.0001**	Yes	Yes
PVR	<0.0001	0.0001	**<0.0001**	Yes	Yes
NT-proBNP	0.0293	0.0001	**<0.0001**	Yes	Yes
WHO functional class	–	–	**0.0026**	Yes	Yes
Time to clinical worsening	0.2180 [a]	–	**0.1724** [b]	No	No
Borg CR 10 scale [c]	–	–	**0.0035**	Yes	No
EQ-5D questionnaire	0.0002	0.0001	**<0.0001**	Yes	No
LPH questionnaire	0.0165	0.0001	**0.1220**	No	No

P-values used to determine statistical significance are given in bold.
[a] Mantel-Haenszel estimate p-value for incidence of clinical worsening
[b] Stratified log-rank test p-value for time to clinical worsening.
[c] Subjects enrolled before amendment 3 used the Modified Borg Dyspnoea Scale.

6.1.6 Other Endpoints

Changes in invasive hemodynamic parameters at right heart cath other than PVR are shown in the table below. The combination of lower pulmonary artery and aortic pressures, together with an increase in CO, drove large reductions in resistances in both circuits:

Table 24: CHEST-1 hemodynamics, change from BL to LV, IDT vs. PBO (mITT set, FSR table 9-8 pg. 111)

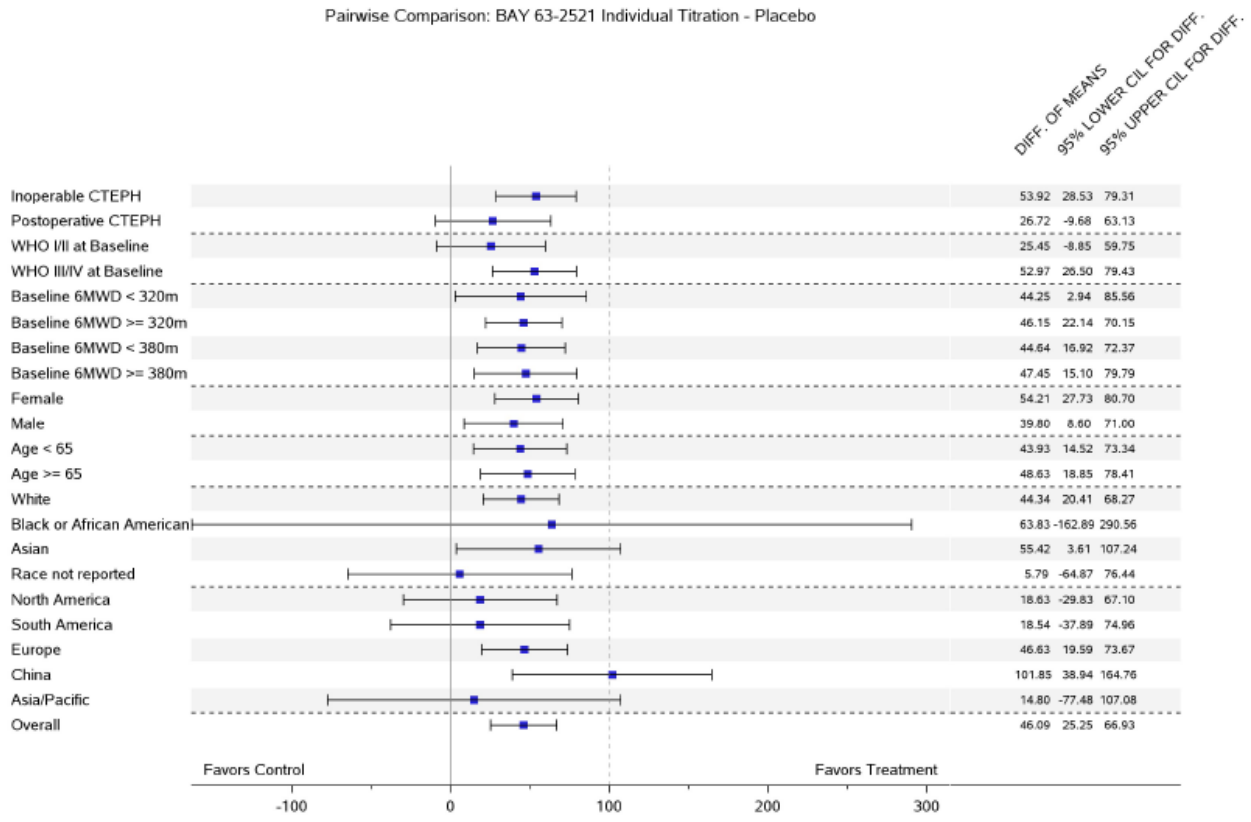
Parameter (unit)	Mean change		LS mean difference	95% CI	ANCOVA	Stratified Wilcoxon test
	RIO	PBO			p-value	p-value
PCWP (mmHg)	0.59	0.18	0.58	–0.36 to 1.53	0.2268	0.2285
RAP (mmHg)	–1.04	–0.55	–0.55	–1.72 to 0.62	0.3566	0.3593
PAPsyst (mmHg)	–6.84	0.95	–7.52	–10.88 to –4.16	<0.0001	<0.0001
PAPdiast (mmHg)	–3.05	0.67	–3.62	–5.30 to –1.95	<0.0001	0.0002
PAPmean (mmHg)	–4.31	0.76	–4.96	–6.75 to –3.16	<0.0001	<0.0001
MAP (mmHg)	–9.27	–0.29	–9.15	–11.83 to –6.46	<0.0001	<0.0001
SvO_2 (%)	2.95	–0.44	3.85	1.46 to 6.25	0.0017	0.0010
CO (L/min)	0.81	–0.03	0.86	0.59 to 1.12	<0.0001	<0.0001
CI (L/min/m^2)	0.45	–0.01	0.47	0.33 to 0.62	<0.0001	<0.0001
PVR (dyn*s*cm^{-5})	–226	23.1	–246.43	–303.33 to –189.53	<0.0001	<0.0001
PVRI (dyn*s*cm^{-5}*m^2)	–397	48.3	–448.95	–553.62 to –344.27	<0.0001	<0.0001
SVR (dyn*s*cm^{-5})	–445	16.6	–478.24	–602.30 to –354.19	<0.0001	<0.0001
SVRI (dyn*s*cm^{-5}*m^2)	–799	53.7	–914.16	–1140.97 to –687.35	<0.0001	<0.0001

ANCOVA model with baseline value, treatment group, and region as fixed effects, stratified Wilcoxon test by region
Last visit = Last observed value post-baseline (not including follow-up)
RIO=Riociguat 1.0-2.5 mg, PBO=Placebo

6.1.7 Subpopulations

Point estimates for riociguat treatment effect were positive for all subgroups, and the lower bound of the 95% CI for most of these analyses were greater than zero:

Figure 31: CHEST-1 mean treatment difference, 6MWD (m) change from BL, last observation to week 16, subgroups (mITT set, FSR Fig 9--2 pg.106)



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only a single active IDT dose arm was tested in CHEST-1. See the exposure response analysis by FDA clinical pharmacology above, section 4.4.3 pg 44.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of effect was evaluated in the CHEST-2 LTE. At week 12 of the extension study, patients from the placebo arm of the double-blind study demonstrated an incremental benefit over their original baseline 6MWD result that was in line with the clinical benefit seen by the riociguat-treated group in the double-blind trial, as is seen in the table below:

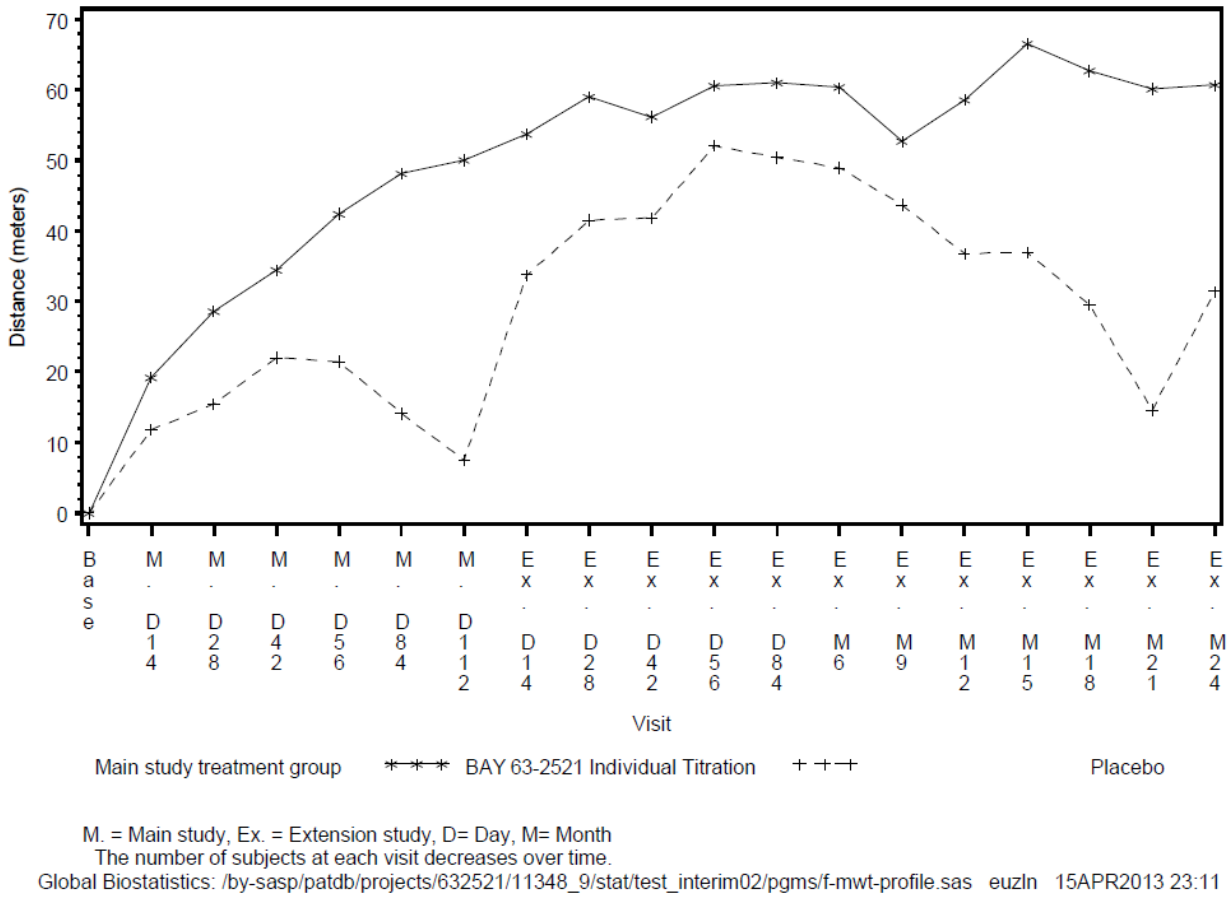
Table 25: CHEST-2 mean change 6MWD (m), BL to LV (week 12 LTE) (LTE safety set, month 4 clinical overview addendum, table 9-1 pg 3)

Statistic	Former Riociguat 1.0–2.5 mg N=129	Former Placebo N=82	Total N=237
Baseline	n=155	n=82	n=237
Mean (SD)	345.3 (81.7)	360.4 (71.3)	350.5 (78.4)
Median (Min-Max)	361.0 (150-557)	372.0 (170-474)	369.0 (150-557)
Change from baseline to CHEST-1 Visit 7 (16 weeks, observed values)	n=154	n=81	n=235
Mean (SD)	50.1 (58.5)	7.5 (62.7)	35.4 (63.2)
Median (Min-Max)	43.5 (–151 to 335)	6.0 (–214 to 226)	36.0 (–214 to 335)
Change from baseline to last visit (week 12) in CHEST-2	n=155	n=82	n=237
Mean (SD)	57.4 (69.0)	43.0 (72.3)	52.4 (70.4)
Median (Min-Max)	60.0 (–320 to 294)	45.5 (–240 to 227)	56.0 (–320 to 294)

Last visit (week 12) = last observed value up to extension week 12 (not including follow-up), except imputed worst value in case of death or clinical worsening prior to reaching extension visit week 12 without any subsequent visit.
Source: Cut-off Mar 2013: (Study 11349 in Module 5.3.5.3) Table 14.2.2/1

Persistence of benefit in the LTE was demonstrated through month 9 of follow-up, as is shown in the following figure:

Figure 32: CHEST-2 6MWD mean change from BL by visit (LTE safety set, month 4 clinical overview addendum fig 9-1 pg 5)



Source: Cut-off Mar 2013: (Study 11349 in Module 5.3.5.3) Figure 14.2.2./1

The ongoing improvement of the actively treated patients from the double blind trial after day 56 may represent hysteresis effect, training effect, dropout effect, or a combination of these. The remarkable improvement of placebo-treated patients in the main trial that rolled over to active treatment in the open label provides internal consistency supporting the overall primary efficacy outcome of CHEST-1.

For further evidence of persistence of benefit, the analysis of the incidence of clinical worsening events in the CHEST-2 LTE to the Mar 2013 cut-off demonstrates an overall lower rate of these events in the group that rolled over from placebo as compared to the group receiving active treatment in the double-blind, suggesting that there was not long-term harm done by starting riociguat therapy in the open label trial in previously treatment naïve patients, as shown in the following table:

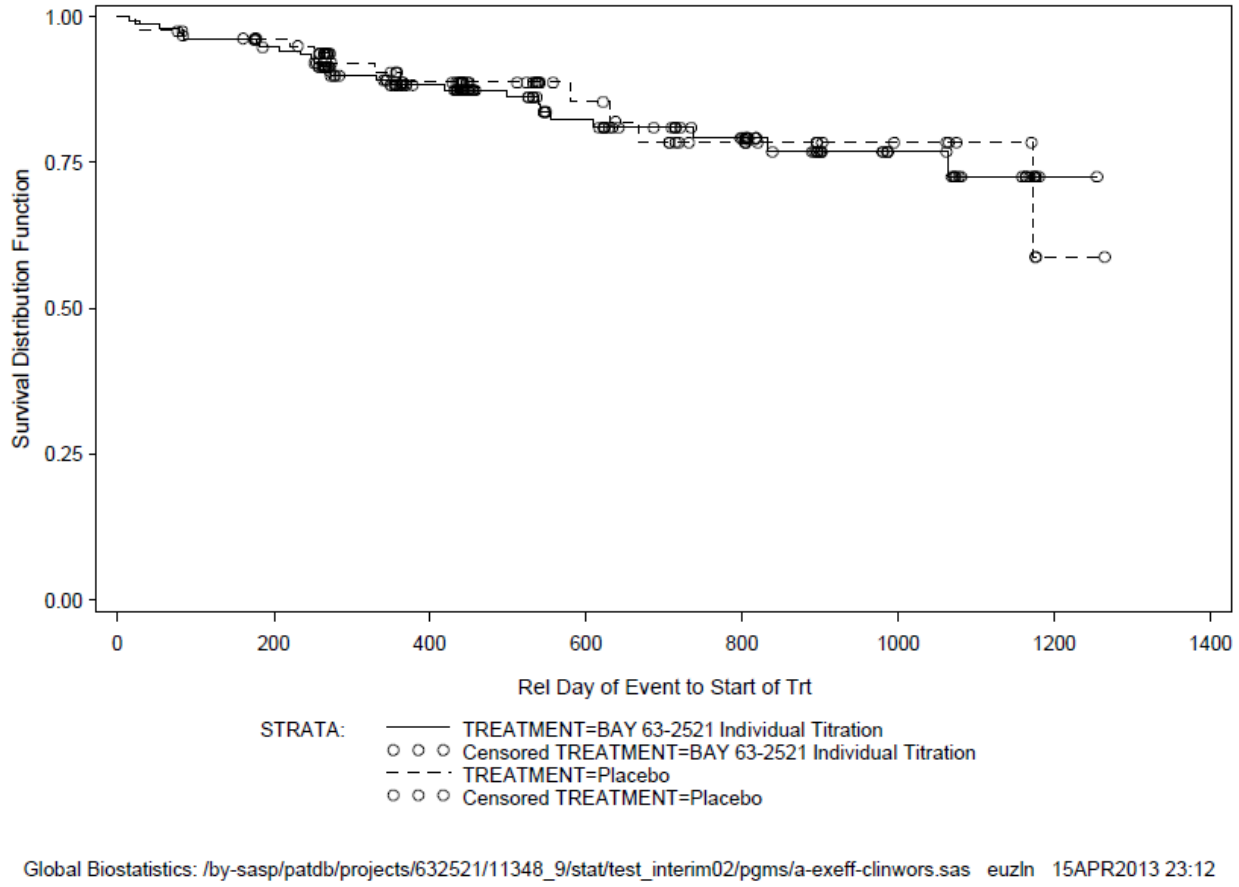
Table 26: CHEST-2 subjects with clinical worsening (LTE safety set, 4 month overview addendum table 9-2 pg 5)

Event	Former Riociguat IDT N=155 (100%)		Former Placebo N=82 (100%)		Total N=237 (100%)	
Number of subjects (%) with clinical worsening	26	(16.8%)	12	(14.6%)	38	(16.0%)
Atrial septostomy[a]	1	(0.6%)	1	(1.2%)	2	(0.8%)
Hospitalization due to PH	5	(3.2%)	1	(1.2%)	6	(2.5%)
Start of new PH treatment	12	(7.7%)	7	(8.5%)	19	(8.0%)
Decrease in 6MWD due to PH	2	(1.3%)	1	(1.2%)	3	(1.3%)
Persistent worsening of functional class due to PH	5	(3.2%)	1	(1.2%)	6	(2.5%)
Death	9	(5.8%)	4	(4.9%)	13	(5.5%)

Note: Numbers denote number and percentage of subjects per treatment group.
a: Note due to an error in coding atrial septostomy is displayed in the table, medically the correct procedure was pulmonary endarterectomy
Source: Cut-off Mar 2013: (Study 11349 in Module 5.3.5.3) Table 14.2.2/5

K-M analysis of time to first clinical worsening event shows that there was not a period of early attrition in the placebo to active rollover group:

Figure 33: CHEST-2 K-M TTCW (LTE safety set, 4 month clinical overview addendum fig 9-2 pg 6)



Source: Cut-off Mar 2013: (Study 11349 in Module 5.3.5.3) Figure 14.2.2./3

An analysis of the various types of CW events that were seen in CHEST-2 as a function of exposure are shown in the following table:

Table 27: CHEST-2 TTCW events/100 p-y (LTE safety set, month 4 clinical overview addendum table 9-3 pg 7)

Event	Former Riociguat IDT N=155		Former Placebo N=82		Total N=237	
	n	r/100sy	n	r/100sy	n	r/100sy
Any clinical worsening	38	15.17	17	13.36	55	14.56
Atrial septostomy[a]	1	0.40	1	0.79	2	0.53
Hospitalization due to PH	7	2.79	1	0.79	8	2.12
Start of new PH treatment	14	5.59	9	7.07	23	6.09
Decrease in 6MWD due to PH	2	0.80	1	0.79	3	0.79
Persistent worsening of functional class due to PH	5	2.00	1	0.79	6	1.59
Death	9	3.59	4	3.14	13	3.44

Note: N in the header is the number of subjects. The total number of events are presented in the body of the table, a subject may have more than one event.
There may also be more than one event within certain categories, eg more than one hospitalization.
Rate per 100 subject years (r/100sy)
is the number of events divided by (total drug exposure in years / 100).
a: Note due to an error in coding atrial septostomy is displayed in the table, medically the correct procedure was pulmonary endarterectomy
Source: Cut-off Mar 2013: (Study 11349 in Module 5.3.5.3) Table 14.2.2/6

Death rates of patient rolling over from placebo to active therapy remained similar to those patients who had continued active therapy from the main trial to the LTE over three years of follow-up, as shown from the table below:

Table 28: CHEST-2 survival and survival w/o clinical worsening events from K-M (LTE safety set, month 4 clinical overview addendum table 9-4 pg 8)

Time Point	Main study treatment group	Survival estimate (%) (survival)	95% CIL	Survival estimate (%) (without clinical worsening)	95% CIL
1 year	Riociguat IDT	97.22	92.71 – 98.95	88.33	81.86 – 92.60
	Placebo	95.48	86.49 – 98.54	88.75	78.57 – 94.26
	Total	96.62	92.99 – 98.39	88.49	83.40 – 92.10
2 years	Riociguat IDT	94.88	88.51 – 97.76	81.02	72.23 – 87.27
	Placebo	92.07	78.51 – 97.22	78.47	62.22 – 88.35
	Total	93.94	88.54 – 96.84	80.34	72.92 – 85.93
3 years	Riociguat IDT	86.18	70.95 – 93.76	72.62	58.79 – 82.47
	Placebo	92.07	78.51 – 97.22	78.47	62.22 – 88.35
	Total	87.98	77.34 – 93.82	74.27	63.58 – 82.25

Note: CIL = Confidence interval limit.
Confidence intervals are based on a loglog transformation of the survival function.
Note: The numbers of patients who completed the respective periods are: 1 year:172 subjects (114 riociguat IDT; 58 placebo); 2 years: 80 subjects (55 riociguat IDT; 25 placebo); 3 years 28 subjects (20 riociguat IDT; 8 placebo) derived from Cut-off Mar 2013: (Study 11349 in Module 5.3.5.3) Table 14.2.2/1
Source: Cut-off Mar 2013: (Study 11349 in Module 5.3.5.3) Table 14.2.2/8 and Table 14.2.2/9

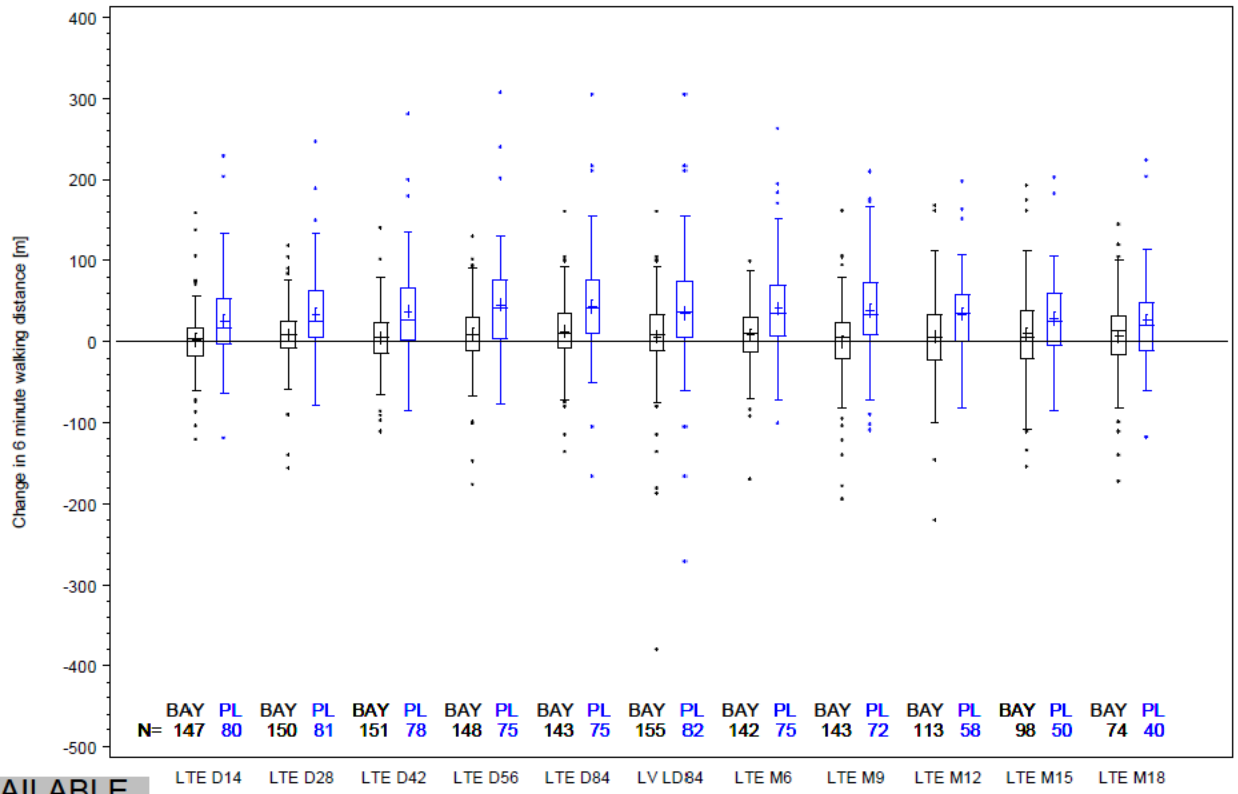
Deterioration rates for WHO function class were similar through LTE month 12 regardless of the trial arm the subject was randomized to in CHEST-1, as shown in the table below:

Table 29: CHEST-2 WHO functional class (LTE safety set, 4 month clinical addendum table 9-5 pg 10)

Visit Change from baseline to visit	WHO FC change	Former Riociguat IDT N=155 n (%)	Former Placebo N=82 n (%)	Total N=237 n (%)
Change from baseline at Last Visit to Week 12	n	155 (100.0%)	81 (100.0%)	236 (100.0%)
	-2	6 (3.9%)	1 (1.2%)	7 (3.0%)
	-1	57 (36.8%)	31 (38.3%)	88 (37.3%)
	0	86 (55.5%)	46 (56.8%)	132 (55.9%)
	1	5 (3.2%)	2 (2.5%)	7 (3.0%)
	2	1 (0.6%)	1 (1.2%)	2 (0.8%)
LTE 6 months	n	150 (100.0%)	79 (100.0%)	229 (100.0%)
	missing	0	1 (1.3%)	1 (0.4%)
	-2	6 (4.0%)	1 (1.3%)	7 (3.1%)
	-1	67 (44.7%)	32 (40.5%)	99 (43.2%)
	0	71 (47.3%)	44 (55.7%)	115 (50.2%)
	1	6 (4.0%)	1 (1.3%)	7 (3.1%)
LTE 12 months	n	118 (100.0%)	60 (100.0%)	178 (100.0%)
	missing	1 (0.8%)	1 (1.7%)	2 (1.1%)
	-2	7 (5.9%)	0	7 (3.9%)
	-1	52 (44.1%)	23 (38.3%)	75 (42.1%)
	0	53 (44.9%)	35 (58.3%)	88 (49.4%)
	1	5 (4.2%)	1 (1.7%)	6 (3.4%)

6MWD was assessed at the time of the 120 day safety update showing persistent improvement over time in placebo patients who rolled over to active therapy in the CHEST-2 open label trial, and no deterioration in subjects who continued active therapy from the main trial into the open label, as shown in the figure below:

Figure 34: CHEST-2 change in 6MWD, LTE with baseline of LTE (4 month safety update figure 1.1.4.2 / 2 pg 99)



6.1.10 Additional Efficacy Issues/Analyses

Serum glucose was not analyzed in either of the pivotal studies. Thus, FDA assess the use of diabetes drugs as con-meds in CHEST-1 to see if there was an indicator that there may have been increases in blood sugars that would have driven more diabetic drug use. As can be seen in the following table, while there were more patients starting ne diabetes drug in the riociguat arm during the course of the trial, the riociguat arm had almost twice as many subjects using these drugs at the beginning of the study:

Table 30: CHEST-1 drugs used in diabetes

Med class / Category	Individual Titration N=173 (100%)	Placebo N=88 (100%)
Drugs Used in Diabetes		
Prior-med	10 (5.8%)	3 (3.4%)
Any Con-med	11 (6.4%)	3 (3.4%)
New Con-med	6 (3.5%)	0

6.2 Indication – PAH (WHO Group I)

For the treatment of adult patients with pulmonary arterial hypertension (PAH, WHO Group1 – FC II-III idiopathic, heritable, or connective tissue induced PAH) to improve exercise capacity, WHO functional class, and to delay clinical worsening, either as monotherapy or in combination with an ERA or a prostanoid.

6.2.1 Methods

A single pivotal trial is submitted to support this indication (PATENT-1, trial 12934). Efficacy data presented in this section is therefore specific to that study only (no pooled data).

PATENT-1 was a randomized, double-blind, placebo-controlled, multi-center, multi-national, 12-week trial to evaluate the efficacy and safety of oral riociguat in in treatment naïve subjects and subjects pre-treated with an endothelin receptor antagonist or a prostacyclin analogue with symptomatic pulmonary arterial hypertension (PAH). This was a three arm trial as follows:

- Placebo

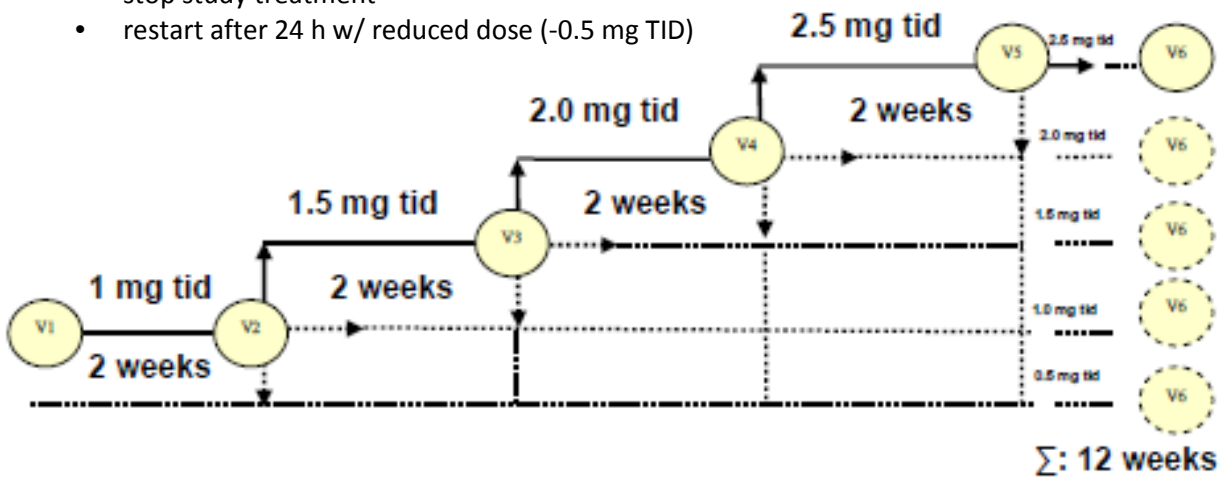
- Riociguat individual dose titration (IDT): riociguat given at an individualized dose after dose titration (starting with 1 mg 3 times a day [TID] and if tolerated up-titrated in steps of 0.5 mg TID every 2 weeks up to 2.5 mg TID) was compared with placebo.

- Riociguat capped dose: riociguat started at 1.0 mg TID and then escalated to 1.5 mg TID as a capped dose for the remainder of the trial. The results of this arm were also compared with placebo; however, this arm was small and not powered for all of the efficacy analyses. It was considered to be exploratory.

The up-titration algorithm of the IDT arm and its SBP cut-off rules were the same as those employed in the CTEPH trial (CHEST-1) and are as shown in the figure below:

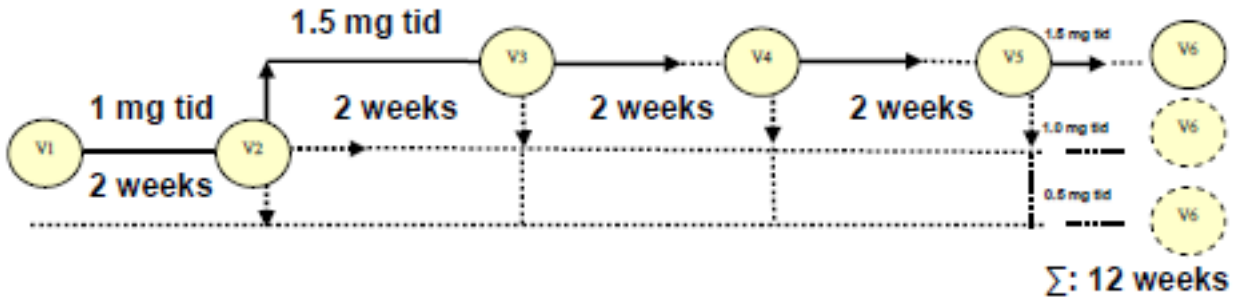
Figure 35: PATENT-1 IDT dosing scheme

- Trough SBP ≥95 mmHg, increase dose (+0.5 mg TID)
- Trough SBP 90 to 94 mmHg, maintain dose
- Trough SBP <90 mmHg without symptoms of hypotension, reduce dose (-0.5 mg TID)
- Trough SBP <90 mmHg with clinical symptoms of hypotension such as dizziness or pre-syncope,
    - stop study treatment
    - restart after 24 h w/ reduced dose (-0.5 mg TID)



The dosing algorithm for the 1.5 mg TID capped dose arm, which was unique to the PAH trial, is shown in the figure below (SBP cut-off and titration rules were the same as for the IDT doing arm):

Figure 36: PATENT-1 capped dosing algorithm



As occurred in the phase II study 12166, while the majority of patients tolerated the up-titration to the highest dose in the IDT arm (2.5 mg TID), 25% did not, as shown in the table below:

Table 31: PATENT-1 total daily riociguat dose at end of study (safety set)

Trial Arm (N/n)	1.5 mg	3.0 mg	4.5 mg	6 mg	7.5 mg
IDT (254/236)	4 (1.7%)	6 (2.5%)	14 (5.9%)	36 (15%)	176 (75%)
Capped (63/57)		3 (5.3%)	54 (95%)		

The primary efficacy variable was the placebo-corrected change in 6MWD from baseline to week 12 (last observation until week 12) in subjects valid for ITT, with imputation of missing values for subjects who withdrew (without termination visit data) or died before 12 weeks. The riociguat 1.0-2.5 mg and placebo groups were compared using analysis of covariance (ANCOVA), with baseline 6MWD as a covariate and treatment group, stratification group (therapy-naïve / add-on), and region as main effects. The primary statistical method would be the stratified Wilcoxon test if the Shapiro-Wilk test for normality of residuals was statistically significant. Least squares (LS) mean and 95% confidence intervals (CIs) of the treatment difference were calculated based on the ANCOVA. Superiority of the riociguat 1.0-2.5 mg group over the placebo group was to be declared if the two-sided significance level was less than or equal to 0.05.

Key PATENT-1 Inclusion Criteria

- Baseline 6-minute walking distance (6MWD) 150 m - 450 m
- PVR >300 dyn*sec*cm^{-5}, and a PAP_{mean} >25 mmHg (lowered from 480 to 300 dyn*sec*cm^{-5} by amendment 5)
- Symptomatic PAH due to the following Group 1 subtypes:
  - Idiopathic/Familial PAH
  - PAH secondary to connective tissue disease
  - PAH associated with congenital heart disease (correction >360 days prior to inclusion)
  - PAH due to portal hypertension/cirrhosis
  - PAH associated with anorexigen or amphetamine use
- Treatment-naïve

- ERA or non-IV prostacyclin analogue treated
    - Doses for specific co-therapies for PAH must be stable for 90 days prior to visit1
    - Oxygen therapy must be stable for 90 days prior to visit 1
    - Treatment-naïve subjects were not permitted to start concomitant endothelin receptor antagonist / prostacyclin analogue therapy during the pre-treatment phase or the treatment phase. Subjects who required concomitant endothelin receptor antagonist / prostacyclin analogue therapy were to be withdrawn from the study medication, and counted as a TTCW endpoint event

Key PATENT-1 General Exclusions

- Subjects taking excluded specific PH co-therapies could not be withdrawn from medically required treatments, and were excluded from PATENT-1
- Patients with a relative difference (i.e. absolute difference/mean) of more than 15% between the eligibility- and the baseline 6MWD test
- For relative > 15%
    - May perform a third test (including Borg Scale)
    - Compared with the second test
    - For relative difference between the second and the third test < 15% the patient can be randomized and the third 6MWD Test (including Borg Scale) will be considered as baseline test.

Key PATENT-1 Con-med Exclusions

- NO donors (e.g. nitrates)
- Endothelin Receptor Antagonists
- IV prostacyclin analogues
- Specific (e.g. sildenafil or tadalafil) or unspecific phosphodiesterase inhibitors (e.g. dipyridamole, theophylline)

Key PATENT-1 Pulmonary Exclusions

- All other Group I causes of PAH other than those listed in the inclusion criteria (excluded by amendment 4)
- Mod to severe COPD (FEV1 < 60% pred)
- Severe restrictive lung dz (TLC < 70% pred)
- Congenital abnormalities of the lungs, thorax, and diaphragm
- SaO2 < 88% despite supplemental oxygen
- PaO2 < 55 mmHg despite supplemental oxygen
- PaCO2 > 45 mmHg

Key PATENT-1 CV Exclusions

- History of uncontrolled arterial hypertension within the last 90 days before Visit 1 and/or
    - Systolic blood pressure >180 mmHg and /or diastolic blood pressure >110
    - Systolic blood pressure <95 mmHg
- Resting heart rate in the awake patient <50 BPM or >105 BPM
- Atrial fibrillation / atrial flutter within the last 90 days
- Left heart failure with an ejection fraction less than 40% within the last 90 days
- pulmonary capillary wedge pressure >15 mmHg (if age is between 18 and 75 years at Visit 1) or >12 mmHg (if age is > 75 years at Visit 1)
- Hypertrophic obstructive cardiomyopathy
- Severe proven or suspected coronary artery disease (patients with Canadian Cardiovascular Society Angina Classification class 2-4, and/or requiring nitrates, and/or myocardial infarction within the last 90 days
- Clinical evidence of symptomatic atherosclerotic disease (e.g. peripheral artery disease with reduced walking distance, history of stroke with persistent neurological deficit etc.
- Congenital or acquired valvular or myocardial disease if clinically significant apart from tricuspid valvular insufficiency due to pulmonary hypertension

Key “Other Organ” Exclusions

- bilirubin >2 times upper limit normal
- ALT (Alanine-Amino-Transferase) or AST (Aspartate-Amino-Transferase) >3 times upper limit normal
- albumin < 32g/l, hepatic encephalopathy > grade 1
- glomerular filtration rate <30 mL/min by CG or MDRD

6.2.2 Demographics

The sample sizes by region for subjects participating in the PATENT-1 double-blind trial are presented the following table:

Table 32: PATENT-1 sample size by region (mITT set, FSR table 8-1 pg 81)

Region Country	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
Asia/Pacific	46	(18.1%)	18	(14.3%)	11	(17.5%)
Australia	11	(4.3%)	5	(4.0%)	3	(4.8%)
Japan	16	(6.3%)	7	(5.6%)	3	(4.8%)
Singapore	4	(1.6%)	1	(0.8%)	4	(6.3%)
South Korea	6	(2.4%)	1	(0.8%)	0	–
Taiwan	6	(2.4%)	3	(2.4%)	1	(1.6%)
Thailand	3	(1.2%)	1	(0.8%)	0	–
China	43	(16.9%)	24	(19.0%)	10	(15.9%)
Europe	118	(46.5%)	59	(46.8%)	30	(47.6%)
Austria	3	(1.2%)	2	(1.6%)	2	(3.2%)
Belgium	4	(1.6%)	2	(1.6%)	1	(1.6%)
Czech Republic	9	(3.5%)	2	(1.6%)	2	(3.2%)
Denmark	3	(1.2%)	0	–	0	–
France	7	(2.8%)	3	(2.4%)	5	(7.9%)
Germany	43	(16.9%)	20	(15.9%)	10	(15.9%)
Greece	3	(1.2%)	2	(1.6%)	0	–
Italy	12	(4.7%)	5	(4.0%)	0	–
Poland	7	(2.8%)	5	(4.0%)	3	(4.8%)
Portugal	2	(0.8%)	2	(1.6%)	0	–
Russia	5	(2.0%)	3	(2.4%)	1	(1.6%)
Spain	2	(0.8%)	0	–	1	(1.6%)
Sweden	1	(0.4%)	3	(2.4%)	1	(1.6%)
Switzerland	4	(1.6%)	4	(3.2%)	0	–
Turkey	3	(1.2%)	1	(0.8%)	1	(1.6%)
United Kingdom	10	(3.9%)	5	(4.0%)	3	(4.8%)
North America	24	(9.4%)	11	(8.7%)	5	(7.9%)
Canada	9	(3.5%)	2	(1.6%)	3	(4.8%)
USA	15	(5.9%)	9	(7.1%)	2	(3.2%)
South America	23	(9.1%)	14	(11.1%)	7	(11.1%)
Argentina	1	(0.4%)	0	–	0	–
Brazil	18	(7.1%)	7	(5.6%)	1	(1.6%)
Mexico	4	(1.6%)	7	(5.6%)	6	(9.5%)

With respect to individual patient demographics, the majority of subjects in PATENT-1 were white and female, with a mean age of approximately 50 years and only about 25% being 65 years of age or older. The majority of patients had never smoked, and most drank little or no alcohol. BMI was similar between the groups. Idiopathic PAH and PAH due to connective tissue disease represented more than 80% of the patients in all three treatment arms, with the remainder a mix of familial PAH, PAH due to congenital heart disease (surgically corrected), portal PH, or PAH due to anorexigens or amphetamine use. Most were WHO FC II or FC III, and the population was almost evenly split between those who were treatment naïve and those who were taking specific PH medications. Demographic details for PATENT-1 patients are shown in the tables 33 – 39 below:

Table 33: PATENT-1 demographics (safety set, FSR table 8-5 pg 89)

Characteristic	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
Sex						
Male	51	(20.1%)	28	(22.2%)	14	(22.2%)
Female	203	(79.9%)	98	(77.8%)	49	(77.8%)
Race / Ethnicity						
White	161	(63.4%)	78	(61.9%)	33	(52.4%)
Black or African American	4	(1.6%)	1	(0.8%)	1	(1.6%)
Asian	79	(31.1%)	38	(30.2%)	22	(34.9%)
Multiple races	1	(0.4%)	1	(0.8%)	0	–
Hispanic or latino	9	(3.5%)	8	(6.3%)	7	(11.1%)
Age (years)						
N	254		126		63	
Mean (SD)	51.1 (16.6)		50.7 (16.5)		48.8 (16.1)	
Median (Min-Max)	52.5 (18-80)		51.0 (18-79)		49.0 (18-77)	
Age group						
Age <65 years	188	(74.0%)	94	(74.6%)	49	(77.8%)
Age ≥65 years	66	(26.0%)	32	(25.4%)	14	(22.2%)
Smoking history						
Never	171	(67.3%)	78	(61.9%)	40	(63.5%)
Former	66	(26.0%)	38	(30.2%)	18	(28.6%)
Current	17	(6.7%)	7	(5.6%)	5	(7.9%)
Missing	0	–	3	(2.4%)	0	–
Alcohol use						
Abstinent	167	(65.7%)	73	(57.9%)	42	(66.7%)
Light	80	(31.5%)	49	(38.9%)	20	(31.7%)
Moderate	7	(2.8%)	3	(2.4%)	1	(1.6%)
Missing	0	–	1	(0.8%)	0	–
Weight (kg) at baseline						
N	254		126		63	
Mean (SD)	68.62 (18.42)		69.60 (17.63)		70.58 (15.77)	
Median (Min-Max)	65.00 (37.7-140)		65.85 (38.4-141)		68.00 (46.0-120)	
Body mass index (kg/m^2) at baseline						
N	254		126		63	
Mean (SD)	25.91 (5.48)		26.26 (5.92)		26.85 (5.35)	
Median (Min-Max)	25.18 (16.3-49.7)		24.89 (17.1-46.6)		26.09 (18.4-45.2)	

Note: Except where indicated, numbers denote number and percentage of subjects per treatment group. Percentages are calculated including missing values. Min = minimum; Max = maximum
Source: Table 14.1/7

Table 34: PATENT-1 PH classification (safety set, Venice definitions, FSR table 8-7 pg 91)

PH subtype (Group I)	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
Idiopathic PAH	149	(58.7%)	84	(66.7%)	39	(61.9%)
Familial PAH	7	(2.8%)	1	(0.8%)	1	(1.6%)
PAH due to connective tissue disease	71	(28.0%)	25	(19.8%)	15	(23.8%)
PAH due to congenital heart disease (operated)	15	(5.9%)	12	(9.5%)	8	(12.7%)
Portal PH	11	(4.3%)	2	(1.6%)	0	–
PAH due to anorexigen or amphetamine use	1	(0.4%)	2	(1.6%)	0	–

Table 35: PATENT-1 disease-specific characteristics at BL (safety set, FSR table 8-8 pg 92)

Characteristic	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
WHO functional class						
I	5	(2.0%)	4	(3.2%)	5	(7.9%)
II	108	(42.5%)	60	(47.6%)	19	(30.2%)
III	140	(55.1%)	58	(46.0%)	39	(61.9%)
IV	1	(0.4%)	3	(2.4%)	0	–
Missing	0	–	1	(0.8%)	0	–
6MWD category						
<320 m	67	(26.4%)	27	(21.4%)	14	(22.2%)
≥320 m	187	(73.6%)	99	(78.6%)	49	(77.8%)
6MWD category						
<380 m	139	(54.7%)	53	(42.1%)	30	(47.6%)
≥380 m	115	(45.3%)	73	(57.9%)	33	(52.4%)
PVR (dyn*s*cm^{-5})						
N	232		107		58	
Mean (SD)	791.0 (452.6)		834.1 (476.7)		847.8 (548.2)	
Median (Min-Max)	685.2 (241.5-2613.3)		740.0 (286.1-2545.5)		729.7 (258.1-3617.4)	
PAPmean (mmHg)						
N	235		109		58	
Mean (SD)	47.1 (14.8)		48.9 (15.2)		52.1 (16.2)	
Median (Min-Max)	45.7 (23.0-96.0)		48.0 (24.3-94.0)		51.2 (26.7-107.0)	

Table 36: PATENT-1 disease-specific treatment status at BL (safety set, FSR table 8-9 pg 94)

Characteristic	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
Stratification						
Therapy-naive	123	(48.4%)	66	(52.4%)	32	(50.8%)
Pre-treated	131	(51.6%)	60	(47.6%)	31	(49.2%)
PH-specific medication and WHO functional class at baseline						
Pre-treated and WHO I/II	45	(17.7%)	25	(19.8%)	9	(14.3%)
Pre-treated and WHO III/IV	86	(33.9%)	34	(27.0%)	22	(34.9%)
Pre-treated and missing	0	–	1	(0.8%)	0	–
Therapy-naive and WHO I/II	68	(26.8%)	39	(31.0%)	15	(23.8%)
Therapy-naive and WHO III/IV	55	(21.7%)	27	(21.4%)	17	(27.0%)
Pre-treated with endothelin receptor antagonist	113	(44.5%)	54	(42.9%)	27	(42.9%)
Pre-treated with prostacyclin analogue	20	(7.9%)	7	(5.6%)	4	(6.3%)

Note: Numbers denote number and percentage of subjects per treatment group. Percentages are calculated including missing values.
Source: Table 14.1/9

Table 37: PATENT-1 sprecific PH con-meds (safety set, FSR table 8-14 pg 103)

Medication class/ category	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
Endothelin receptor antagonists						
Prior medication	114	(44.9%)	54	(42.9%)	27	(42.9%)
Any concomitant medication	113	(44.5%)	52	(41.3%)	27	(42.9%)
Any new concomitant medication	4	(1.6%)	1	(0.8%)	0	–
Prostacyclins (inc. analogues)						
Prior medication	43	(16.9%)	24	(19.0%)	14	(22.2%)
Any concomitant medication	22	(8.7%)	12	(9.5%)	5	(7.9%)
Any new concomitant medication	4	(1.6%)	5	(4.0%)	3	(4.8%)
Phosphodiest. Type 5 inhibitors						
Prior medication	1	(0.4%)	1	(0.8%)	1	(1.6%)
Any concomitant medication	0	–	1	(0.8%)	0	–
Any new concomitant medication	0	–	1	(0.8%)	0	–

Note: Numbers denote number and percentage of subjects per treatment group.
Source: Tables 14.1/15, 14.1/17, and 14.1/19

Table 38: PATENT-1 non-specific PH con-meds (safety set, FSR table 8-15 pg 104)

Medication class/ category	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
Calcium channel blockers						
Any concomitant medication	66	(26.0%)	25	(19.8%)	17	(27.0%)
Any new concomitant medication	8	(3.1%)	4	(3.2%)	1	(1.6%)
Digitalis glycosides						
Any concomitant medication	42	(16.5%)	18	(14.3%)	9	(14.3%)
Any new concomitant medication	6	(2.4%)	1	(0.8%)	0	–
Oral anticoagulants						
Any concomitant medication	139	(54.7%)	72	(57.1%)	36	(57.1%)
Any new concomitant medication	36	(14.2%)	18	(14.3%)	15	(23.8%)
Loop or high ceiling diuretics						
Any concomitant medication	135	(53.1%)	66	(52.4%)	36	(57.1%)
Any new concomitant medication	55	(21.7%)	25	(19.8%)	13	(20.6%)
Thiazides or low ceiling diuretics						
Any concomitant medication	44	(17.3%)	21	(16.7%)	12	(19.0%)
Any new concomitant medication	12	(4.7%)	6	(4.8%)	2	(3.2%)

Note: Numbers denote number and percentage of subjects per treatment group. Only the main classes of diuretics are included in the table. For information on other, less frequent classes of diuretics, see the main statistical tables.
Source: Tables 14.1/15 and 14.1/17

Table 39: PATENT-1 adjunctive therapies (safety set, FSR table 8-16 pg 105)

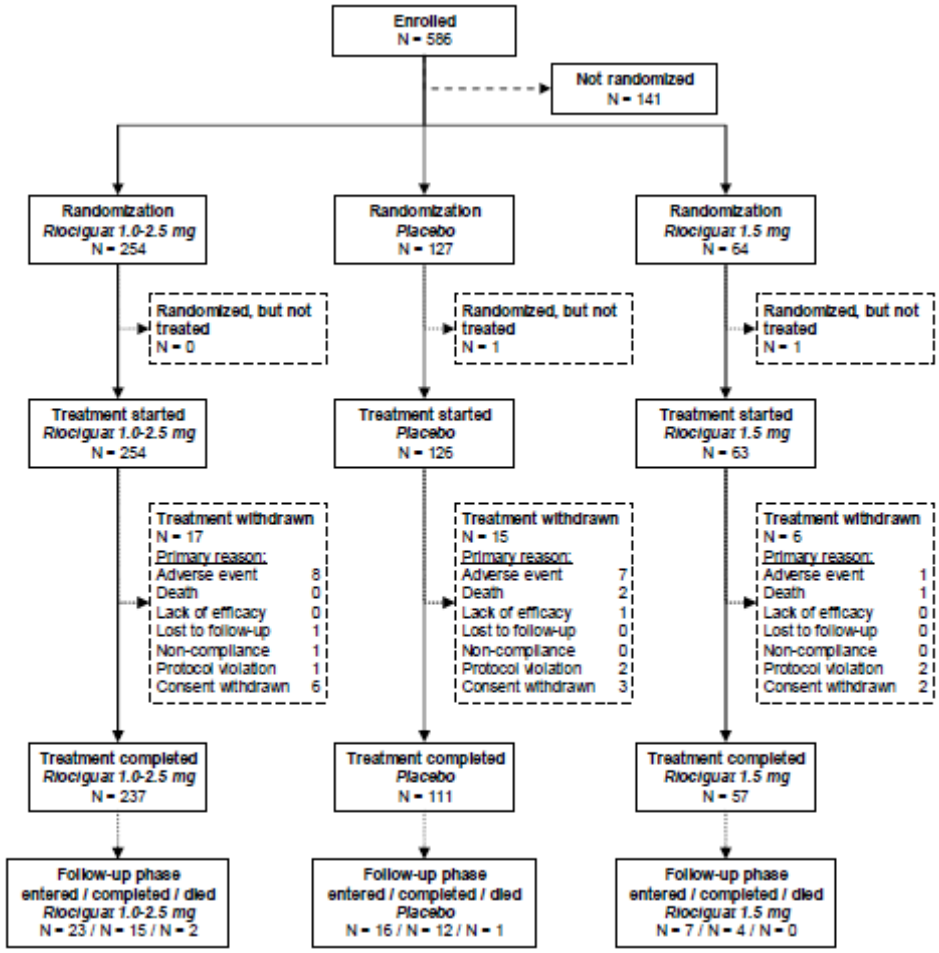
Type of therapy	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
Supplemental oxygen						
Prior therapy	47	(18.5%)	22	(17.5%)	16	(25.4%)
Concomitant therapy	50	(19.7%)	24	(19.0%)	18	(28.6%)
New concomitant therapy	9	(3.5%)	6	(4.8%)	5	(7.9%)
Supportive physical training						
Prior therapy	0	–	1	(0.8%)	0	–
Concomitant therapy	1	(0.4%)	1	(0.8%)	2	(3.2%)
New concomitant therapy	1	(0.4%)	0	–	2	(3.2%)

Note: Numbers denote number and percentage of subjects per treatment group.
Source: Tables 14.1/23, 14.1/24 and 14.1/25

6.2.3 Subject Disposition

The disposition of patients from PATENT-1 is shown in the following figure:

Figure 37. Subject disposition in trial 12934



Note: Subjects entered the safety follow-up phase only if they were prematurely withdrawn from the treatment phase (for reasons other than death) or if they completed the treatment phase but did not enter the extension study PATENT-2.

From this diagram, it is seen that with the exception of one patient that was randomized to the riociguat capped-dose arm but not treated and one patient that was randomized to the placebo arm but not treated, the ITT set is identical to the safety set. Because of this difference of one patient in the two arms as noted, I refer to the efficacy analysis set as the mITT set, whereas the sponsor refers to it as the ITT set. A smaller percentage of randomized patients withdrew from the riociguat treatment arms as compared to the placebo arm (6.6%, 7.9%, and 12% for the IDT, fixed dose, and placebo arms respectively). Patients who entered the safety follow-up phase had a safety follow-up visit at day 30. The following table defines the various analysis sets of PATENT-1:

Table 40: PATENT-1 analysis sets (FSR table 8-4 pg 86)

	Riociguat 1.0–2.5 mg	Placebo	Riociguat 1.0–1.5 mg	Total
Enrolled				586
Randomized	254 (100%)	127 (100%)	64 (100%)	445 (100%)
Valid for safety	254 (100%)	126 (99.2%)	63 (98.4%)	443 (99.6%)
Valid for ITT	254 (100%)	126 (99.2%)	63 (98.4%)	443 (99.6%)
Valid for per protocol	218 (85.8%)	106 (83.5%)	55 (85.9%)	379 (85.2%)

Source: Tables 14.1/1 and 14.1/2

Imputation rules for missing data were the same as those used for the CTEPH trial. Specifically, for those patients who withdrew early due to death or a CW event with no termination visit, the following imputation rules were applied:

- 6MWD = 0
- Borg scale = 10 (worst scale on mod Borg)
- $EQ^{-5}D$ and LPH worst possible score
- WHO FC
  - TTCW event – worst possible score (IV)
  - Death – worst possible score +1 (V)

For all other withdrawals with no termination visit data, LOCF of the most recent data (baseline if no post-baseline data) was utilized.

6.2.4 Analysis of Primary Endpoint(s)

The sponsor's analysis of the 6MWD primary endpoint for the PATENT-1 trial is shown in the following table:

Table 41: PATENT-1 change in 6MWD (m) from BL to LV (mITT set, Resp to FDA IR-26, table 9-2A pg 2)

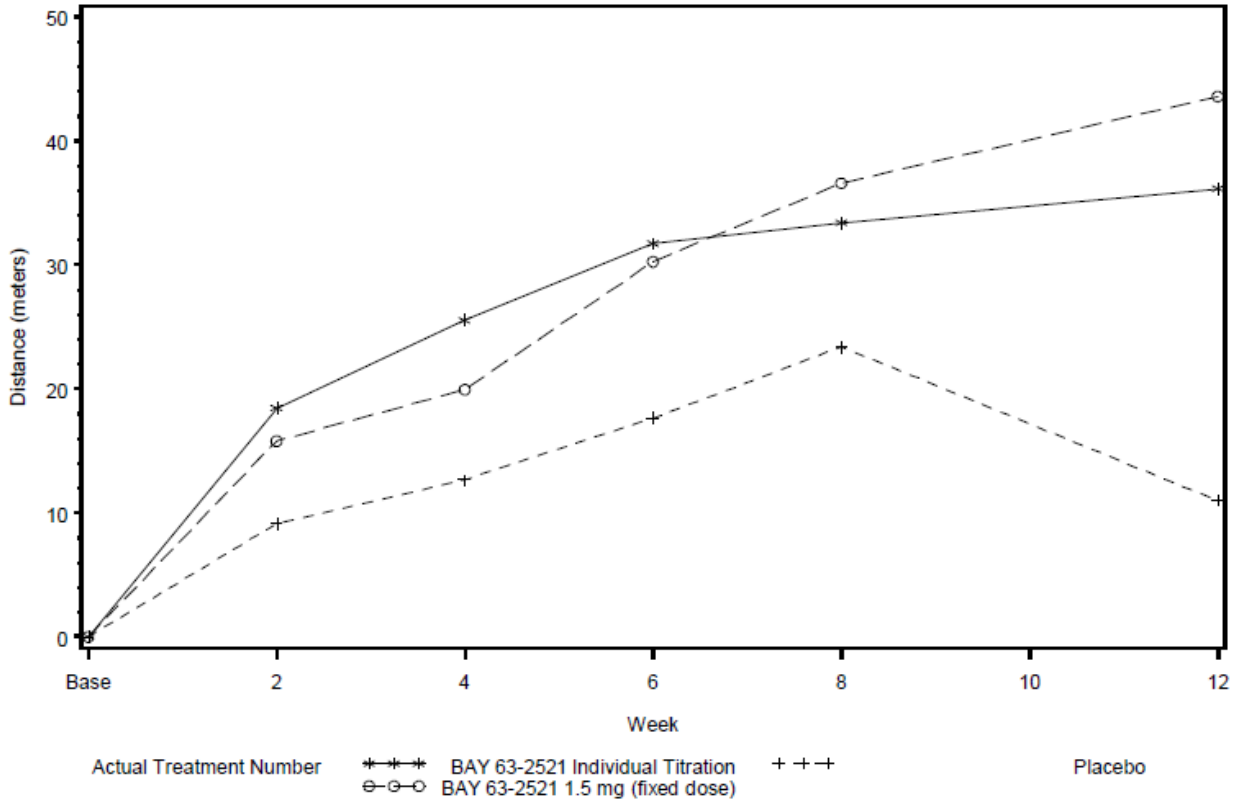
Statistic	Riociguat 1.0–2.5 mg N=254	Placebo N=126	Riociguat 1.0–1.5 mg N=63
Baseline			
Mean (SD)	361.4 (67.7)	367.8 (74.6)	363.2 (66.6)
Median (Min-Max)	374.5 (160-468)	391.0 (150-450)	385.0 (158-448)
Change from baseline to last visit			
Mean (SD)	29.6 (65.8)	–5.6 (85.5)	31.1 (79.3)
Median (Min-Max)	30.0 (–430-279)	8.5 (–400-204)	32.0 (–415-190)
Treatment comparison	**Riociguat 1.0-2.5 mg – placebo**		
LS mean difference	35.78		
95% CI	20.06 to 51.51		
p-value (ANCOVA)	<0.0001		
p-value (stratified Wilcoxon test)	<0.0001		
Treatment comparison	**Riociguat 1.0-1.5 mg – placebo**		
LS mean difference	37.35		
95% CI	11.93 to 62.77		
p-value (ANCOVA)	0.0042		
p-value (stratified Wilcoxon test)	<0.0001		

ANCOVA model with baseline value, treatment group, region, and stratification group as fixed effects, stratified Wilcoxon test by region and stratification group
Last visit = Last observed value (not including follow-up) for subjects who completed the study or withdrew, except imputed worst value in case of death or clinical worsening without a termination visit or a measurement at that termination visit. Worst value imputation for 6MWD at last visit was performed for 2 subjects in the riociguat 1.0-2.5 mg group and 6 subjects in the placebo group. Details can be found in Table 16.1.9.3/3.
LS = least squares
Source: Tables 14.2.2/1, 14.2.2/2 and 14.2.2/4 A62510 (Study 12934 in Module 5.3.5.1)
Table 14.2.2 / 1, Table 14.2.2 / 2and Table 14.2.2 / 3

Note that although the primary efficacy endpoint had been defined only to compare the IDT result with placebo, the incremental benefit of the 1.5 mg TID capped arm was numerically greater, with small p-values by either the ANCOVA or the Wilcoxon testing procedure.

The sponsor also provided the following graphical display of the six minute walk results by visit:

Figure 38: PATENT-1 mean 6MWD change from BL (mITT set, FSR fig 9-1 pg 110)

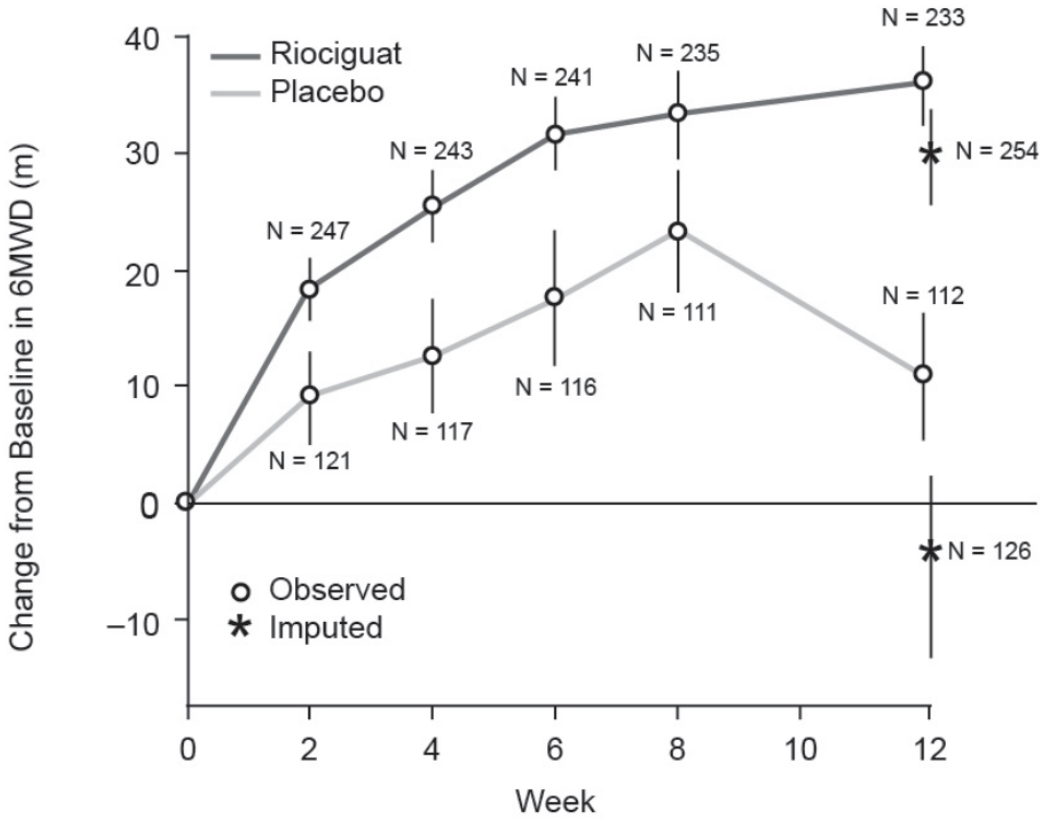


Number of subjects at each timepoint

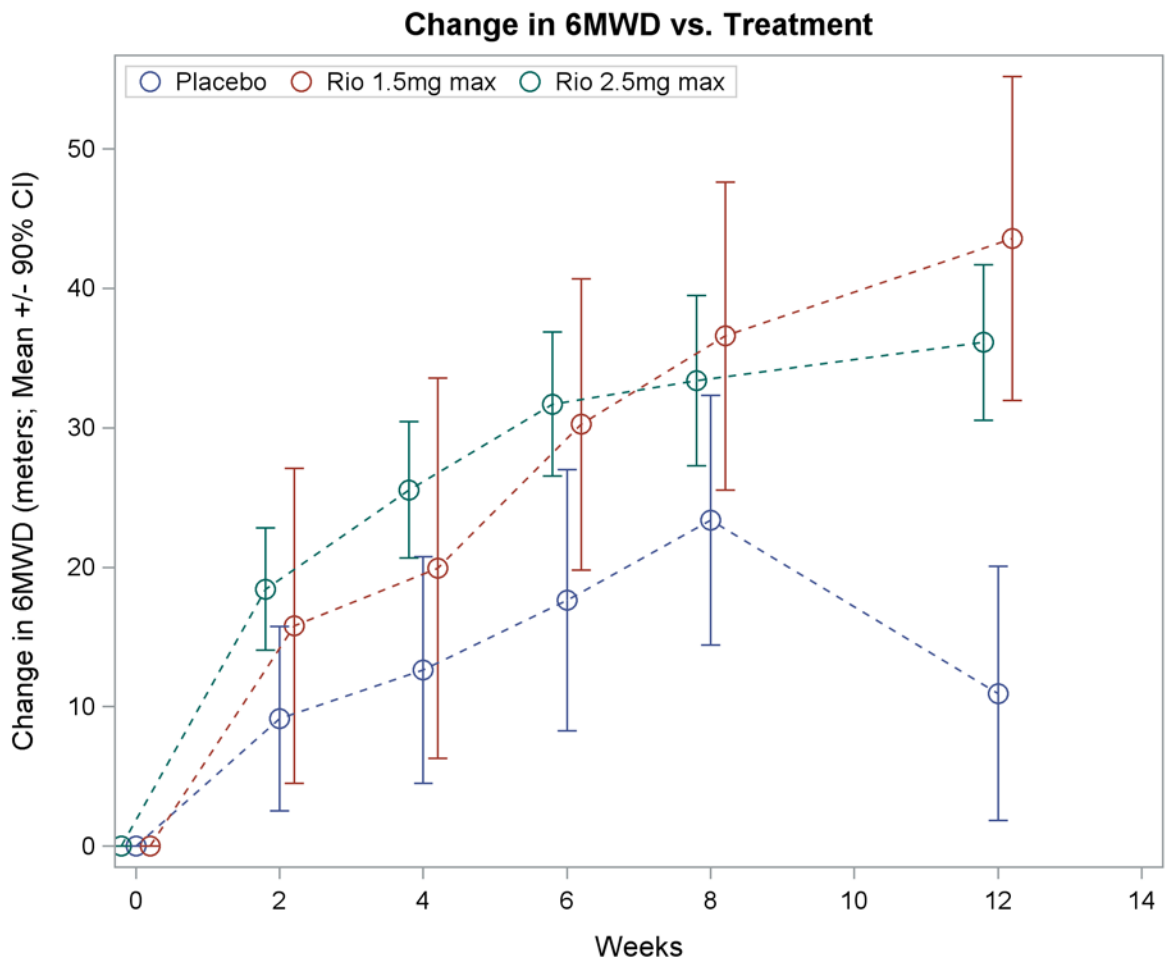
	Week 2	Week 4	Week 6	Week 8	Week 12
Riociguat 1.0-2.5 mg (individual dose titration)	N=247	N=243	N=241	N=235	N=233
Placebo	N=121	N=117	N=116	N=111	N=112
Riociguat 1.0-1.5 mg (capped titration)	N=63	N=59	N=56	N=56	N=56

The proposed product label contains the following graphical display of by-visit results that includes standard error bars, showing only the placebo arm and the IDT arm results:

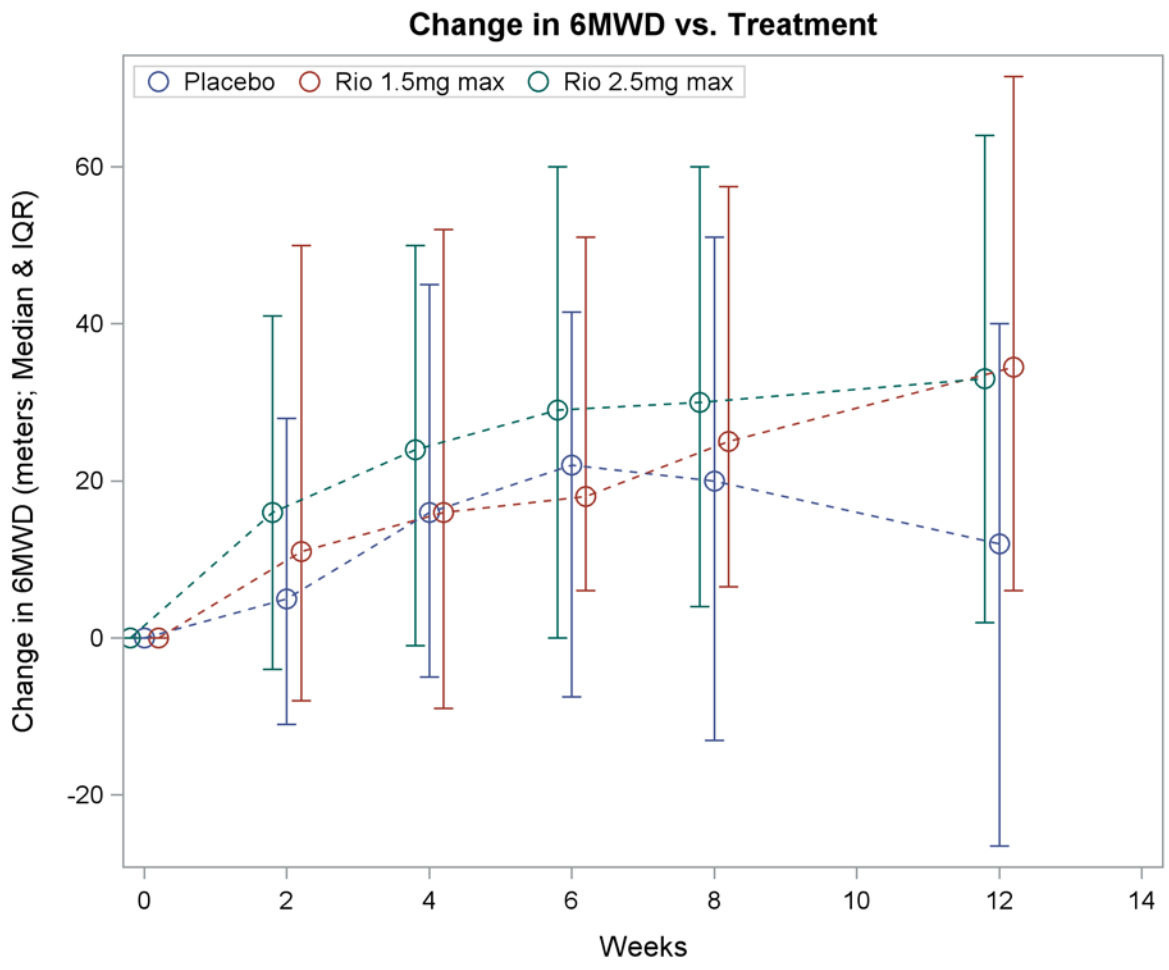
PATENT-1 Efficacy IDT, Label



The primary analyses by the sponsor were reproduced/confirmed by FDA biometrics and FDA clinical pharmacology. The following figure displays FDA's un-adjusted reanalysis of the raw primary efficacy datasets from PATENT-1:



Similar results were obtained using median values and interquartile ranges, as are shown in the following figure:



As was the case with the primary mITT analysis, efficacy for the 1.5 mg TID capped dose arm was likewise similar to the higher IDT dosing in the per protocol analysis, as shown in the following table:

Table 42: PATENT-1 6MWD change from BL to LV (PP set, Resp to FDA IR-26, table 9-3A pg 3)

Statistic	Riociguat 1.0–2.5 mg N=218	Placebo N=106	Riociguat 1.0–1.5 mg N=55
Baseline			
Mean (SD)	364.0 (65.2)	373.5 (69.0)	362.2 (69.0)
Median (Min-Max)	375.0 (160-450)	394.5 (155-450)	385.0 (158-448)
Change from baseline to last visit			
Mean (SD)	36.3 (55.7)	2.9 (73.0)	35.3 (81.5)
Median (Min-Max)	35.0 (–180-279)	12.0 (–348-204)	34.0 (–415-190)
Treatment comparison	**Riociguat 1.0-2.5 mg – placebo**		
LS mean difference	33.52		
95% CI	18.99 to 48.04		
p-value (ANCOVA)	<0.0001		
p-value (stratified Wilcoxon test)	<0.0001		
Treatment comparison	**Riociguat 1.0-1.5 mg – placebo**		
LS mean difference	32.12		
95% CI	7.18 to 57.07		
p-value (ANCOVA)	0.0119		
p-value (stratified Wilcoxon test)	0.0001		

ANCOVA model with baseline value, treatment group, region, and stratification group as fixed effects, stratified Wilcoxon test by region and stratification group
Last visit = Last observed value (not including follow-up) for subjects who completed the study or withdrew, except imputed worst value in case of death or clinical worsening without a termination visit or a measurement at that termination visit
Source: Tables 14.2.2/7, 14.2.2/8 and 14.2.2/10 A62510 (Study 12934 in Module 5.3.5.1) Table 14.2.2 / 4; Table 14.2.2 / 5 and Table 14.2.2 / 6

While the overall treatment effect of the IDT arm was maintained in multiple sensitivity analyses, the benefit that was maintained for the 1.5 mg TID fixed dose arm tended to be numerically greater, as can be seen in the following two tables:

Table 43: PATENT-1 6MWD (m) change from BL sensitivity analyses for IDT dosing arm (mITT set, FSR table 9-4 pg 112)

Analysis	Estimated treatment difference [a]	95% CI
Mixed model at Visit 6	30.02	16.11 to 43.94
Multiple imputation – Fixed penalty: Riociguat 1.0-2.5 mg –60 m and placebo –60 m	33.10	18.49 to 47.71
Multiple imputation – Decreasing slope: Riociguat 1.0-2.5 mg –20 m and placebo –20 m per visit	35.03	20.49 to 49.57
Multiple imputation – Fixed penalty: Riociguat 1.0-2.5 mg –60 m and placebo –0 m	26.31	12.32 to 40.30
Multiple imputation – Decreasing slope: Riociguat 1.0-2.5 mg –20 m and placebo –0 m per visit	27.16	13.36 to 40.96
Robust regression	30.00	18.91 to 41.10

[a] Riociguat 1.0 2.5 mg – placebo
Source: Tables 14.2.4/86, 14.2.4/87, and 14.2.4/91

Table 44: PATENT-1 6MWD (m) change from BL sensitivity analyses for 1.5 mg capped dosing arm (mITT set, Resp to FDA IR-26, table 9-4A pg 4)

Analysis	Estimated treatment difference [a]	95% CI
Mixed model at Visit 6	36.27	17.77 to 54.76
Multiple imputation – Fixed penalty: Riociguat 1.0-1.5 mg –60 m and placebo –60 m	37.62	15.45 to 59.79
Multiple imputation – Decreasing slope: Riociguat 1.0-1.5 mg –20 m and placebo –20 m per visit	39.24	16.82 to 61.67
Multiple imputation – Fixed penalty: Riociguat 1.0-1.5 mg –60 m and placebo –0 m	30.86	10.33 to 51.39
Multiple imputation – Decreasing slope: Riociguat 1.0-1.5 mg –20 m and placebo –0 m per visit	31.51	11.02 to 52.00
Robust regression	32.61	16.36 to 48.87

[a] Riociguat 1.0 1.5 mg – placebo
Source: Table 14.2.4 / 37; Table 14.2.4 / 38; Table 14.2.4 / 39

Finally, as examined by FDA biometrics, there were no individual sites, countries, or regions that if removed would have neutralized the overall treatment effect (data not shown).

6.2.5 Analysis of Secondary Endpoints(s)

Time to Clinical Worsening (TTWC)

Clinical worsening (CW) was defined by the occurrence of any of the following clinical events:

- Death (all-cause mortality)
- Heart/lung transplantation
- Rescue pulmonary endarterectomy for persistent worsening of PH
- Hospitalization for persistent worsening of PH
- New PH therapy for worsened PH (ERA, PDE5i,Prost)
- Persistent decrease of more than 15 % from baseline or more than 30% compared to the last study related 6MWD due to worsening PH
    - Must be confirmed by second measure after 14 days
- Persistent worsening of functional class due to deterioration of Pulmonary Hypertension
    - deteriorate from class II or III to class IV
    - Must be confirmed by second measure after 14 days

Any subject suffering a clinical worsening event was withdrawn from the trial, and if no termination visit testing was performed, worst case imputation of final visit data used for the purpose of endpoint analyses (see above, imputation of missing data, page 76 of this review). The number of CW events was very small, but percentages of patients experiencing these events is numerically lower for both the IDT and the 1.5 mg TID capped dosing arm, and statistically lower for the larger IDT arm. The analysis of CW events from PATENT-1 is shown in the table below (p-values for TTCW):

Table 45: CHEST-1 Clinical Worsening (mITT set, Resp to FDA IR-26, table 9-11A pg 8)

Event	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
Any clinical worsening	3	(1.2%)	8	(6.3%)	2	(3.2%)
Hospitalization due to PH	1	(0.4%)	4	(3.2%)	0	–
Start of new PH treatment	1	(0.4%)	5	(4.0%)	1	(1.6%)
Decrease in 6MWD due to PH	1	(0.4%)	2	(1.6%)	1	(1.6%)
Persistent worsening of functional class due to PH	0	–	1	(0.8%)	0	–
Death	2	(0.8%)	3	(2.4%)	1	(1.6%)
Treatment comparison	**Riociguat 1.0-2.5 mg – placebo**					
p-value (stratified log-rank test)	0.0046					
p-value (Mantel-Haenszel estimate)	0.0285					
Treatment comparison	**Riociguat 1.0-1.5 mg – placebo**					
p-value (stratified log-rank test)	0.3939					
p-value (Mantel-Haenszel estimate)	0.3258					

The mean/median results for the remaining secondary endpoints are summarized in the following table:

Table 46: PATENT-1 mean/median change from BL to LV for secondary outcome parameters

	RIO IDT	Rio Capped	Placebo
PVR (dyn*s*cm^{-5})	-223/-183	-168/-147	-9/-29
NT-proBNP (pg/mL)	-198/-44	-472/-48	232/27
Borg Scale	-0.44/0	-0.33/0	0.09/0
EQ^{-5}D-u	0.033/0	0.078/0	-0.032/0
EQ^{-5}D-v	3.6/0	6.1/5.0	-1.4/0
LPH-total	-6.0/-4.0	-10 /-7.5	0.36/0
LPH-Physical	-3.1/-3.0	-4.9/-4.0	0.54/1.0
LPH-Emotional	-1.3/-1.0	-2.2/-1.5	-0.39/0

P-values for these secondary efficacy endpoints, together with a determination of the significance of the finding in hierarchical testing, are shown below (IDT arm only):

Table 47: PATENT-1 secondary efficacy endpoints, hierarchical testing (mITT set, IDT arm only, FSR table 9-6 pg 118)

Variable	Treatment effect ANCOVA p-value	Shapiro-Wilk test p-value	Stratified Wilcoxon test p-value	Statistically significant	Statistically significant in hierarchical testing
6MWD (primary)	<0.0001	0.0001	**<0.0001**	Yes	Yes
PVR	<0.0001	0.0001	**<0.0001**	Yes	Yes
NT-proBNP	0.0157	0.0001	**<0.0001**	Yes	Yes
WHO functional class	–	–	**0.0033**	Yes	Yes
Time to clinical worsening	0.0285 [a]	–	**0.0046** [b]	Yes	Yes
Borg CR 10 scale [c]	–	–	**0.0022**	Yes	Yes
EQ-5D questionnaire	0.0197	0.0001	**0.0663**	No	No
LPH questionnaire	0.0009	0.0001	**0.0019**	Yes	No

P-values used to determine statistical significance are given in bold.
[a] Mantel-Haenszel estimate p-value for incidence of clinical worsening
[b] Stratified log-rank test p-value for time to clinical worsening.
[c] Subjects enrolled before amendment 4 used the Modified Borg Dyspnoea Scale.
Source: Tables 14.2.2/2, 14.2.2/3, 14.2.2/4, 14.2.3/2, 14.2.3/3, 14.2.3/4, 14.2.3/14, 14.2.3/15, 14.2.3/16, 14.2.3/26, 14.2.3/32, 14.2.3/33, 14.2.3/40, 14.2.3/44, 14.2.3/45, 14.2.3/46, 14.2.3/56, 14.2.3/57, and 14.2.3/58.

P-values for some of these secondary analyses for the 1.5 mg TID capped arm were larger, as would be expected, due to the smaller sample size, as shown below:

Table 48: PATENT-1 secondary efficacy endpoints, hierarchical testing (mITT set, 1.5 mg TID capped arm only, Resp to FDA IR-26, table 9-4A pg 4)

Variable	Treatment effect ANCOVA p-value	Shapiro-Wilk test p-value	Stratified Wilcoxon test p-value	Statistically significant	Statistically significant in hierarchical testing
6MWD (primary)	0.0042	0.0001	**<0.0001**	Yes	Yes
PVR	0.0020	0.0001	**<0.0001**	Yes	Yes
NT-proBNP	<0.0001	0.0001	**<0.0001**	Yes	Yes
WHO functional class	–	–	**0.0674**	No	No
Time to clinical worsening	0.3258 [a]	–	**0.3939** [b]	No	No
Borg CR 10 scale [c]	–	–	**0.1068**	No	No
EQ-5D questionnaire	0.0523	0.0001	**0.0914**	No	No
LPH questionnaire	0.0005	0.0001	**<0.0001**	Yes	No

Combining the two active treatment arms from PATENT-1 produced the following hierarchical analysis of secondary outcomes:

Table 49: PATENT-1 secondary efficacy endpoints, hierarchical testing (mITT set, combined IDT and 1.5 mg TID capped riociguat treatment groups vs. placebo, Resp to FDA IR-28, table 1 pg 2)

Variable	Treatment effect ANCOVA p-value	Shapiro-Wilk test p-value	Stratified Wilcoxon test p-value	Statistically significant	Statistically significant in hierarchical testing
6MWD (primary)	<0.0001	0.0001	**<0.0001**	Yes	Yes
PVR	<0.0001	0.0001	**<0.0001**	Yes	Yes
NT-proBNP	0.0027	0.0001	**<0.0001**	Yes	Yes
WHO functional class	–	–	**0.0029**	Yes	Yes
Time to clinical worsening	0.0422 [a]	–	**0.0072** [b]	Yes	Yes
Borg CR 10 scale [c]	–	–	**0.0025**	Yes	Yes
EQ-5D questionnaire	0.0095	0.0001	**0.0378**	Yes	Yes
LPH questionnaire	0.0002	0.0001	**0.0001**	Yes	Yes

An identical result is obtained for hierarchical testing of secondary endpoints after integrating CHEST-1 and PATENT-1 results, as shown below:

Table 50: **POOL-1 (studies 11348 [CHEST-1] and 12934 [PATENT-1]) secondary efficacy endpoints, hierarchical testing (mITT set, combined riociguat treatment groups vs. placebo, Resp to FDA IR-28, table 2 pg 3)**

Variable	Treatment effect ANCOVA p-value	Shapiro-Wilk test p-value	Stratified Wilcoxon test p-value	Statistically significant	Statistically significant in hierarchical testing
6MWD (primary)	<0.0001	0.0001	**<0.0001**	Yes	Yes
PVR	<0.0001	0.0001	**<0.0001**	Yes	Yes
NT-proBNP	0.0003	0.0001	**<0.0001**	Yes	Yes
WHO functional class	–	–	**<0.0001**	Yes	Yes
Time to clinical worsening	0.0156 [a]	–	**0.0031** [b]	Yes	Yes
Borg CR 10 scale [c]	–	–	**<0.0001**	Yes	Yes
EQ-5D questionnaire	<0.0001	0.0001	**<0.0001**	Yes	Yes
LPH questionnaire	<0.0001	0.0001	**<0.0001**	Yes	Yes

6.2.6 Other Endpoints

Changes in invasive hemodynamic parameters at right heart cath other than PVR are shown in the table below for the IDT arm of PATENT-1. The combination of lower pulmonary artery and aortic pressures, together with an increase in CO, drove large reductions in resistances in both circuits:

Table 51: PATENT-1 hemodynamics, change from baseline to last visit vs. placebo (mITT set, IDT arm only, FSR table 9-8, pg 121)

Parameter (unit)	Mean change		LS mean difference	95% CI	ANCOVA	Stratified Wilcoxon test
	RIO	PBO			p-value	p-value
PCWP (mmHg)	1.08	0.46	0.41	–0.36 to 1.18	0.2972	0.0830
RAP (mmHg)	–0.20	0.97	–1.01	–2.15 to 0.13	0.0832	0.0734
PAPsyst (mmHg)	–5.39	0.78	–6.73	–9.43 to –4.04	<0.0001	<0.0001
PAPdiast (mmHg)	–3.19	–1.12	–2.41	–4.15 to –0.68	0.0066	0.0110
PAPmean (mmHg)	–3.93	–0.50	–3.83	–5.61 to –2.06	<0.0001	0.0002
MAP (mmHg)	–8.54	–1.40	–7.25	–9.60 to –4.90	<0.0001	<0.0001
SvO_2 (%)	3.15	–2.33	5.02	3.20 to 6.84	<0.0001	<0.0001
CO (L/min)	0.93	–0.01	0.93	0.70 to 1.15	<0.0001	<0.0001
CI (L/min/m^2)	0.54	–0.02	0.56	0.44 to 0.69	<0.0001	<0.0001
PVR (dyn*s*cm^{-5})	–223	–8.9	–225.72	–281.37 to –170.08	<0.0001	<0.0001
PVRI (dyn*s*cm^{-5}*m^2)	–374	–22.4	–376.81	–468.90 to –284.72	<0.0001	<0.0001
SVR (dyn*s*cm^{-5})	–448	–67.5	–394.57	–472.95 to –316.19	<0.0001	<0.0001
SVRI (dyn*s*cm^{-5}*m^2)	–753	–130	–675.31	–800.84 to –549.79	<0.0001	<0.0001

ANCOVA model with baseline value, treatment group, region, and stratification group as fixed effects, stratified Wilcoxon test by region and stratification group
Last visit = Last observed value post-baseline (not including follow-up)
RIO=Riociguat 1.0-2.5 mg, PBO=Placebo
Source:
PVR: Tables 14.2.3/1, 14.2.3/2 and 14.2.3/4
Other parameters: Tables 14.2.4/1, 14.2.4/2, 14.2.4/4, 14.2.4/5, 14.2.4/6, 14.2.4/8, 14.2.4/9, 14.2.4/10, 14.2.4/12, 14.2.4/13, 14.2.4/14, 14.2.4/16, 14.2.4/17, 14.2.4/18, 14.2.4/20, 14.2.4/21, 14.2.4/22, 14.2.4/24, 14.2.4/25, 14.2.4/26, 14.2.4/28, 14.2.4/29, 14.2.4/30, 14.2.4/32, 14.2.4/33, 14.2.4/34, 14.2.4/36, 14.2.4/37, 14.2.4/38, 14.2.4/40, 14.2.4/41, 14.2.4/42, 14.2.4/44, 14.2.4/45, 14.2.4/46, and 14.2.4/48

It is notable that hemodynamic responses in the 1.5 mg TID capped arm were qualitatively identical, though all were somewhat smaller in magnitude, including the fall in mean systemic arterial pressure, as can be seen comparing the IDT responses in table 51 above with the 1.5 mg TID capped dose responses in table 52 below:

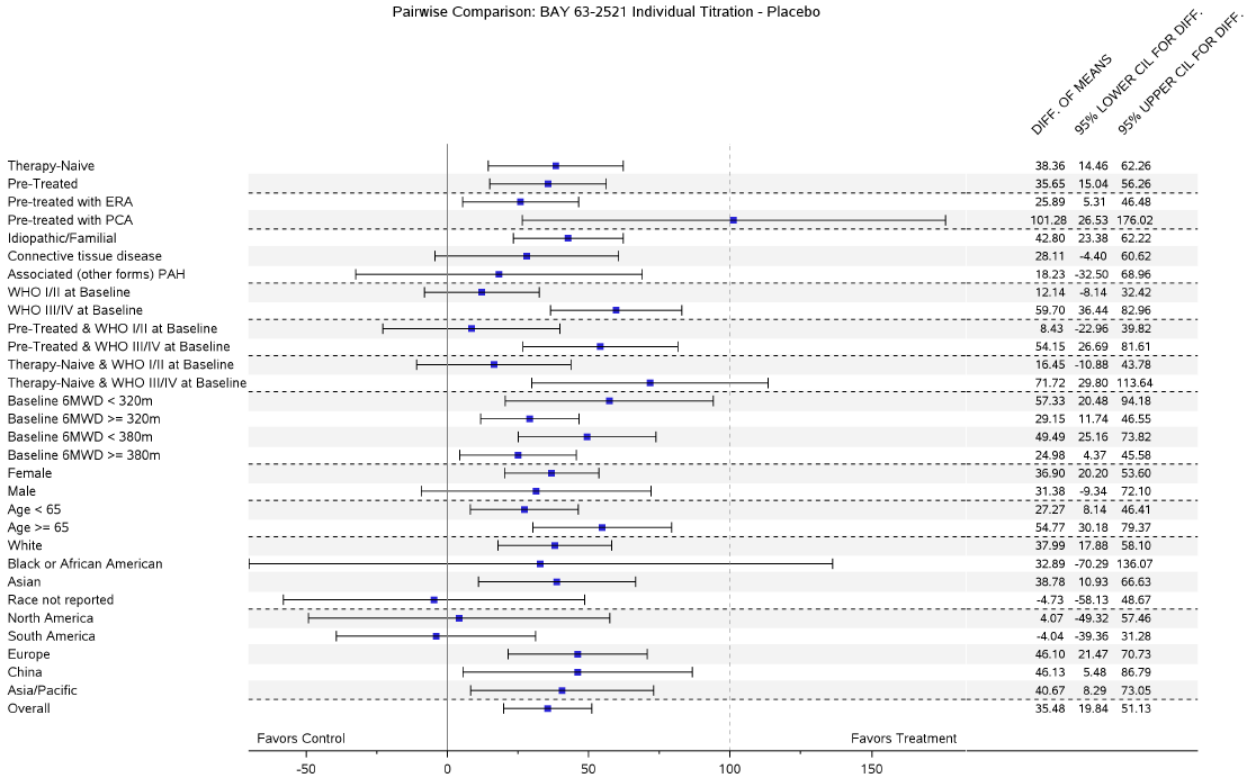
Table 52: : PATENT-1 hemodynamics, change from baseline to last visit vs. placebo (mITT set, 1.5 mg TID capped arm only, Resp to FDA IR-26, table 9-8A pg 7)

Parameter (unit)	Mean change		LS mean difference	95% CI	ANCOVA	Stratified Wilcoxon test
	RIO	PBO			p-value	p-value
PCWP (mmHg)	1.29	0.46	0.69	-0.54 to 1.93	0.2699	0.0711
RAP (mmHg)	–0.75	0.97	–1.41	–2.76 to -0.06	0.0406	0.0219
PAPsyst (mmHg)	–5.81	0.78	–6.01	–9.94 to –2.08	0.0029	0.0004
PAPdiast (mmHg)	–3.88	–1.12	–2.26	–5.12 to 0.61	0.1215	0.0063
PAPmean (mmHg)	–4.49	–0.50	–3.53	–6.36 to –0.70	0.0148	0.0031
MAP (mmHg)	–6.39	–1.40	–5.97	–9.46 to –2.47	0.0009	0.0067
SvO_2 (%)	3.12	–2.33	5.16	2.46 to 7.87	0.0002	<0.0001
CO (L/min)	0.42	–0.01	0.56	0.22 to 0.90	0.0015	0.0154
CI (L/min/m^2)	0.25	–0.02	0.35	0.16 to 0.54	0.0003	0.0155
PVR (dyn*s*cm^{-5})	–168	–8.9	–151.47	–246.48 to –56.46	0.0020	<0.0001
PVRI (dyn*s*cm^{-5}*m^2)	–282	–22.4	–244.42	–407.99 to –80.84	0.0036	<0.0001
SVR (dyn*s*cm^{-5})	–233	–67.5	–288.83	–416.75 to –160.92	<0.0001	0.0071
SVRI (dyn*s*cm^{-5}*m^2)	–391	–130	–461.72	–675.29 to –248.15	<0.0001	0.0044

6.2.7 Subpopulations

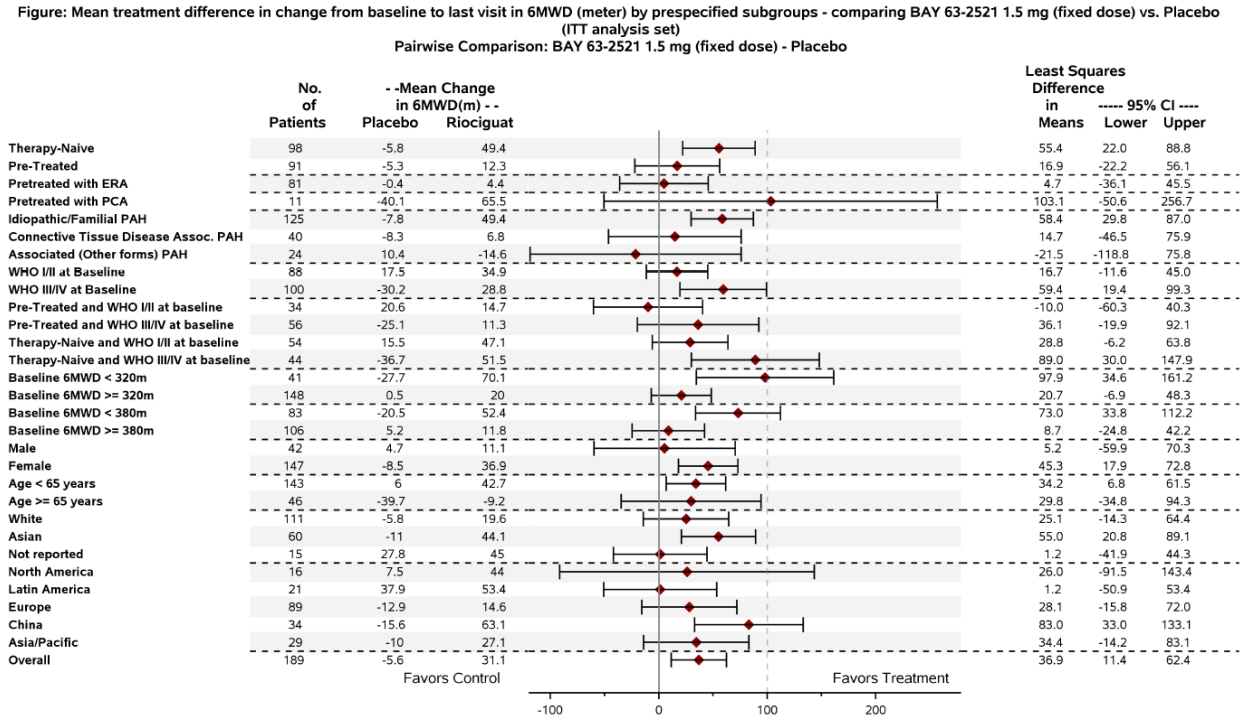
Point estimates for riociguat treatment effect were positive for almost all subgroups for the IDT arm analysis versus placebo (exceptions being “race not reported and South America), and the lower bound of the 95% CI for most of these analyses was greater than zero:

Figure 39: PATENT-1 mean treatment difference, 6MWD (m) change from BL to last observation to week 12, subgroups (mITT set, FSR fig 9-2 pg 115)



Subgroup analyses for the small 1.5 mg TID capped arm showed the expectedly larger confidence intervals, but qualitatively, the results were very similar, as seen in the figure below:

Figure 40: PATENT-1 mean treatment difference, 6MWD (m) change from BL to last observation to week 12, subgroups (mITT set, 1.5 mg TID capped arm, Resp to FDA IR-26 pg 119)



6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

PATENT-1 was the only pivotal trial to test the IDT dosing strategy versus placebo in the same trial with a lower dose (1.5 mg TID capped), though the capped dose arm was small and underpowered for some outcome measures. Clinical outcomes measures were not demonstrated to be different between the two active arms, and the lower dose performed just as well as the higher dose on the primary efficacy outcome 6MWD analysis (see sections 6.2.4 through 6.2.7 above).

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of effect was evaluated in the PATENT-2 LTE. At week 12 of the extension study, patients from the placebo arm of the double-blind study demonstrated an incremental benefit over their original baseline 6MWD result that was in line with the clinical benefit seen by the riociguat-treated group in the double-blind trial, as is seen in the table below:

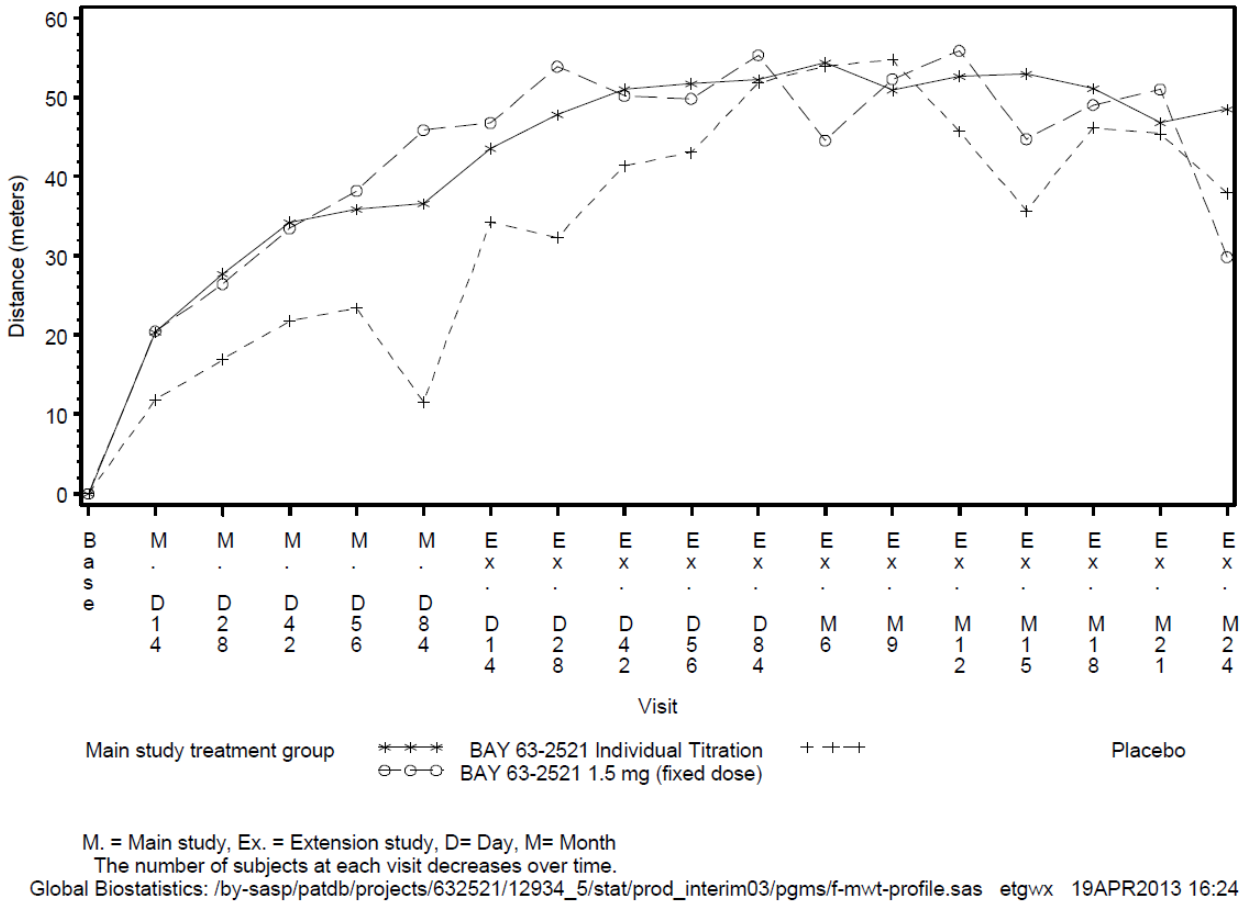
Table 53: PATENT-2 mean change 6MWD (m), BL to LV (week 12 LTE) (LTE safety set, month 4 clinical overview addendum, table 9-7 pg 14)

Statistic	Former Riociguat IDT 1.0–2.5 mg N=231	Former Placebo N=109	Former Riociguat capped titration 1.0–1.5 mg N=56	Total N=396
Baseline	n=231	n=109	n=56	n=396
Mean (SD)	363.7 (67.0)	378.0 (65.5)	358.9 (68.4)	366.9 (67.0)
Median (Min to Max)	375.0 (160 to 468)	395.0 (174 to 450)	376.0 (158 to 448)	380.0 (158 to 468)
Change from baseline to PATENT-1 Visit 6 (12 weeks, observed values)	n=228	n=108	n=55	n=391
Mean (SD)	36.6 (52.0)	11.5 (58.0)	45.9 (50.5)	31.0 (54.8)
Median (Min to Max)	34.0 (–138 to 279)	12.5 (–142 to 204)	35.0 (–35 to 190)	28.0 (–142 to 279)
Change from baseline to last visit (week 12) in PATENT-2	n=231	n=109	n=56	n=396
Mean (SD)	51.9 (61.1)	44.6 (73.8)	54.0 (66.3)	50.2 (65.5)
Median (Min to Max)	46.0 (–105 to 309)	37.0 (–233 to 292)	52.0 (–86 to 279)	46.0 (–233 to 309)

Last visit (week 12) = last observed value up to extension week 12 (not including follow-up), except imputed worst value in case of death or clinical worsening prior to reaching extension visit week 12 without any subsequent visit.
Source: Cut-off Mar 2013: (Study 12935 in Module 5.3.5.3) Table 14.2.2/1

Persistence of benefit in the LTE was demonstrated through month 9 of follow-up (and probably well beyond), as is shown in the following figure demonstrates:

Figure 41: PATENT-2 6MWD mean change from BL by visit (LTE safety set, month 4 clinical overview addendum fig 9-3 pg 15)



Source: Cut-off Mar 2013: (Study 12935 in Module 5.3.5.3) Figure 14.2.2./1

Reviewer's comment: From figure 40 above, several observations are relevant:

- *The continued improvement of both active arms in the double blind trial following day 56 may be due to hysteresis effect, training effect, or dropout effect*
- *The IDT and capped dose 6MWD curves are no different through the LTE period*
- *As was the case with CHEST-1, a striking treatment effect is noted on placebo patients from the double-blind trial who roll over to the main trial, lending internal consistency to the primary efficacy outcome of PATENT-1.*

For further evidence of persistence of benefit, the analysis of the incidence of clinical worsening events in the CHEST-2 LTE to the Mar 2013 cut-off demonstrates a similar rate of these events in the group that rolled over from placebo as compared to the group receiving active treatment in the double-blind trial, suggesting that there was no long-term harm done by starting riociguat therapy in the open label trial in previously treatment-naïve patients, as shown in the following table:

Table 54: PATENT-2 subjects with clinical worsening (LTE safety set, 4 month overview addendum table 9-8 pg 16)

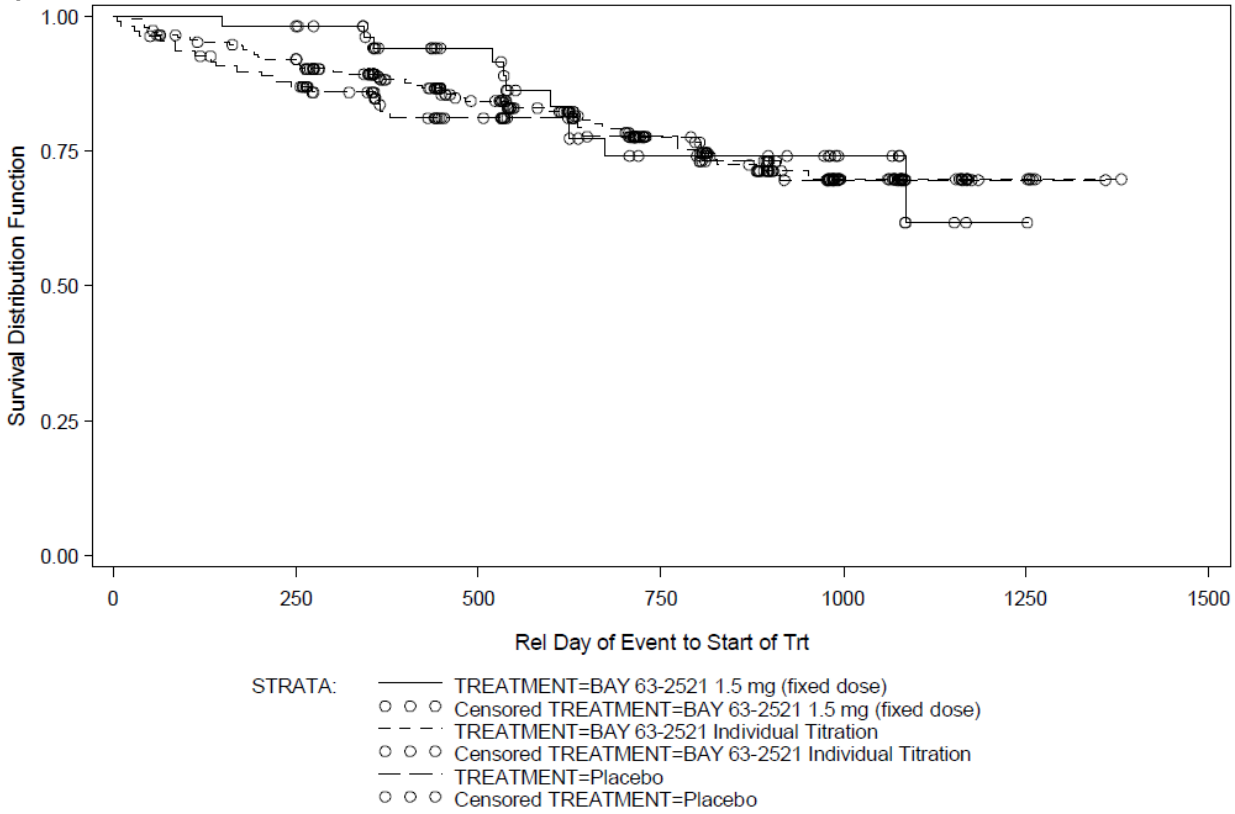
Event	Former Riociguat IDT 1.0–2.5 mg N=231 (100%)		Former Placebo N=109 (100%)		Former Riociguat capped titration 1.0-1.5 mg N=56 (100%)		Total N=396 (100%)	
Number of subjects (%) with clinical worsening	49	(21.2%)	24	(22.0%)	11	(19.6%)	84	(21.2%)
Heart/Lung transplantation	1	(0.4%)	0	-	1	(1.8%)	2	(0.5%)
Hospitalization due to PH	25	(10.8%)	11	(10.1%)	5	(8.9%)	41	(10.4%)
Start of new PH treatment	34	(14.7%)	17	(15.6%)	9	(16.1%)	60	(15.2%)
Decrease in 6MWD due to PH	6	(2.6%)	3	(2.8%)	1	(1.8%)	10	(2.5%)
Persistent worsening of functional class due to PH	4	(1.7%)	1	(0.9%)	0	-	5	(1.3%)
Death	14	(6.1%)	9	(8.3%)	4	(7.1%)	27	(6.8%)

Note: Numbers denote number and percentage of subjects per treatment group.

Source: Cut-off Mar 2013: (Study 12935 in Module 5.3.5.3) Table 14.2.2/5

K-M analysis of time to first clinical worsening event confirms similar rates of these events over time, and does not suggest an early attrition of patients who rolled over from placebo to IDT therapy, as shown in the figure below:

Figure 42: PATENT-2 K-M TTCW (LTE safety set, 4 month clinical overview addendum fig 9-4 pg 17)



Source: Cut-off Mar 2013: (Study 12935 in Module 5.3.5.3) Figure 14.2.2./2

An analysis of the various types of CW events that were seen in CHEST-2 as a function of exposure is shown in the following table:

Table 55: PATENT-2 TTCW event/100 p-y (LTE safety set, month 4 clinical overview addendum table 9-9 pg 18)

Event	Former Riociguat IDT 1.0–2.5 mg N=231		Former Placebo N=109		Former Riociguat capped titration 1.0-1.5 mg N=56		Total N=396	
	n	r/100sy	n	r/100sy	n	r/100sy	n	r/100sy
Any clinical worsening	121	28.69	54	28.72	22	20.24	197	27.42
Heart/Lung transplantation	1	0.24	0	-	1	0.92	2	0.28
Hospitalization due to PH	35	8.30	13	6.91	5	4.60	53	7.38
Start of new PH treatment	61	14.46	27	14.36	11	10.12	99	13.78
Decrease in 6MWD due to PH	6	1.42	4	2.13	1	0.92	11	1.53
Persistent worsening of functional class due to PH	4	0.95	1	0.53	0	-	5	0.70
Death	14	3.32	9	4.79	4	3.68	27	3.76

Note: N in the header is the number of subjects. The total number of events are presented in the body of the table, a subject may have more than one event. There may also be more than one event within certain categories, eg more than one hospitalization.
Rate per 100 subject years (r/100sy) is the number of events divided by (total drug exposure in years / 100).

Source: Cut-off Mar 2013: (Study 12935 in Module 5.3.5.3) Table 14.2.2/6

Death rates of patient rolling over from placebo to active therapy remained similar to those patients who had continued active therapy from the main trial to the LTE over three years of follow-up, as shown from the table below:

Table 56: PATENT-2 survival and survival w/o clinical worsening events from K-M (LTE safety set, month 4 clinical overview addendum table 9-10 pg 19)

Time Point	Main study treatment group	Survival estimate (%) (survival)	95% CIL	Survival estimate (%) (without clinical worsening)	95% CIL
1 year	Riociguat IDT	97.70	94.56 – 99.04	88.27	83.24 – 91.87
	Placebo	94.93	88.22 – 97.86	83.59	74.87 – 89.50
	Riociguat capped titration	96.25	85.80 – 99.05	94.13	82.86 – 98.07
	Total	96.76	94.36 – 98.15	87.82	84.06 – 90.74
2 years	Riociguat IDT	93.47	88.23 – 96.42	77.61	70.62 – 83.13
	Placebo	91.08	82.81 – 95.48	77.72	67.44 – 85.10
	Riociguat capped titration	96.25	85.80 – 99.05	74.13	56.68 – 85.39
	Total	93.26	89.71 – 95.62	77.08	71.82 – 81.49
3 years	Riociguat IDT	91.26	84.89 – 95.02	69.81	61.11 – 76.93
	Placebo	88.80	78.86 – 94.23	69.66	56.08 – 79.78
	Riociguat capped titration	91.88	74.51 – 97.59	61.77	32.67 – 81.27
	Total	90.63	86.01 – 93.77	67.83	59.54 – 74.79

Note: CIL = Confidence interval limit.
Confidence intervals are based on a loglog transformation of the survival function.
Note: The numbers of patients who completed the respective periods are: 1 year:327 subjects (192 riociguat IDT; 85 placebo; 50 riociguat capped titration); 2 years: 184 subjects (108 riociguat IDT; 48 placebo; 28 riociguat capped titration); 3 years 58 subjects (35 riociguat IDT; 13 placebo; 10 riociguat capped titration) derived from Cut-off Mar 2013: (Study 12935 in Module 5.3.5.3) Table 14.2.2/1
Source: Cut-off Mar 2013: (Study 12935 in Module 5.3.5.3) Table 14.2.2/8 and Table 14.2.2/9

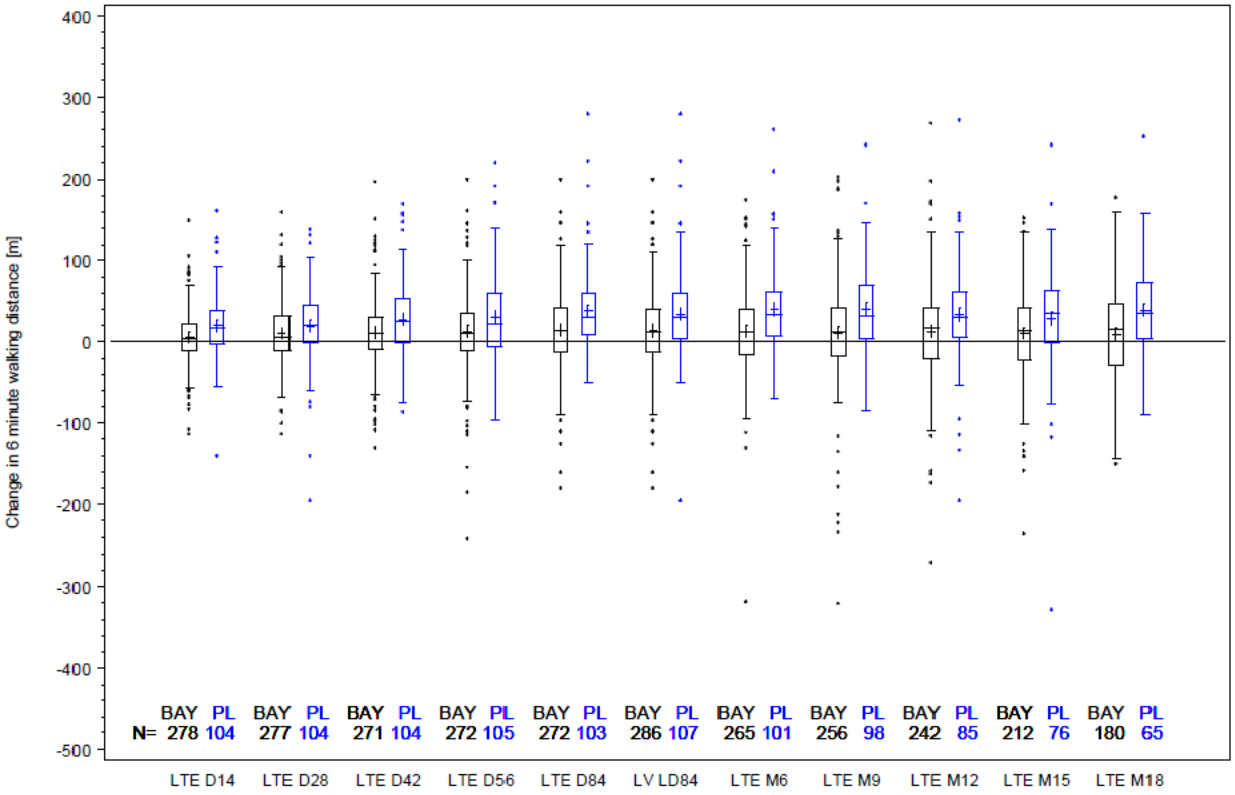
Deterioration rates for WHO functional class were similar through LTE month 12 regardless of the trial arm the subject was randomized to in PATENT-1, as shown in the table below:

Table 57: PATENT-2 WHO functional class (LTE safety set, 4 month clinical addendum table 9-12 pg 21)

Visit Change from baseline to visit	WHO FC change	Former Riociguat IDT N=231 n (%)	Former Placebo N=109 n (%)	Former Riociguat capped titration N=56 n (%)	Total N=396 n (%)
Change from baseline at Last Visit to Week 12	n	231 (100.0%)	108 (100.0%)	56 (100.0%)	395 (100.0%)
	-2	2 (0.9%)	0	3 (5.4%)	5 (1.3%)
	-1	73 (31.6%)	22 (20.4%)	16 (28.6%)	111 (28.1%)
	0	150 (64.9%)	76 (70.4%)	36 (64.3%)	262 (66.3%)
	1	6 (2.6%)	9 (8.3%)	1 (1.8%)	16 (4.1%)
	2	0	1 (0.9%)	0	1 (0.3%)
LTE 6 months	n	218 (100.0%)	104 (100.0%)	55 (100.0%)	377 (100.0%)
	-2	1 (0.5%)	2 (1.9%)	0	3 (0.8%)
	-1	75 (34.4%)	25 (24.0%)	18 (32.7%)	118 (31.3%)
	0	134 (61.5%)	68 (65.4%)	37 (67.3%)	239 (63.4%)
	1	8 (3.7%)	9 (8.7%)	0	17 (4.5%)
LTE 12 months	n	199 (100.0%)	89 (100.0%)	51 (100.0%)	339 (100.0%)
	-2	2 (1.0%)	0	0	2 (0.6%)
	-1	70 (35.2%)	23 (25.8%)	16 (31.4%)	109 (32.2%)
	0	113 (56.8%)	59 (66.3%)	34 (66.7%)	206 (60.8%)
	1	14 (7.0%)	7 (7.9%)	1 (2.0%)	22 (6.5%)

6MWD was assessed at the time of the 120 day safety update showing persistent improvement over time in placebo patients who rolled over to active therapy in the PATENT-2 open label trial, and no deterioration in subjects who continued active therapy from the main trial into the open label, as shown in the figure below:

Figure 43: PATENT-2 change in 6MWD, LTE with baseline of LTE (4 month safety update figure 1.2.4.2 / 2 pg 360)



6.2.10 Additional Efficacy Issues/Analyses

Serum glucose was not analyzed in either of the pivotal studies. Thus, FDA assessed the use of diabetes drugs as con-meds in CHEST-1 to see if there was an indicator that there may have been increases in blood sugars that would have driven more diabetic drug use. As can be seen in the following table, new diabetic drug use was similar between the three trial arms:

Table 58: PATENT-1 drugs used in diabetes

Med class / Category	Individual Titration N=254 (100%)	Placebo N=126 (100%)	1.5 mg fixed dose N=63 (100%)
Drugs Used in Diabetes			
Prior-med	22 (8.7%)	10 (7.9%)	6 (9.5%)
Any Con-med	23 (9.1%)	10 (7.9%)	7(11.1%)
New Con-med	6 (2.4%)	3 (2.4%)	3 (4.8%)

7 Review of Safety

Safety Summary

Exposure

CTEPH

CHEST-1 double blind was followed by the CHEST-2 LTE in which all patient underwent dose titration targeting the 2.5 mg TID dose (i.e., patients who had been in the placebo arm underwent IDT dose titration to the highest tolerated dose based on systolic blood pressure, to a maximal dose of 2.5 mg TID). At the time of the 4 month safety update (cutoff March 2013), the mean duration of exposure for the total CHEST-2 population was 582.2 days (+ 317.4). As of the Mar 2013 cut-off date, approximately 89% of subjects rolled over to PATENT-2 LTE remained in the study, and over 85% of all subjects in PATENT-2 LTE were receiving the 2.5 mg TID dose. Total exposure as of Mar 2013 in the CHEST-1/2 trials was 429 person-years.

PAH

PATENT-1 double-blind was followed by the PATENT-2 LTE in which all patient underwent dose titration targeting the 2.5 mg TID dose (i.e., patients who had been on the 1.5 mg TID capped dose in PATENT-1 or on Placebo were reinitiated on drug according to the IDT dose escalation algorithm to the highest tolerated dose based on systolic blood pressure, to a maximum dose of 2.5 mg TID). At the time of the 4 month safety update (cutoff March 2013), the mean duration of exposure for the total PATENT-2 population was 662.7 days (+ 319.3). As of the Mar 2013 cut-off date, approximately 82% of subjects rolled over to PATENT-2 LTE remained in the study, and over 80% of all subjects in PATENT-2 LTE were receiving the 2.5 mg TID dose. Total exposure as of Mar 2013 in the PATENT-1/2 trials was 789 person-years.

Metabolic, Clearance, and Interaction

- No dose adjustments are necessary in renal impairment
- No dose adjustments are necessary in mild hepatic impairment
- No dose adjustments are necessary based on age or gender
- There is a profound potentiation of blood pressure effects with NO donors that resulted in hypotensive syncope in a clinical trial testing the interaction with nitroglycerin. The Division agrees with the contraindication of NO donors as concomitant medications, and specifically in CAD patients who may need to take

SL nitroglycerin to abort an angina attack (in whom hypotension would be poorly tolerated).

- PDE inhibitors potentiate the action of riociguat by inhibiting the breakdown of cGMP, and their concomitant use was associated with poor outcomes in the open label phase of PATENT-PLUS (hypotension, syncope, and death). Efficacy was not improved by the combined use of riociguat and PDE inhibitors. Therefore, PDE inhibitors should not be used with riociguat (the sponsor proposes a label warning, but it is the opinion of this reviewer that a contraindication for this combination is warranted)
- Antacids decrease the absorption of riociguat so their dosing should be staggered
- Ketoconazole increases AUC 2-3X but impacts Cmax less than 2x, so there is not advice for dose adjustment with multi-CYP inhibitors
- Riociguat did not effect the PK of midazolam or vice versa
- Riociguat did not effect the PK/PD of warfarin
- Smoking increases clearance by 2-3 fold due to CYP1A1 induction. Therefore, increasing the maximal dose in smokers to twice that in non-smokers should be considered

Major Safety Results

There were fewer deaths in the active arms of both CHEST-1 and PATENT-1 as compared to the placebo arms (as a percentage of the arm sizes), and there did not appear to be attrition in placebo patients who were rolled over to active therapy in the long-term extensions by cumulative function survival analyses.

CW events are few in CHEST-1 and PATENT-1, but numerically favor riociguat therapy in both. There is no evidence of early of late harm of placebo rollovers to open label in either trial with respect to CW events.

The numbers of premature discontinuations was low in CHEST-1 (5.7% and 8.0% for placebo and riociguat respectively). The same was true for PATENT-1, where trial completion was 93.3%, 87.4%, and 89.1% for riociguat-IDT, placebo, and riociguat-fixed/capped, respectively.

The majority of the most frequent adverse events with riociguat can be attributed to its mode of action as a smooth muscle dilator, especially its GI effects (nausea, vomiting, diarrhea, constipation, and dysphagia). Adverse effects of concern of in this submission included bleeding (especially those at risk for hemoptysis), hypotension, and the possibility that lowered SBP may worsen renal function in some patients. The possibility that hypotension may be poorly tolerated in some patients was suggested by the high dropout rates form the Part-1 extension of PATENT-PLUS. The effect of the strict inclusion and exclusion criteria in these trials to create a testing population that does not

reflect the risk of hypotensive events in the general PH population gives further merit to considering that the data do not support dosing patients with higher than 1.5 mg TID due to lack of evidence of incremental efficacy with a concomitant increased risk of hypotension. It is noted that in the CTEPH trial, even patients dosed to 2.5 mg TID under the IDT dosing scheme seem not to have excess rates of hypotensive events, probably as a reflection of higher baseline SBP in this patient group.

Syncope was more common in the placebo arms of both CHEST-1 and PATENT-1 that it was in the active therapy arms of the trials, though hypotension adverse events were markedly higher in the riociguat IDT arms of both trials. About 45% of SBP <90 events occur within the first 2 days of therapy, the remainder occurring later and in a dose-related fashion

Anemia is reported as an adverse event more often with riociguat therapy in both CHEST-1 and PATENT-1, but there was no difference noted in the use of anti-anemia medications between the groups. There is likewise an increase in serious hemorrhage TEAEs in both CHEST-1 (6 in the riociguat group and 0 in the placebo group) and PATENT-1 (4 in the riociguat group, 0 in the placebo group). Half of these cases were hemoptysis, while the other half were a combination of GI, vaginal, catheter, and nose bleeds, as well as one subdural hematoma and one intra-abdominal hemorrhage. It is unclear the degree to which the anemia with this therapy is a consequence of occult bleeding in some patients, versus direct hematopoietic toxicity.

The TQT studies provide reasonable evidence that a group of selected doses of riociguat did not prolong the QTc interval more than 20 msec. There may be a small incremental risk of atrial arrhythmias with riociguat, but the numbers of cases in the double-blind trials was small, and the background rate in the LTEs probably in line with what would be expected in a group of patients at risk for the development of atrial arrhythmias (syndromes of high atrial back-pressure).

The NO-sGC-cGMP pathway is known to be involved in the regulation of bone metabolism. Extensive review of high dose effects of riociguat in juvenile and adolescent rodents suggests that the proposed lower dose range (0.5 mg TID to 1.5 mg TID) would increase the margin for bone safety in children, and thus facilitate pediatric studies in children with PAH.

Riociguat is a bone and a cardiac teratogen and will require a REMs that is aligned the REMS of other known teratogens used to treat pulmonary hypertension.

There is no evidence for clinical liver toxicity, drug-induced intra-pulmonary shunting, or clinically significant drug-induced glucose intolerance,

Ongoing LTE Studies

It is reassuring that the vast majority of subjects in both pivotal trials had received riociguat at a dose of 2.5 mg TID until the end of the extended treatment (> 85% of all subjects in CHEST-2 during LTE and > 80 % of all subjects in PATENT-2 during LTE). The 2-year survival rates during long-term extended treatment with riociguat were >90% for subject diagnosed with CTEPH as well as for subjects diagnosed with PAH, and the 2-year rates of survival without clinical worsening events were >75% for subjects of both indications.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The single phase II study that is relevant to the safety analysis of this application is trial 12166 (main) and its LTE. This trial (and it's LTE) is described in detail in section 5.3 in that it was small, non-randomized, non-blinded, non-controlled, and included a mix of both PAH and CTEPH patients in its single enrollment arm.

The etiologies of PH in CTEPH versus PAH are unique, though they share common clinical manifestations. Therefore, just as was done in the efficacy analysis, the safety analysis will consider the safety of riociguat separately for the CTEPH indication (CHEST-1 and its LTE extension CHEST-2) and then for the PAH indication (PATENT-1 and its LTE extension PATENT-2), except where specifically noted for potentially exposure-related safety effects that are not PH related (e.g. hematologic effects).

7.1.2 Categorization of Adverse Events

In CHEST-1, discontinuations for adverse event were few (4 in the active treatment arm, 2 in the placebo control arm). This was also the case for adverse events leading to discontinuation in PATENT-1 (9 in the active treatment arms and 9 in the placebo control arm). Causes of withdrawal were clear – there was no evidence that "lumping" or "splitting" of PTs influenced the safety outcomes of these trials.

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

Due to the unique etiologies of CTEPH and PAH, and the fact that there is only one trial submitted for each of these indications, the safety databases are considered independently in each section below, using "CTEPH" and "PAH" sub-headers in each

section. If pooled safety data is shown for a non-PH related condition (e.g. hematologic effects), it will be specifically noted.

7.2 Adequacy of Safety Assessments

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

CTEPH

CHEST-1 double blind was followed by the CHEST-2 LTE in which all patient underwent dose titration targeting the 2.5 mg TID dose (i.e., patients who had been in the placebo arm underwent IDT dose titration to the highest tolerated dose based on systolic blood pressure, to a maximal dose of 2.5 mg TID). At the time of the 4 month safety update (cutoff March 2013), the mean duration of exposure for the total CHEST-2 population was 582.2 days (± 317.4). As of the Mar 2013 cut-off date, approximately 89% of subjects rolled over to PATENT-2 LTE remained in the study, and over 85% of all subjects in PATENT-2 LTE were receiving the 2.5 mg TID dose.

Exposures of the CTEPH population during the double-blind phase of CHEST-1 and its LTE extension CHEST-2 are as follows in table 59 (treatment duration), table 60 (cumulative total time exposure), table 61 (cumulative dose), and table 62 (person-year exposure) through the month 4 safety update:

Table 59: CHEST-1/2 treatment duration (safety set, 4msu-iss table 1.1.4.1/2 pg 55)

	BAY 63-2521 (main) N=173 (100%)	Placebo (main) N=88 (100%)	BAY 63-2521 (LTE, main) N=155 (100%)	BAY 63-2521 (LTE, placebo in main) N=82 (100%)	LTE total N=237 (100%)
Duration of treatment (months)					
< 1 month	4 (2.3%)	1 (1.1%)	1 (0.6%)	2 (2.4%)	3 (1.3%)
1-<2 months	6 (3.5%)	2 (2.3%)	2 (1.3%)	1 (1.2%)	3 (1.3%)
2-<3 months	3 (1.7%)	1 (1.1%)	2 (1.3%)	0	2 (0.8%)
3-<4 months	149 (86.1%)	82 (93.2%)	0	1 (1.2%)	1 (0.4%)
4-<5 months	11 (6.4%)	2 (2.3%)	0	0	0
5-<6 months	0	0	5 (3.2%)	1 (1.2%)	6 (2.5%)
6-<7 months	0	0	0	1 (1.2%)	1 (0.4%)
8-<9 months	0	0	15 (9.7%)	9 (11.0%)	24 (10.1%)
9-<10 months	0	0	9 (5.8%)	4 (4.9%)	13 (5.5%)
10-<11 months	0	0	1 (0.6%)	1 (1.2%)	2 (0.8%)
11-<12 months	0	0	13 (8.4%)	4 (4.9%)	17 (7.2%)
12-<15 months	0	0	20 (12.9%)	16 (19.5%)	36 (15.2%)
15-<18 months	0	0	14 (9.0%)	8 (9.8%)	22 (9.3%)
18-<21 months	0	0	11 (7.1%)	5 (6.1%)	16 (6.8%)
21-<24 months	0	0	9 (5.8%)	7 (8.5%)	16 (6.8%)
24-<27 months	0	0	13 (8.4%)	4 (4.9%)	17 (7.2%)
27-<30 months	0	0	9 (5.8%)	4 (4.9%)	13 (5.5%)
30-<33 months	0	0	8 (5.2%)	1 (1.2%)	9 (3.8%)
33-<36 months	0	0	9 (5.8%)	5 (6.1%)	14 (5.9%)
36-<39 months	0	0	8 (5.2%)	1 (1.2%)	9 (3.8%)
39-<42 months	0	0	5 (3.2%)	5 (6.1%)	10 (4.2%)
42-<45 months	0	0	1 (0.6%)	2 (2.4%)	3 (1.3%)
Duration of treatment (months)					
n	173	88	155	82	237
Nmiss	0	0	0	0	0
Min	0	1	1	1	1
Mean	3.6	3.7	19.7	19.0	19.5
SD	0.7	0.5	10.5	10.7	10.6
Median	3.8	3.8	17.7	16.0	17.6
Max	4	4	42	43	43

Table 60: CHEST-1/2 cumulative total time exposure (safety set, 4msu-iss table 1.1.4.1/4 pg 57)

	BAY 63-2521 (main) N=173 (100%)	Placebo (main) N=88 (100%)	BAY 63-2521 (LTE, main) N=155 (100%)	BAY 63-2521 (LTE, placebo in main) N=82 (100%)	LTE total N=237 (100%)
Treatment exposure (weeks)					
At least one dose	173 (100.0%)	88 (100.0%)	155 (100.0%)	82 (100.0%)	237 (100.0%)
At least 2 weeks	169 (97.7%)	88 (100.0%)	155 (100.0%)	82 (100.0%)	237 (100.0%)
At least 4 weeks	169 (97.7%)	87 (98.9%)	154 (99.4%)	81 (98.8%)	235 (99.2%)
At least 6 weeks	166 (96.0%)	87 (98.9%)	154 (99.4%)	80 (97.6%)	234 (98.7%)
At least 8 weeks	166 (96.0%)	87 (98.9%)	153 (98.7%)	79 (96.3%)	232 (97.9%)
At least 12 weeks	161 (93.1%)	84 (95.5%)	150 (96.8%)	79 (96.3%)	229 (96.6%)
At least 24 weeks	0	0	149 (96.1%)	78 (95.1%)	227 (95.8%)
At least 36 weeks	0	0	145 (93.5%)	76 (92.7%)	221 (93.2%)
At least 48 weeks	0	0	119 (76.8%)	62 (75.6%)	181 (76.4%)
At least 60 weeks	0	0	102 (65.8%)	53 (64.6%)	155 (65.4%)
At least 72 weeks	0	0	80 (51.6%)	41 (50.0%)	121 (51.1%)
At least 84 weeks	0	0	68 (43.9%)	31 (37.8%)	99 (41.8%)
At least 96 weeks	0	0	58 (37.4%)	27 (32.9%)	85 (35.9%)
At least 108 weeks	0	0	49 (31.6%)	21 (25.6%)	70 (29.5%)
At least 120 weeks	0	0	36 (23.2%)	17 (20.7%)	53 (22.4%)
At least 132 weeks	0	0	28 (18.1%)	13 (15.9%)	41 (17.3%)
At least 144 weeks	0	0	23 (14.8%)	12 (14.6%)	35 (14.8%)
At least 156 weeks	0	0	13 (8.4%)	8 (9.8%)	21 (8.9%)
At least 168 weeks	0	0	4 (2.6%)	5 (6.1%)	9 (3.8%)
At least 180 weeks	0	0	1 (0.6%)	2 (2.4%)	3 (1.3%)

Table 61: CHEST-1/2 extent of exposure – total dose (safety set, 4msu-iss table 1.1.4.1/3 pg 56)

	BAY 63-2521 (main) N=173 (100%)	Placebo (main) N=88 (100%)	BAY 63-2521 (LTE, main) N=155 (100%)	BAY 63-2521 (LTE, placebo in main) N=82 (100%)	LTE total N=237 (100%)
Extent of exposure (mg)					
0 - 100 mg	4 (2.3%)	87 (98.9%)	1 (0.6%)	2 (2.4%)	3 (1.3%)
100.5 - 200 mg	3 (1.7%)	1 (1.1%)	0	1 (1.2%)	1 (0.4%)
200.5 - 300 mg	2 (1.2%)	0	0	0	0
300.5 - 400 mg	9 (5.2%)	0	3 (1.9%)	0	3 (1.3%)
400.5 - 500 mg	6 (3.5%)	0	1 (0.6%)	1 (1.2%)	2 (0.8%)
500.5 - 600 mg	14 (8.1%)	0	1 (0.6%)	0	1 (0.4%)
600.5 - 800 mg	133 (76.9%)	0	0	1 (1.2%)	1 (0.4%)
800.5 - 1000 mg	2 (1.2%)	0	2 (1.3%)	0	2 (0.8%)
1000.5 - 1500 mg	0	0	7 (4.5%)	3 (3.7%)	10 (4.2%)
1500.5 - 2000 mg	0	0	14 (9.0%)	11 (13.4%)	25 (10.5%)
2000.5 - 2500 mg	0	0	12 (7.7%)	3 (3.7%)	15 (6.3%)
2500.5 - 3000 mg	0	0	13 (8.4%)	9 (11.0%)	22 (9.3%)
3000.5 - 3500 mg	0	0	25 (16.1%)	10 (12.2%)	35 (14.8%)
3500.5 - 4000 mg	0	0	8 (5.2%)	10 (12.2%)	18 (7.6%)
4000.5 - 4500 mg	0	0	5 (3.2%)	4 (4.9%)	9 (3.8%)
4500.5 - 5000 mg	0	0	10 (6.5%)	3 (3.7%)	13 (5.5%)
5000.5 - 5500 mg	0	0	8 (5.2%)	5 (6.1%)	13 (5.5%)
5500.5 - 6000 mg	0	0	5 (3.2%)	3 (3.7%)	8 (3.4%)
6000.5 - 6500 mg	0	0	9 (5.8%)	1 (1.2%)	10 (4.2%)
6500.5 - 7000 mg	0	0	9 (5.8%)	3 (3.7%)	12 (5.1%)
7000.5 - 7500 mg	0	0	2 (1.3%)	1 (1.2%)	3 (1.3%)
7500.5 - 8000 mg	0	0	5 (3.2%)	5 (6.1%)	10 (4.2%)
8000.5 - 8500 mg	0	0	5 (3.2%)	0	5 (2.1%)
8500.5 - 9000 mg	0	0	8 (5.2%)	3 (3.7%)	11 (4.6%)
9000.5 - 9500 mg	0	0	2 (1.3%)	3 (3.7%)	5 (2.1%)
Extent of exposure (mg)					
n	173	88	155	82	237
Nmiss	0	0	0	0	0
Min	6	0	98	45	45
Mean	644.7	1.2	4204.7	3990.6	4130.7
SD	166.4	11.2	2351.4	2362.5	2352.4
Median	714.0	0.0	3420.0	3399.0	3420.0
Max	846	105	9480	9396	9480

Table 62: CHEST-1/2 cumulative riociguat exposure over all subjects (safety set, FSR table 10-2 pg 127, and LT safety set, 4 month update-2-chest table 14.2.1/12 pg 125)

	Rio IDT (main) N=173	Rio (LTE,main) N=155	Rio (LTE, PBO in main) N=82	LTE Total N=237	DB+LTE Total Exposure
Person-yrs	51.25	250.53	127.21	377.74	428.99

PAH

PATENT-1 double-blind was followed by the PATENT-2 LTE in which all patient underwent dose titration targeting the 2.5 mg TID dose (i.e., patients who had been on the 1.5 mg TID capped dose in PATENT-1 or on Placebo were reinitiated on drug according to the IDT dose escalation algorithm to the highest tolerated dose based on systolic blood pressure, to a maximum dose of 2.5 mg TID). At the time of the 4 month safety update (cutoff March 2013), the mean duration of exposure for the total PATENT-2 population was 662.7 days (+ 319.3). As of the Mar 2013 cut-off date, approximately 82% of subjects rolled over to PATENT-2 LTE remained in the study, and over 80% of all subjects in PATENT-2 LTE were receiving the 2.5 mg TID dose.

Exposures of the PAH population during the double-blind phase of PATENT-1 and its LTE extension PATENT-2 are as follows in table 53 (treatment duration), table 64, (cumulative total time exposure), table 65 (cumulative dose), and table 66 (person-year exposure) through the month 4 safety update:

Table 63: PATENT-1/2 treatment duration (safety set, 4msu-iss table 1.2.4.1/2 pg 303)

	BAY 63-2521 (main) N=317 (100%)	Placebo (main) N=126 (100%)	BAY 63-2521 (LTE, main) N=287 (100%)	BAY 63-2521 (LTE, placebo in main) N=109 (100%)	LTE total N=396 (100%)
Duration of treatment (months)					
< 1 month	14 (4.4%)	9 (7.1%)	3 (1.0%)	1 (0.9%)	4 (1.0%)
1-<2 months	8 (2.5%)	5 (4.0%)	4 (1.4%)	1 (0.9%)	5 (1.3%)
2-<3 months	272 (85.8%)	107 (84.9%)	3 (1.0%)	1 (0.9%)	4 (1.0%)
3-<4 months	23 (7.3%)	5 (4.0%)	1 (0.3%)	2 (1.8%)	3 (0.8%)
4-<5 months	0	0	2 (0.7%)	1 (0.9%)	3 (0.8%)
6-<7 months	0	0	1 (0.3%)	1 (0.9%)	2 (0.5%)
7-<8 months	0	0	2 (0.7%)	0	2 (0.5%)
8-<9 months	0	0	10 (3.5%)	9 (8.3%)	19 (4.8%)
9-<10 months	0	0	12 (4.2%)	4 (3.7%)	16 (4.0%)
10-<11 months	0	0	2 (0.7%)	2 (1.8%)	4 (1.0%)
11-<12 months	0	0	19 (6.6%)	7 (6.4%)	26 (6.6%)
12-<15 months	0	0	32 (11.1%)	11 (10.1%)	43 (10.9%)
15-<18 months	0	0	19 (6.6%)	10 (9.2%)	29 (7.3%)
18-<21 months	0	0	26 (9.1%)	5 (4.6%)	31 (7.8%)
21-<24 months	0	0	26 (9.1%)	11 (10.1%)	37 (9.3%)
24-<27 months	0	0	17 (5.9%)	6 (5.5%)	23 (5.8%)
27-<30 months	0	0	29 (10.1%)	11 (10.1%)	40 (10.1%)
30-<33 months	0	0	24 (8.4%)	11 (10.1%)	35 (8.8%)
33-<36 months	0	0	23 (8.0%)	4 (3.7%)	27 (6.8%)
36-<39 months	0	0	19 (6.6%)	7 (6.4%)	26 (6.6%)
39-<42 months	0	0	8 (2.8%)	3 (2.8%)	11 (2.8%)
42-<45 months	0	0	3 (1.0%)	0	3 (0.8%)
45-<48 months	0	0	2 (0.7%)	1 (0.9%)	3 (0.8%)
Duration of treatment (months)					
n	317	126	287	109	396
Nmiss	0	0	0	0	0
Min	0	0	1	0	0
Mean	2.7	2.6	22.5	21.1	22.2
SD	0.5	0.7	10.7	10.6	10.6
Median	2.8	2.8	22.1	20.9	21.2
Max	3	3	45	45	45

Table 64: PATENT-1/2 cumulative total time exposure (safety set, 4msu-iss table 1.2.4.1/4 pg 57)

	BAY 63-2521 (main) N=317 (100%)	Placebo (main) N=126 (100%)	BAY 63-2521 (LTE, main) N=287 (100%)	BAY 63-2521 (LTE, placebo in main) N=109 (100%)	LTE total N=396 (100%)
Treatment exposure (weeks)					
At least one dose	317 (100.0%)	126 (100.0%)	287 (100.0%)	109 (100.0%)	396 (100.0%)
At least 2 weeks	309 (97.5%)	120 (95.2%)	287 (100.0%)	108 (99.1%)	395 (99.7%)
At least 4 weeks	305 (96.2%)	118 (93.7%)	284 (99.0%)	108 (99.1%)	392 (99.0%)
At least 6 weeks	300 (94.6%)	116 (92.1%)	281 (97.9%)	108 (99.1%)	389 (98.2%)
At least 8 weeks	295 (93.1%)	114 (90.5%)	280 (97.6%)	107 (98.2%)	387 (97.7%)
At least 12 weeks	258 (81.4%)	90 (71.4%)	278 (96.9%)	106 (97.2%)	384 (97.0%)
At least 24 weeks	0	0	274 (95.5%)	103 (94.5%)	377 (95.2%)
At least 36 weeks	0	0	267 (93.0%)	102 (93.6%)	369 (93.2%)
At least 48 weeks	0	0	247 (86.1%)	87 (79.8%)	334 (84.3%)
At least 60 weeks	0	0	217 (75.6%)	76 (69.7%)	293 (74.0%)
At least 72 weeks	0	0	191 (66.6%)	67 (61.5%)	258 (65.2%)
At least 84 weeks	0	0	163 (56.8%)	57 (52.3%)	220 (55.6%)
At least 96 weeks	0	0	142 (49.5%)	50 (45.9%)	192 (48.5%)
At least 108 weeks	0	0	121 (42.2%)	41 (37.6%)	162 (40.9%)
At least 120 weeks	0	0	98 (34.1%)	34 (31.2%)	132 (33.3%)
At least 132 weeks	0	0	73 (25.4%)	22 (20.2%)	95 (24.0%)
At least 144 weeks	0	0	48 (16.7%)	13 (11.9%)	61 (15.4%)
At least 156 weeks	0	0	25 (8.7%)	7 (6.4%)	32 (8.1%)
At least 168 weeks	0	0	10 (3.5%)	3 (2.8%)	13 (3.3%)
At least 180 weeks	0	0	5 (1.7%)	1 (0.9%)	6 (1.5%)
At least 192 weeks	0	0	2 (0.7%)	1 (0.9%)	3 (0.8%)

Table 65: PATENT-1/2 extent of exposure – total dose (safety set, 4msu-iss table 1.2.4.1/3 pg 56)

	BAY 63-2521 (main) N=317 (100%)	Placebo (main) N=126 (100%)	BAY 63-2521 (LTE, main) N=287 (100%)	BAY 63-2521 (LTE, placebo in main) N=109 (100%)	LTE total N=396 (100%)
Extent of exposure (mg)					
0 - 100 mg	13 (4.1%)	125 (99.2%)	1 (0.3%)	1 (0.9%)	2 (0.5%)
100.5 - 200 mg	12 (3.8%)	1 (0.8%)	4 (1.4%)	0	4 (1.0%)
200.5 - 300 mg	12 (3.8%)	0	2 (0.7%)	2 (1.8%)	4 (1.0%)
300.5 - 400 mg	69 (21.8%)	0	1 (0.3%)	0	1 (0.3%)
400.5 - 500 mg	49 (15.5%)	0	1 (0.3%)	2 (1.8%)	3 (0.8%)
500.5 - 600 mg	162 (51.1%)	0	1 (0.3%)	2 (1.8%)	3 (0.8%)
600.5 - 800 mg	0	0	2 (0.7%)	0	2 (0.5%)
800.5 - 1000 mg	0	0	5 (1.7%)	1 (0.9%)	6 (1.5%)
1000.5 - 1500 mg	0	0	3 (1.0%)	4 (3.7%)	7 (1.8%)
1500.5 - 2000 mg	0	0	19 (6.6%)	10 (9.2%)	29 (7.3%)
2000.5 - 2500 mg	0	0	11 (3.8%)	7 (6.4%)	18 (4.5%)
2500.5 - 3000 mg	0	0	28 (9.8%)	9 (8.3%)	37 (9.3%)
3000.5 - 3500 mg	0	0	20 (7.0%)	7 (6.4%)	27 (6.8%)
3500.5 - 4000 mg	0	0	16 (5.6%)	10 (9.2%)	26 (6.6%)
4000.5 - 4500 mg	0	0	21 (7.3%)	2 (1.8%)	23 (5.8%)
4500.5 - 5000 mg	0	0	20 (7.0%)	8 (7.3%)	28 (7.1%)
5000.5 - 5500 mg	0	0	23 (8.0%)	8 (7.3%)	31 (7.8%)
5500.5 - 6000 mg	0	0	15 (5.2%)	8 (7.3%)	23 (5.8%)
6000.5 - 6500 mg	0	0	13 (4.5%)	1 (0.9%)	14 (3.5%)
6500.5 - 7000 mg	0	0	19 (6.6%)	7 (6.4%)	26 (6.6%)
7000.5 - 7500 mg	0	0	18 (6.3%)	8 (7.3%)	26 (6.6%)
7500.5 - 8000 mg	0	0	5 (1.7%)	5 (4.6%)	10 (2.5%)
8000.5 - 8500 mg	0	0	17 (5.9%)	2 (1.8%)	19 (4.8%)
8500.5 - 9000 mg	0	0	12 (4.2%)	4 (3.7%)	16 (4.0%)
9000.5 - 9500 mg	0	0	7 (2.4%)	1 (0.9%)	8 (2.0%)
9500.5 - 10000 mg	0	0	1 (0.3%)	0	1 (0.3%)
10000.5 - 10500 mg	0	0	2 (0.7%)	0	2 (0.5%)
Extent of exposure (mg)					
n	317	126	287	109	396
Nmiss	0	0	0	0	0
Min	3	0	41	3	3
Mean	432.9	0.9	4810.3	4341.8	4681.4
SD	125.7	9.6	2407.4	2396.5	2410.5
Median	501.0	0.0	4680.0	3981.0	4604.3
Max	579	108	10148	9375	10148

Table 66: PATENT-1/2 Cumulative riociguat exposure over all subjects (safety set, FSR table 10-2 pg 127, and LT safety set, 4 month update-2-PATENT table 14.2.1/12 pg 140)

Rio IDT (main) N=254 Person-yrs	Rio 1.5 TID (main) N=63 Person-yrs	Rio (LTE,main) N=287 Person-yrs	Rio (LTE, PBO in main) N=109 Person-yrs	LTE Total N=396 Person-yrs	DB+LTE Total Exposure Person-yrs
56.58	13.80	530.43	188.02	718.45	788.83

7.2.2 Explorations for Dose Response

CTEPH and PAH

IDT dose escalation to highest tolerated dose created what is essentially a single active therapy arm with multiple individual doses. However, all subjects who were treated with 2.0 TID or 1.5 mg TID escalated through 1.5 mg TID. There was a flat exposure-response relationship in CHEST-1 with respect to the six minute walk (see figure 9 in section 4.4.3). Furthermore, the 1.5 mg TID capped arm from PATENT-1 demonstrates progressive improvement after week 2 of the dose escalation when patients are raised to and held at 1.5 mg TID. This may be a combination of training effect and progressive drug effect, but there is no demonstrated incremental efficacy in PATENT-1 from further dose escalation above 1.5 mg TID (see figure 32 in section 6.2.4). Of note, the exposure response relationship in PATENT-1 is also flat (see figure 8 in section 4.4.3).

7.2.3 Special Animal and/or In Vitro Testing

See a review of the animal bone toxicity studies in section 4.3, the sponsor's response to FDA IR-19 and IR-21 appended to section 9.4 (Appendices A and B), and the DRUP consult regarding bone effects seen in preclinical and clinical studies (section 9.4 Appendix C). Also see section 7.6.3 (Pediatrics and Assessment of Effects on Growth).

7.2.4 Routine Clinical Testing

With respect to clinical routine testing, the Division has long been concerned that the very tight SBP limits on which decrease (< 90 mmHg)/maintain (90 – 94 mmHg)/increase (≥95 mmHg) dosing decisions are to be made during the IDT dose escalation period cannot be reliably reproduced in the clinic. However, the failure modes of this methodology will bias SBP readings to be lower than they really are (e.g., low blood pressures due to poor technique in the clinic will correlate to substantially higher central aortic pressures in the cath lab, so that any readings at or above 95 mmHg will be at least that high, and most likely higher). Therefore, the ability of patients to either be seen frequently in the clinic, or to take their own blood pressures at home, will likely be adequate. This will be especially true if the dose range is decreased to 0.5 mg TID as a starting dose, capping the escalation at 1.5 mg TID – an approach that is associated with substantially fewer SBP < 90 mmHg events.

The toxicology reviewer noted that serum glucose was increased in both fed a fasted rats. At the highest dose of 3 mg/kg, fasted rats showed increases of 14% of mean baseline ($p<0.05$) and fed rats showed 2% increase ($p<0.05$) over baseline. The sponsor chose not to measure serum glucose in the phase III trials, so the data to assess the need for laboratory monitoring of serum glucose is limited. We discussed this with the sponsor during the course of the review, and it explained that serum glucose was not measured during the phase III studies because in the uncontrolled phase II trial 12166, serum glucose actually decreased on therapy. Indeed, per this reviewer's assessment the following are reassuring:

- From the integrated summary of safety, in single dose studies in health subjects, high glucose values were less frequent in those receiving riociguat than placebo (7.8% versus 13.8%, respectively)
- Only one treatment emergent high glucose values (> 1x ULN) was seen in multiple dose studies in healthy subjects treated with riociguat. This elevation was not profound, as there were no elevations in this cohort > 2x ULN
- From the phase II study 12166 LTE report, "mean changes from baseline in blood glucose concentrations appeared to decrease rather than increase.

The toxicology reviewer also noted that in the dog, T3 and T4 values were slightly depressed for the HD group. There was no histological correlate for this and it's possible that the values are simply "sick euthyroid" or a basically healthy thyroid in a stressed animal. Changes in thyroid hormones can also occur secondary to gastrointestinal changes. Since thyroid function tests were not assessed in the phase II/III pivotal trials, this has not been further assessed.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the clinical pharmacology review for details. The main points of interest in this regard are that::

- No dose adjustments are necessary in renal impairment
- No dose adjustments are necessary in mild hepatic impairment
- No dose adjustments are necessary based on age or gender
- There is a profound potentiation of blood pressure effects with NO donors that resulted in hypotensive syncope in a clinical trial testing the interaction with nitroglycerin. The Division agrees with the contraindication of NO donors as concomitant medications, and specifically in CAD patients who may need to take SL nitroglycerin to abort an angina attack (in whom hypotension would be poorly tolerated).
- PDE inhibitors potentiate the action of riociguat by inhibiting the breakdown of cGMP, and their concomitant use was associated with poor outcomes in the

open label phase of PATENT-PLUS (hypotension, syncope, and death). Efficacy was not improved by the combined use of riociguat and PDE inhibitors. Therefore, PDE inhibitors should not be used with riociguat (the sponsor proposes a label warning, but it is the opinion of this reviewer that a contraindication for this combination is warranted)

- Antacids decrease the absorption of riociguat so their dosing should be staggered
- Ketoconazole increases AUC 2-3X but impacts Cmax less than 2x, so there is not advice for dose adjustment with multi-CYP inhibitors
- Riociguat did not effect the PK of midazolam or vice versa
- Riociguat did not effect the PK/PD of warfarin
- Smoking increases clearance by 2-3 fold due to CYP1A1 induction. Therefore, increasing the maximal dose in smokers to twice that in non-smokers should be considered

See section 4.4.3 (PK drug-drug interactions) for details of potential interactions.

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

Riociguat is a first in class NME that is not approved or marketed for use in any jurisdiction world-wide. Therefore, the potential for side effects for similar drugs in this drug class cannot be made. However, it has been shown that riociguat , NO donors, and PDE inhibitors all stimulate the NO-sGC-cGMP intracellular signaling pathway, and synergistic effects on dropping blood pressure have been seen with the concomitant use of riociguat with either NO donors or a PDE5 inhibitor. These drugs should not be used together. Likewise, this pathway is known to be involved in the regulation of bone metabolism, and effects in juvenile/adolescent rats have been observed (see section 7.6.3, Pediatrics and Assessment of Growth).

7.3 Major Safety Results

7.3.1 Deaths

CTEPH

Five subjects died during CHEST-1: 2 (1.2%) in the riociguat IDT arm and 3 (3.4%) in the placebo arm. MedDRA PTs associated with these deaths are given in the table below:

Table 67: CHEST-1 deaths (safety set, FSR table 10-11 pg 138)

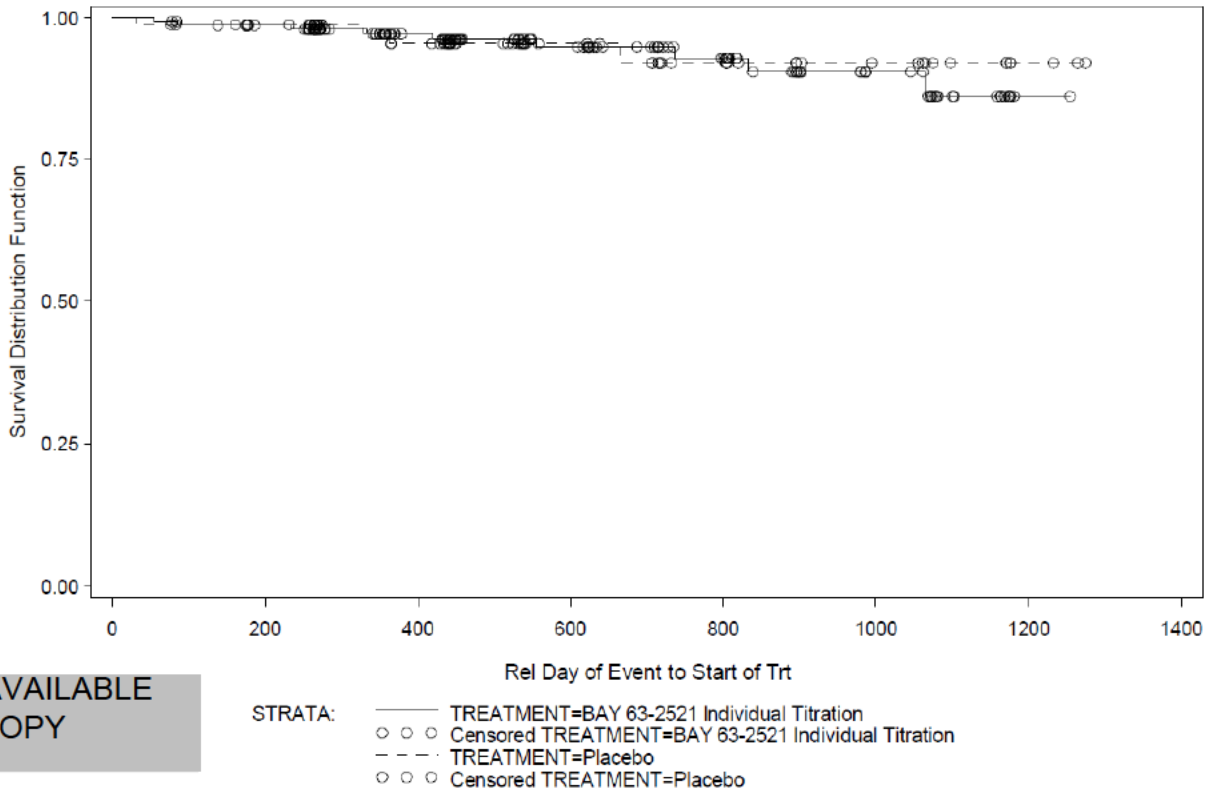
Subject No.	Randomized treatment	Age/ Sex	Event description (MedDRA preferred term)	Day of onset of AE	Day of death	Day of stop of study med.	AE related to study med.?
380018020	RIOC 1.0-2.5	74/F	Cardiac failure	88	88	82 [a]	No
470028004	RIOC 1.0-2.5	46/F	Anaemia	57	64	64	No
			Catheter site haemorrhage	57	64	64	No
			Renal failure acute	54	64	64	Yes
100068003	Placebo	73/F	Cardiopulmonary failure	70	70	55 [a]	No
220018005	Placebo	66/F	Cardiac arrest	68	71	68	No
540028032	Placebo	45/F	Cardiac arrest	19	19	14 [a]	No

RIOC 1.0-2.5 = Riociguat 1.0-2.5 mg ; F = female

As might be expected, 4 of the 5 deaths were associated with cardiac or cardiopulmonary adverse events. One of these deaths occurred in a patient who suffered catheter site hemorrhage and acute renal failure. This case is discussed further in the analysis of renal failure during the overall program (see Laboratory Findings Section 7.4.2, subsection Renal Function).

In the CHEST-2 LTE, there was no difference in fatality rates based on what treatment was received in CHEST-1, as shown in the figure below:

Figure 44: CHEST-2 LTE K-M for survival by Rx group in blinded trial (4 mo. update-2-CHEST, fig 14.2.2/5 pg 162)



PAH

Six deaths occurred during PATENT-1: 2 (0.8%) in the riociguat IDT arm, 3 (2.4%) in the placebo arm, and 1 (1.6%) in the riociguat 1.5 mg TID capped arm. MedDRA PTs associated with these deaths are given in the table below:

Table 68: PATENT-1 deaths (safety set, FSR table 10-11 pg 151)

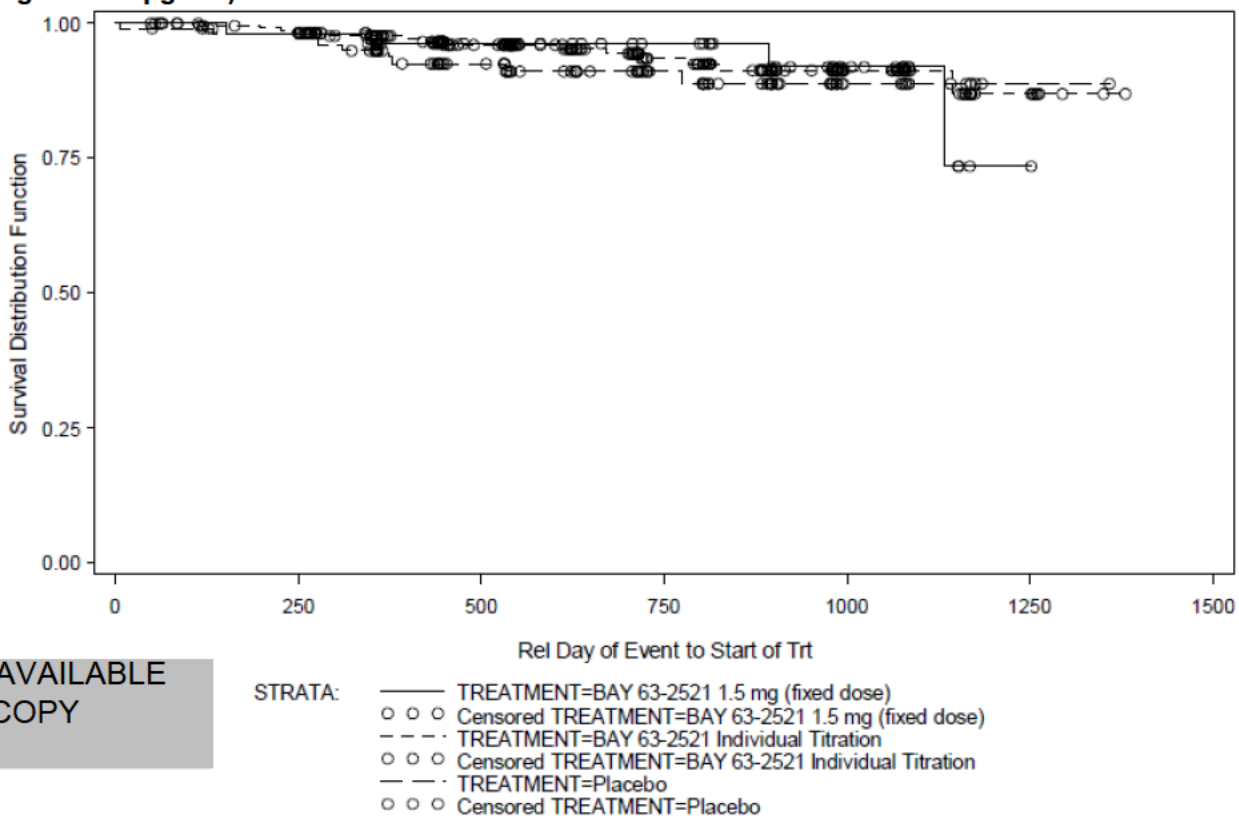
Subject No.	Randomized treatment	Age/ Sex	Event description (MedDRA preferred term)	Day of onset of AE	Day of death	Day of stop of study med.	AE related to study med.?
220024001	RIOC 1.0-2.5	61/F	Sepsis	5	8	3	No
540044008	RIOC 1.0-2.5	26/M	Haemoptysis	55	55	55	No
140054001	Placebo	73/F	Pulmonary arterial 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.

Of note is the single fatal case of hemoptysis in the blinded program. Bleeding adverse events are discussed in detail in section 7.3.4 below (Significant Adverse Events).

In the PATENT-2 LTE, there was no difference in fatality rates based on what treatment was received in PATENT-1, as shown in the figure below:

Figure 45: PATENT-2 LTE K-M for survival by Rx group in blinded trial (4 mo. update-2-PATENT, fig 14.2.2/4 pg 192)



7.3.2 Nonfatal Serious Adverse Events

CTEPH

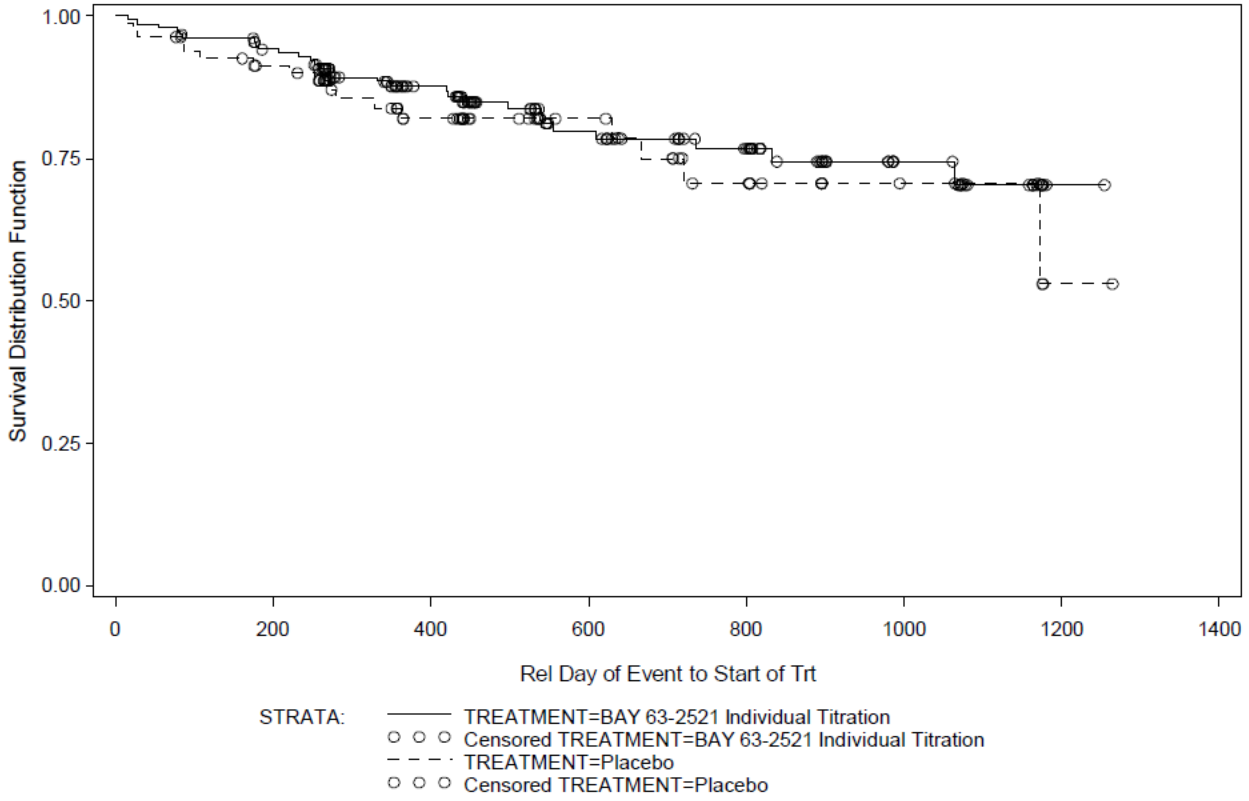
Time to clinical worsening (TTCW) during the CHEST-1 trial is reviewed as a secondary endpoint in section 6.1.5. For the CHEST-2 LTE, TTCW events are shown in the table below (cut-off Mar 2013):

Table 69: CHEST-2 TTCW events (Mar 2013 cut-off, 4msu-2-CHEST table 14.2.2/5 pg 147

Event	BAY 63-2521 Individual Titration N=155 (100%)	Placebo N=82 (100%)	Total N=237 (100%)
Number of subjects (%) with clinical worsening	26 (16.8%)	12 (14.6%)	38 (16.0%)
ATRIAL SEPTOSTOMY	1 (0.6%)	1 (1.2%)	2 (0.8%)
HOSPITALIZATION DUE TO PULMONARY HYPERTENSION	5 (3.2%)	1 (1.2%)	6 (2.5%)
START OF NEW PULMONARY HYPERTENSION TREATMENT	12 (7.7%)	7 (8.5%)	19 (8.0%)
DECREASE IN 6MWT DUE TO PULMONARY HYPERTENSION	2 (1.3%)	1 (1.2%)	3 (1.3%)
PERSISTANT WORSENING OF FUNCTIONAL CLASS DUE TO PH	5 (3.2%)	1 (1.2%)	6 (2.5%)
DEATH	9 (5.8%)	4 (4.9%)	13 (5.5%)

Though the numbers of these events are uncontrolled, and therefore without reference for interpretation, what is notable and can be seen from a K-M curve of time to first TTCW event in the CHEST-2 LTE is that there was no early attrition in the group rolling over from placebo to active therapy, as can be seen in the figure below:

Figure 46: CHEST-2 LTE K-M for TTCW by Rx group in blinded trial (4 mo. update-2-CHEST, fig 14.2.2/3 pg 159)



PAH

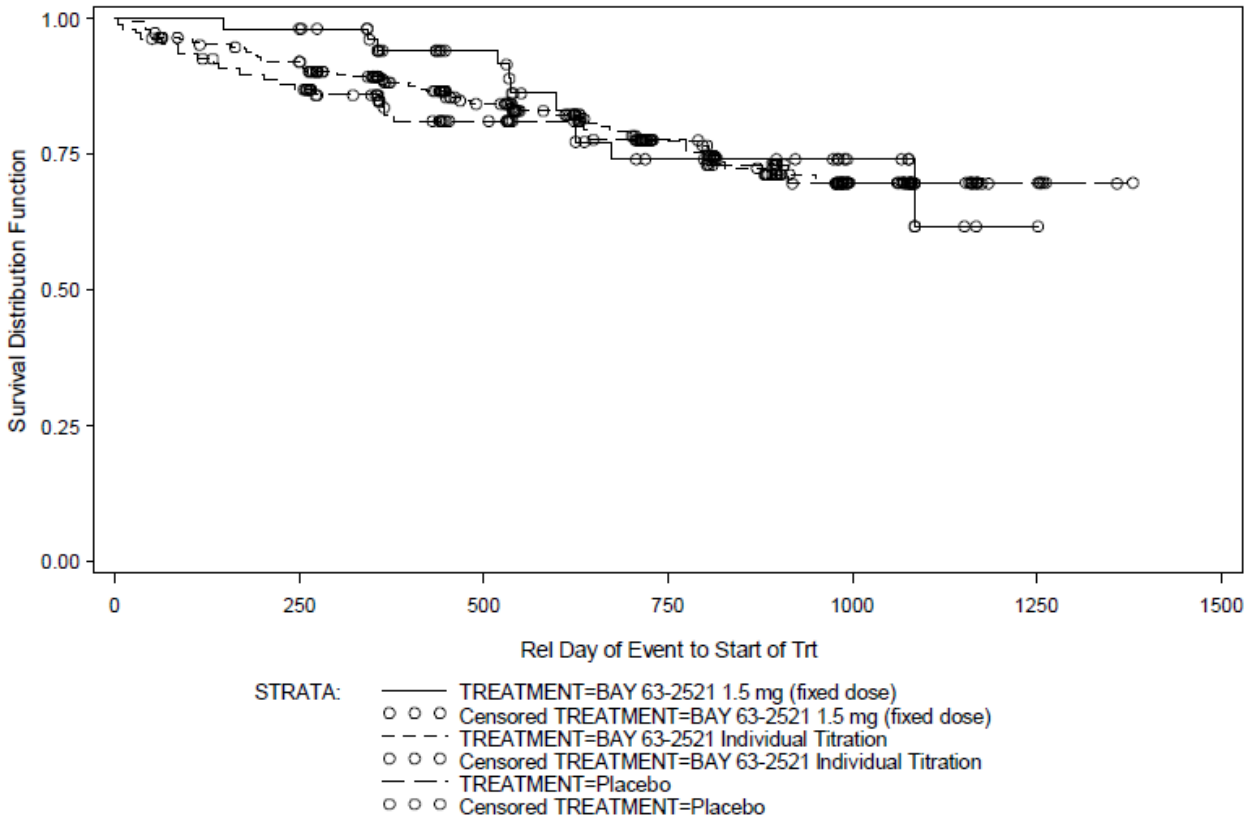
Time to clinical worsening (TTCW) during the PATENT-1 trial is reviewed as a secondary endpoint in section 6.2.5. For the PATENT-2 LTE, TTCW events are shown in the table below (cut-off Mar 2013):

Table 70: PATENT-2 TTCW events (Mar 2013 cut-off, 4msu-2-PATENT table 14.2.2/5 pg 165)

Event	BAY 63-2521 Individual Titration N=231 (100%)	Placebo N=109 (100%)	BAY 63-2521 1.5 mg (fixed dose) N=56 (100%)	Total N=396 (100%)
Number of subjects (%) with clinical worsening	49 (21.2%)	24 (22.0%)	11 (19.6%)	84 (21.2%)
HEART/LUNG TRANSPLANTATION	1 (0.4%)	0	1 (1.8%)	2 (0.5%)
HOSPITALIZATION DUE TO PULMONARY HYPERTENSION	25 (10.8%)	11 (10.1%)	5 (8.9%)	41 (10.4%)
START OF NEW PULMONARY HYPERTENSION TREATMENT	34 (14.7%)	17 (15.6%)	9 (16.1%)	60 (15.2%)
DECREASE IN 6MWT DUE TO PULMONARY HYPERTENSION	6 (2.6%)	3 (2.8%)	1 (1.8%)	10 (2.5%)
PERSISTANT WORSENING OF FUNCTIONAL CLASS DUE TO PH	4 (1.7%)	1 (0.9%)	0	5 (1.3%)
DEATH	14 (6.1%)	9 (8.3%)	4 (7.1%)	27 (6.8%)

Though the numbers of these events are uncontrolled, and therefore without reference for interpretation, what is notable and can be seen from a K-M curve of time to first TTCW event in the PATENT-2 LTE is that there is little difference in the occurrence of CW events over time with respect to the treatment group the patients were randomized to in PATENT-1, though the group rolling over from the 1.5 mg TID capped arm had numerically fewer CW events over most of the first two years, as can be seen in the figure below:

Figure 47: PATENT-2 LTE K-M for TTCW by Rx group in blinded trial (4 mo. update-2-CHEST, fig 14.2.2/2 pg 189)



7.3.3 Dropouts and/or Discontinuations

CTEPH

Premature discontinuation of study medication occurred in relative few patients in CHEST-1, and the numbers that discontinued were reasonably similar between the active treatment and the placebo arms (8.0% vs. 5.7%, respectively). The primary reasons for premature discontinuation of study medication in CHEST-1 are shown in the table below:

Table 71: CHEST-1 premature discontinuation of study medications (randomized set, FSR table 8-2 pg 81)

	Riociguat 1.0–2.5 mg N=174 (100%)		Placebo N=88 (100%)	
Completed treatment	160	(92.0%)	83	(94.3%)
Prematurely discontinued	14	(8.0%)	5	(5.7%)
Adverse event	4	(2.3%)	2	(2.3%)
Death	2	(1.1%)	2	(2.3%)
Lack of efficacy	2	(1.1%)	1	(1.1%)
Non-compliance with study drug	1	(0.6%)	0	–
Protocol violation	3 [a]	(1.7%)	0	–
Withdrawal by subject	2	(1.1%)	0	–

[a] Including one randomized subject who did not receive study medication.

Among those who discontinued prematurely, there were equal rates of adverse event-mediated pre-mature withdrawals between the groups, and fewer deaths in the IDT active therapy group. All patients experiencing CW events were withdrawn from the trial and are included in these numbers.

PAH

Premature discontinuation of study medication occurred in a numerically higher percentage of placebo-treated patients in PATENT-1. The primary reasons for premature discontinuation of study medication in PATENT-1 are shown in the table below:

Table 72: PATENT-1 premature discontinuation of study medications (randomized set, FSR table 8-2 pg 81)

	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=127 (100%)		Riociguat 1.0–1.5 mg N=64 (100%)	
Completed treatment	237	(93.3%)	111	(87.4%)	57	(89.1%)
Prematurely discontinued	17	(6.7%)	16	(12.6%)	7	(10.9%)
Adverse event	8	(3.1%)	7	(5.5%)	1	(1.6%)
Death	0	–	2	(1.6%)	1	(1.6%)
Lack of efficacy	0	–	1	(0.8%)	0	–
Lost to follow-up	1	(0.4%)	0	–	0	–
Non-compliance with study drug	1	(0.4%)	0	–	0	–
Protocol violation	1	(0.4%)	3 [a]	(2.4%)	3 [a]	(4.7%)
Withdrawal by subject	6	(2.4%)	3	(2.4%)	2	(3.1%)

Among those that discontinued prematurely from PATENT-1, the highest adverse event-related withdrawal rates occurred in placebo-treated patients while the lowest rate occurred in the 1.5 mg TID capped dose arm. 2 placebo-treated patients died, whereas 1 patient treated with riociguat 1.5 mg TID died. The rates for premature "withdrawal by subject" were similar across the groups.

7.3.4 Significant Adverse Events

Hypotension

See section 7.4.3 (vital signs).

Syncope

CTEPH:

In CHEST-1, though hypotension occurred much more frequently in riociguat-treated subjects than in placebo-treated subjects (see section 7.4.3, vital signs), syncope as a TEAE was reported less commonly in the riociguat-treated arm of CHEST-1, occurring in 4 (2.3%) of patients in the IDT treatment arm, and 3 (3.4%) of patients in the placebo treatment arm. Syncope was reported as a drug-related serious TEAE for 3 (1.7%) subjects in the riociguat-IDT group and 1 (1.1%) subject in the placebo group. Pre-syncope was more common in the IDT group. No CHEST-1 subjects discontinued study medication because of syncope or hypotension. A tabular summary of these findings is given below:

Table 73: CHEST-1 TEAEs of special interest - syncope, presyncope, and hypotension (safety set, FSR table 10-14 pg 144)

MedDRA system organ class/ preferred term	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
ANY EVENT	24	(13.9%)	7	(8.0%)
Investigations	3	(1.7%)	1	(1.1%)
Blood pressure decreased	3	(1.7%)	1	(1.1%)
Nervous system disorders	6	(3.5%)	3	(3.4%)
Presyncope	2	(1.2%)	0	–
Syncope	4	(2.3%)	3	(3.4%)
Vascular disorders	17	(9.8%)	3	(3.4%)
Hypotension	16	(9.2%)	3	(3.4%)
Orthostatic hypotension	1	(0.6%)	0	–

In the CHEST-2 LTE to the Mar 2013 cut-off, syncope occurred in 17 (7.2%) of patients, with slightly more of these events occurring in patients who had rolled over from placebo to active drug (8.5% versus 6.5% of those subgroups, respectively). Presyncope occurred in 3 (1.3% of subjects), occurring with a higher incidence among those rolling over from placebo to active (2.4% vs. 0.6%).

PAH:

The syncope, pre-syncope, and hypotension occurrences in PATENT-1 are seen in the table below:

Table 74: PATENT-1 TEAEs of special interest - syncope, presyncope, and hypotension (safety set, FSR table 10-14 pg 157)

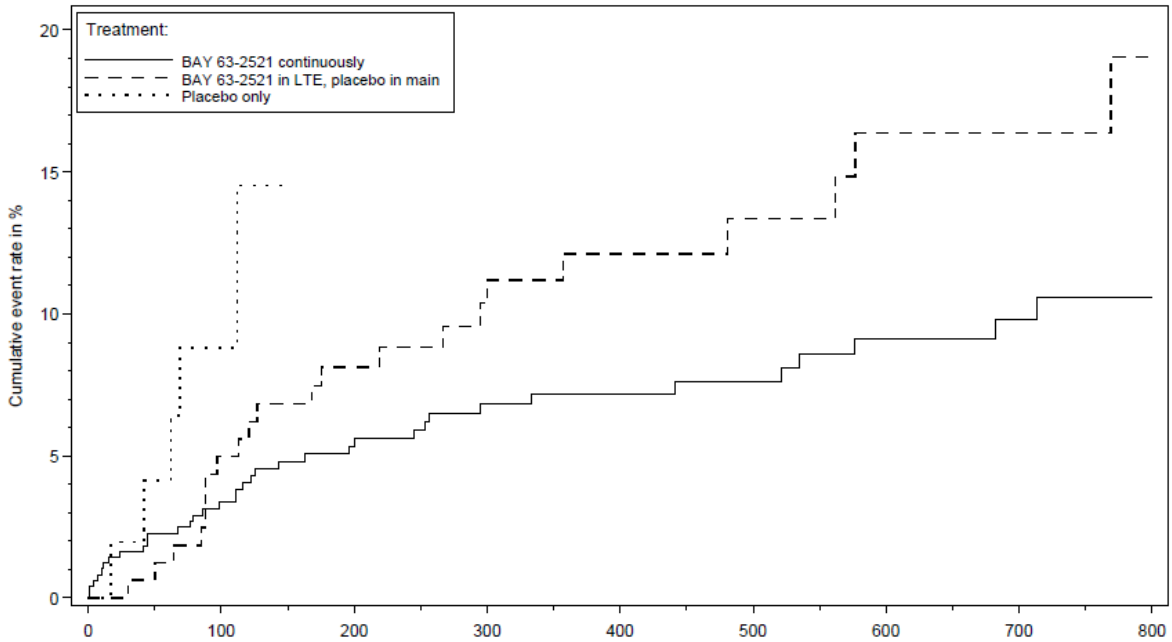
MedDRA system organ class/ preferred term	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
ANY EVENT	34	(13.4%)	11	(8.7%)	4	(6.3%)
Investigations	1	(0.4%)	1	(0.8%)	1	(1.6%)
Blood pressure decreased	1	(0.4%)	1	(0.8%)	1	(1.6%)
Nervous system disorders	8	(3.1%)	7	(5.6%)	2	(3.2%)
Loss of consciousness	0	–	1	(0.8%)	0	–
Presyncope	5	(2.0%)	1	(0.8%)	2	(3.2%)
Syncope	3	(1.2%)	5	(4.0%)	0	–
Vascular disorders	25	(9.8%)	3	(2.4%)	2	(3.2%)
Hypotension	25	(9.8%)	3	(2.4%)	2	(3.2%)

Accordingly, syncope and/or loss of consciousness were more common in the placebo group, while pre-syncope occurred more frequently in the riociguat treatment arms.

All Pivotal Trials

As with the CHEST-1 syncope data, lower rates of syncope occurred in PATENT-1 in spite of a predilection for hypotension in the riociguat IDT treatment arms. This raises the possibility that deleterious peripheral manifestations of low central aortic pressures may be partially offset by vasodilation in local tissue vascular beds. Of note, when all syncopal events across all pivotal trial data (PATENT-1, PATENT-2, CHEST-1 AND CHEST-2) are integrated to the most recent Mar 2013 cutoff, patients who only took placebo in the blinded trials had the highest K-M syncope rates, whereas patients who were on active therapy during both the blinded and LTE trials had the lowest K-M syncope rates, as seen in the figure below:

Figure 48: K-M time to first syncope after starting study drug, all pivotals (safety set, FSR ph37089 pg 7392)



Bleeding Events

CTEPH:

The preferred term “anemia” was more frequently reported in riociguat-treated subjects (riociguat 1.0-2.5 mg 3.5% vs. placebo 1.1%; see FSR table 10-8) and when differences in related laboratory values were seen in the analysis (see FSR table 10-16). Treatment-emergent bleeding events were reported for 23 (13.3%) subjects in the riociguat 1.0-2.5 mg group and 10 (11.4%) subjects in the placebo group (see FSR table 16.1.9.3/9). The most frequently reported bleeding event was hemoptysis (4 subjects [2.3%] in the riociguat 1.0-2.5 mg group vs. 0 subjects in the placebo group). Serious treatment-emergent bleeding events were reported for 6 (3.5%) subjects in the riociguat 1.0-2.5 mg group vs. 0 subjects in the placebo group of CHEST-1, as is seen in the table below:

Table 75: CHEST-1 serious hemorrhage TEAEs (safety set, 11348-statistical, table 16.1.9.3/10 pg 20)

Primary system organ class Preferred term MedDRA version 15.0	BAY 63-2521 Individual Titration N=173 (100%)	Placebo N=88 (100%)
Number of subjects (%) with at least one such adverse event	6 (3.5%)	0
General disorders and administration site conditions	2 (1.2%)	0
Catheter site haemorrhage	2 (1.2%)	0
Reproductive system and breast disorders	1 (0.6%)	0
Vaginal haemorrhage	1 (0.6%)	0
Respiratory, thoracic and mediastinal disorders	3 (1.7%)	0
Haemoptysis	3 (1.7%)	0

The sponsor reports no differences between the treatment groups with regard to aPTT or INR.

PAH:

Similar to the CTEPH findings, in PATENT-1, the preferred term “anemia” was more frequently reported in the riociguat 1.0-2.5 mg group than in the placebo group (riociguat 1.0-2.5 mg 8.3% vs. placebo 2.4% vs. riociguat 1.0-1.5 mg 1.6%; see FSR table 10-8).

Treatment-emergent bleeding events were reported for 28 (11.0%) subjects in the riociguat 1.0-2.5 mg group, 12 (9.5%) subjects in the placebo group, and 7 (11.1%) subjects in the riociguat 1.0-1.5 mg group, showing that the events occurred at a similar frequency in all treatment groups (see FSR table 16.1.9.3/9). The most frequently reported bleeding events were epistaxis (11

subjects [4.3%] in the riociguat 1.0-2.5 mg group vs. 1 subject [0.8%] in the placebo group vs. 1 subject [1.6%] in the riociguat 1.0-1.5 mg group) and hemoptysis (6 subjects [2.4%] vs. 2 subjects [1.6%] vs. 0 subjects).

Serious treatment-emergent bleeding events were reported for 4 (1.6%) subjects in the riociguat 1.0-2.5 mg group vs. 0 subjects in the placebo group vs. 2 (3.2%) subjects in the riociguat 1.0-1.5 mg group. The most frequently reported serious bleeding event was hemoptysis (2 subjects [0.8%], both in the riociguat 1.0-2.5 mg group). These serious bleeding TEAEs from PATENT-1 are shown in the table below:

Table 76: PATENT-1 serious hemorrhage TEAEs (safety set, 11348-statistical, table 16.1.9.3/10 pg 20)

Primary system organ class Preferred term MedDRA version 15.0	BAY 63-2521 Individual Titration N=254 (100%)	Placebo N=126 (100%)	BAY 63-2521 1.5 mg (fixed dose) N=63 (100%)
Number of subjects (%) with at least one such adverse event	4 (1.6%)	0	2 (3.2%)
Gastrointestinal disorders	1 (0.4%)	0	1 (1.6%)
Haematemesis	0	0	1 (1.6%)
Intra-abdominal haemorrhage	1 (0.4%)	0	0
Injury, poisoning and procedural complications	1 (0.4%)	0	0
Subdural haematoma	1 (0.4%)	0	0
Reproductive system and breast disorders	0	0	1 (1.6%)
Vaginal haemorrhage	0	0	1 (1.6%)
Respiratory, thoracic and mediastinal disorders	2 (0.8%)	0	0
Haemoptysis	2 (0.8%)	0	0

There were no differences between the treatment groups with regard to aPTT or INR.

7.3.5 Submission Specific Primary Safety Concerns

Bone Toxicity

The NO-sGC-cGMP pathway is known to be involved in the regulation of bone metabolism, and dose-dependent histopathology abnormalities have been seen in animal studies (particularly juvenile and adolescent rat studies), to include hyperostosis, disorganized bone/bone marrow cavity, reduced epiphyseal bone marrow cells, marked hypertrophy of the growth plate cartilage, and thickening of primary and secondary spongiosa in the metaphysis and diaphyseal funnel. See section 7.6.3 (Pediatrics and Assessment of Effects on Growth), the Toxicology Review, the sponsor's review of bone histology findings in response to FDA IR-19 and IR-21 (Appendices A and B in section

9.4 of this review) and the DRUP consult (Appendix C in section 9.4 of this review) for details.

However, a definitive juvenile animal study using lower doses than the pilot study showed effects on serum electrolytes but without histologic correlates in bone or any other apparent effects. A 26-week mechanistic study in adult rats demonstrated no finding s in animals surviving to the end of the study. Finally, in dogs which were almost full grown at start of treatment, in repeat-dose studies from 2-weeks up to 52-weeks, no skeletal findings were observed at an exposure range up to 3.8 times the human exposure at 2.5 TID.

These latter studies give some confidence that the dose-dependent bone toxic effects seen in the earlier animal studies will not be a problem in humans at lower exposure. This is especially true if the dosing algorithm is shifted downward to a starting dose of 0.5 mg TID, capping at 1.5 mg TID, a change I favor based on the flat E-R relationship seen in both pivotal trials, as well as the parity of efficacy demonstrated in the 1.5 mg TID capped dose arm of PATENT-1. However, in addition to the in-depth review performed by FDA's internal expert on bone metabolism in the DRUP consult, we examined the musculoskeletal safety data from both of the large pivotal trials, and discuss the musculoskeletal safety data from the CTEPH (CHEST-1) and PAH (PATENT-1) trials individually as follows:

CTEPH:

" Musculoskeletal and connective tissue disorders" (MSCTD) was one of the MedDRA primary system organ classes from which TEAEs were most commonly reported in CHEST-1, occurring in 34 (19.7%) of riociguat-treated patients and 19 (21.6%) of placebo-treated patients (table 10-5 pg 131, CHEST-1 FSR), however this SOC was not included in the most commonly reported drug-related TEAEs. The most commonly reported PTs in MSCTD SOC were back pain and pain in extremity, both of which occurred more commonly in the placebo group. None of the MSCTD TEAEs were serious, none were severe, none resulted in study discontinuation, and no MSCTD TEAEs were associated with fatal outcomes. Subjects with MSCTD TEAEs from CHEST-1 are shown in the table below:

Table 77: CHEST-1 subjects with MSCTD TEAEs (safety set, FSR table 14.3.1 / 6 pg 704)

Musculoskeletal and connective tissue disorders	34 (19.7%)	19 (21.6%)
Arthralgia	5 (2.9%)	1 (1.1%)
Arthritis	3 (1.7%)	0
Arthropathy	1 (0.6%)	0
Back pain	7 (4.0%)	5 (5.7%)
Bone pain	1 (0.6%)	1 (1.1%)
Haemarthrosis	1 (0.6%)	0
Joint effusion	1 (0.6%)	0
Joint swelling	0	2 (2.3%)
Muscle haemorrhage	1 (0.6%)	0
Muscle spasms	4 (2.3%)	2 (2.3%)
Muscle tightness	1 (0.6%)	0
Musculoskeletal chest pain	0	2 (2.3%)
Musculoskeletal pain	5 (2.9%)	2 (2.3%)
Musculoskeletal stiffness	2 (1.2%)	0
Myalgia	4 (2.3%)	1 (1.1%)
Myofascial pain syndrome	1 (0.6%)	0
Neck pain	2 (1.2%)	0
Osteoarthritis	2 (1.2%)	0
Pain in extremity	3 (1.7%)	5 (5.7%)
Pain in jaw	1 (0.6%)	0
Plantar fascial fibromatosis	1 (0.6%)	0
Spinal osteoarthritis	1 (0.6%)	0

In the CHEST-2 LTE study FSR (cut-off Mar 2012), MSCTD TEAEs occurred in 58/194 (29.9%) of subjects (Table 10-5, pg 89, CHEST-2 FSR), but these were not among the most frequent drug-related TEAEs (≥ 5% of subjects in any treatment group). Arthralgia and back pain were the most commonly reported PTs. None of the MSCTD TEAEs were severe, none were serious, and none resulted in death.

No CTEPH patients discontinued riociguat therapy due to MSCTD TEAEs as of the Nov 2012 cut-off of the ISS, nor were there discontinuations of therapy between Nov 2012 and time of the 4 month safety update (cut-off Mar 2013).

PAH:

" Musculoskeletal and connective tissue disorders" (MSCTD) was one of the MedDRA primary system organ classes from which TEAEs were most commonly reported in PATENT-1, occurring in 50 (15.8%) of riociguat-treated patients and 20 (15.8%) of placebo-treated patients (table 10-5 pg 142, PATENT-1 FSR), however this SOC was not included in the most commonly reported drug-related TEAEs. The most commonly reported PTs in MSCTD SOC were back pain (more common in the riociguat capped dose arm) and "pain in extremity" (more common in placebo arm). None of the MSCTD TEAEs were serious, none were severe, and no MSCTD TEAEs were associated with fatal outcomes. Only one subject (0.4%) in the riociguat IDT arm discontinued study drug due to a MSCTD TEAE (neck pain and generalized edema, severe but non-serious, related to

study drug). Subjects with MSCTD TEAEs from PATENT-1 are shown in the table below:

Table 78: PATENT-1 subjects with MSCTD TEAEs (safety set, FSR table 14.3.1 / 6 pg 949)

Musculoskeletal and connective tissue disorders	40 (15.7%)	20 (15.9%)	10 (15.9%)
Arthralgia	8 (3.1%)	3 (2.4%)	0
Arthritis	2 (0.8%)	0	0
Back pain	9 (3.5%)	4 (3.2%)	3 (4.8%)
Connective tissue disorder	0	1 (0.8%)	0
Groin pain	1 (0.4%)	1 (0.8%)	0
Intervertebral disc protrusion	1 (0.4%)	1 (0.8%)	0
Joint stiffness	0	1 (0.8%)	0
Joint swelling	3 (1.2%)	0	1 (1.6%)
Muscle haemorrhage	0	0	1 (1.6%)
Muscle spasms	3 (1.2%)	4 (3.2%)	1 (1.6%)
Muscular weakness	0	1 (0.8%)	1 (1.6%)
Musculoskeletal chest pain	1 (0.4%)	0	0
Musculoskeletal discomfort	0	1 (0.8%)	0
Musculoskeletal pain	4 (1.6%)	3 (2.4%)	0
Musculoskeletal stiffness	1 (0.4%)	0	0
Myalgia	2 (0.8%)	1 (0.8%)	2 (3.2%)
Neck pain	2 (0.8%)	0	1 (1.6%)
Pain in extremity	11 (4.3%)	6 (4.8%)	0
Pain in jaw	2 (0.8%)	0	0
Pathological fracture	1 (0.4%)	0	0
Plantar fasciitis	1 (0.4%)	0	0
Sjogren's syndrome	1 (0.4%)	0	0
Systemic lupus erythematosus	0	0	1 (1.6%)

In the PATENT-2 LTE study FSR (cut-off Feb 2012), MSCTD TEAEs occurred in 99/363 (27.3%) of subjects (Table 14.3.1/6, pg 1058, PATENT-2 FSR), with 11/363 (3.0%) listed as drug-related. Arthralgia and back pain were the most commonly reported PTs. Four of the back pain TEAEs were severe, but none of the MSCTD TEAEs were serious, and none resulted in death.

No PAH patients discontinued riociguat therapy due to MSCTD TEAEs as of the Nov 2012 cut-off of the ISS, nor were there discontinuations of therapy between Nov 2012 and time of the 4 month safety update (cut-off Mar 2013).

Atrial fibrillation

CTEPH. Atrial fibrillation and/or atrial flutter and/or atrial tachycardia occurred in 6 (3.5%) of the riociguat-IDT-treated patients versus 1 (1.1%) of the placebo-treated patient in CHEST-1.

PAH. Atrial fibrillation occurred in 2 (0.8%) of patients in the IDT arm only. There were no cases of atrial flutter of atrial tachycardia in PATENT-1.

Pooled. In follow-up to this observation from the blinded data, the sponsor noted the following integrated analysis for atrial fibrillation across the riociguat development programs:

> *The difference in incidence between treatment groups observed in Pool 1 was more pronounced in Pool 3, with TEAEs of atrial fibrillation reported in 13 subjects (1.7%) for riociguat and no subjects for placebo in the pooled main studies and in 11 subjects (1.7%) in the pooled LTE studies (Technical Report PH-37089 in Module 5.3.5.3, Tables 3.2.2.1/5). These events were non-serious in most subjects: atrial fibrillation was reported as a serious TEAE in 4 subjects (0.5%) in the pooled riociguat group in the main studies and in 5 subjects (0.8%) in the pooled LTE studies (Technical Report PH-37089 in Module 5.3.5.3, Tables 3.2.2.1/6). The total number of atrial fibrillation TEAEs observed in Pool 3 (19 in the pooled riociguat group in the main studies and 15 in the pooled LTE studies; Technical Report PH-37089 in Module 5.3.5.3, Tables 3.2.2.1/11) was higher than the number of subjects experiencing such events, indicating recurrent atrial fibrillation in some subjects. The treatment difference suggested by the adverse event profile was not supported by ECG findings which showed evidence of atrial fibrillation in 38 subjects (5.0%) in the pooled riociguat group and 12 subjects (4.2%) in the pooled placebo group in the main studies (Technical Report PH-37089 in Module 5.3.5.3, Table 3.2.5/1). These ECG findings suggest the need for caution in interpreting the incidence of atrial fibrillation as a TEAE. It is known from the literature that atrial fibrillation has a higher incidence in a PH population than in a normal population of similar age (5). The atrial fibrillation observed is in line with the expected background incidence in this population.*

Reviewer's note: I agree with the sponsor's overall interpretation here. The numbers of these cases in the controlled PH trials was very small, and a single patient with frequent paroxysms can drive occurrence numbers in follow-up. This population is at risk for the occurrence of atrial fibrillation due to the high intra-atrial back-pressures on the right side of the heart. It would be interesting to know if the occurrence of atrial arrhythmias in any way relates to the degree by which blood pressure fell in titration phase of IDT drug initiation.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

CTEPH

Overall, there were more adverse events experienced by patients on riociguat-IDT therapy, and these tended to be more drug-related and more serious, and more prone to lead to discontinuation, as can be seen in the following summary of AEs from CHEST-1:

Table 79: CHEST-1 summary of adverse events (safety set, FSR table 10-4 pg 129)

Type of AE	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
Any AE	160	(92.5%)	78	(88.6%)
Any TEAE	159	(91.9%)	76	(86.4%)
Any drug-related TEAE	103	(59.5%)	36	(40.9%)
Any severe TEAE	19	(11.0%)	10	(11.4%)
Any drug-related severe TEAE	4	(2.3%)	2	(2.3%)
Any serious TEAE	34	(19.7%)	14	(15.9%)
Any drug-related serious TEAE	6	(3.5%)	1	(1.1%)
Any TEAE leading to discontinuation of study medication	5	(2.9%)	2	(2.3%)
Any drug-related TEAE leading to discontinuation of study medication	1	(0.6%)	0	–
Any TEAE leading to death	2	(1.2%)	3	(3.4%)

Insight into what drove these trends can be seen in the treatment emergent adverse events occurring more frequently in the riociguat-IDT arm than in the placebo group, as seen in the following table:

Table 80: CHEST-1 TEAE preferred terms occurring more than 2% more frequently in riociguat-IDT arm than placebo (safety set, FSR table 10-8 pg 134)

MedDRA preferred term	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
Headache	43	(24.9%)	12	(13.6%)
Dizziness	39	(22.5%)	11	(12.5%)
Dyspepsia	31	(17.9%)	7	(8.0%)
Nasopharyngitis	26	(15.0%)	8	(9.1%)
Nausea	19	(11.0%)	7	(8.0%)
Diarrhoea	17	(9.8%)	4	(4.5%)
Vomiting	17	(9.8%)	3	(3.4%)
Hypotension	16	(9.2%)	3	(3.4%)
Constipation	10	(5.8%)	1	(1.1%)
Activated partial thromboplastin time prolonged	8	(4.6%)	2	(2.3%)
Gastrooesophageal reflux disease	7	(4.0%)	0	–
Anaemia	6	(3.5%)	1	(1.1%)
Dysphagia	6	(3.5%)	0	–
Gastritis	6	(3.5%)	0	–
Abdominal pain	4	(2.3%)	0	–
Haemoptysis	4	(2.3%)	0	–
Pulmonary hypertension	4	(2.3%)	0	–
Respiratory failure	4	(2.3%)	0	–

Most of these events can be attributed to riociguat's mode of action as a smooth muscle dilator (headache, dizziness, hypotension, constipation, GI reflux). Arguably the most severe TEAEs of cardiac arrest and RV failure occurred predominantly in the placebo arm, as seen in the following table:

Table 81: CHEST-1 severe TEAEs occurring in >1 subject in any treatment group (safety set, FSR table 10-10 pg 136)

MedDRA preferred term	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
ANY EVENT	19	(11.0%)	10	(11.4%)
Cardiac arrest	0	–	2	(2.3%)
Headache	2	(1.2%)	0	–
Right ventricular failure	3	(1.7%)	3	(3.4%)

GI disorders, catheter site hemorrhage, chronic renal failure, hemoptysis, pulmonary hypertension, and respiratory failure were TE serious adverse events occurring more frequently in the riociguat treatment arm, as can be seen in the following table:

Table 82: CHEST-1 serious TEAEs occurring in >1 subject in any treatment group (safety set, FSR table 10-12 pg 140)

MedDRA system organ class/ preferred term	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
ANY EVENT	34	(19.7%)	14	(15.9%)
Cardiac disorders	10	(5.8%)	6	(6.8%)
Cardiac arrest	0	–	2	(2.3%)
Right ventricular failure	6	(3.5%)	3	(3.4%)
Gastrointestinal disorders	4	(2.3%)	1	(1.1%)
Gastritis	2	(1.2%)	0	–
General disorders and administration site conditions	4	(2.3%)	0	–
Catheter site haemorrhage	2	(1.2%)	0	–
Nervous system disorders	4	(2.3%)	3	(3.4%)
Syncope	4	(2.3%)	3	(3.4%)
Renal and urinary disorders	4	(2.3%)	1	(1.1%)
Renal failure chronic	2	(1.2%)	0	–
Respiratory, thoracic and mediastinal disorders	11	(6.4%)	2	(2.3%)
Haemoptysis	3	(1.7%)	0	–
Pulmonary hypertension	2	(1.2%)	0	–
Respiratory failure	2	(1.2%)	0	–

PAH

Overall, there were more adverse events experienced by patients on riociguat-IDT and riociguat-capped therapy than were experienced by placebo-treated patients. Of particular note, the occurrence of severe drug-related TEAEs was least frequent in the riociguat-capped arm, followed by placebo, and then by riociguat-IDT, whereas serious drug-related TEAEs were most frequent in the placebo arm, and fairly evenly split between the riociguat arms. TEAEs leading to discontinuation were least frequent in the riociguat-capped arm. The number of deaths was low in all groups, as shown in the PATENT-1 summary of adverse events table below:

Table 83: PATENT-1 summary of adverse events (safety set, FSR table 10-4 pg 140)

Type of AE	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
Any AE	230	(90.6%)	111	(88.1%)	59	(93.7%)
Any TEAE	227	(89.4%)	108	(85.7%)	58	(92.1%)
Any drug-related TEAE	162	(63.8%)	66	(52.4%)	39	(61.9%)
Any severe TEAE	28	(11.0%)	19	(15.1%)	6	(9.5%)
Any drug-related severe TEAE	15	(5.9%)	5	(4.0%)	1	(1.6%)
Any serious TEAE	29	(11.4%)	23	(18.3%)	11	(17.5%)
Any drug-related serious TEAE	8	(3.1%)	5	(4.0%)	2	(3.2%)
Any TEAE leading to discontinuation of study medication	8	(3.1%)	9	(7.1%)	1	(1.6%)
Any drug-related TEAE leading to discontinuation of study medication	6	(2.4%)	5	(4.0%)	0	–
Any TEAE leading to death	2	(0.8%)	3	(2.4%)	1	(1.6%)

As in the CTEPH trial, most of the riociguat TEAEs could be ascribed to the smooth muscle dilatory action of the drug, as can be seen in the following table:

Table 84: PATENT-1 TEAE preferred terms occurring more than 2% more frequently in riociguat-IDT arm than placebo (safety set, FSR table 10-8 pg 146

MedDRA preferred term	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
Headache	69	(27.2%)	25	(19.8%)	20	(31.7%)
Dyspepsia	48	(18.9%)	10	(7.9%)	8	(12.7%)
Oedema peripheral	44	(17.3%)	14	(11.1%)	14	(22.2%)
Dizziness	40	(15.7%)	15	(11.9%)	15	(23.8%)
Nausea	40	(15.7%)	16	(12.7%)	10	(15.9%)
Diarrhoea	35	(13.8%)	13	(10.3%)	6	(9.5%)
Hypotension	25	(9.8%)	3	(2.4%)	2	(3.2%)
Anaemia	21	(8.3%)	3	(2.4%)	1	(1.6%)
Palpitations	20	(7.9%)	6	(4.8%)	5	(7.9%)
Gastrooesophageal reflux disease	14	(5.5%)	4	(3.2%)	4	(6.3%)
Epistaxis	11	(4.3%)	1	(0.8%)	1	(1.6%)
Insomnia	9	(3.5%)	1	(0.8%)	1	(1.6%)
Abdominal discomfort	7	(2.8%)	1	(0.8%)	0	–
Gastroenteritis	7	(2.8%)	1	(0.8%)	1	(1.6%)

Once again, both cases of severe renal failure occurred in the riociguat-IDT arm, per the following table:

Table 85: PATENT-1 severe TEAEs occurring in >1 subject in any treatment group (safety set, FSR table 10-10 pg 149)

MedDRA preferred term	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
ANY EVENT	28	(11.0%)	19	(15.1%)	6	(9.5%)
Abdominal pain	2	(0.8%)	0	–	0	–
Back pain	2	(0.8%)	1	(0.8%)	1	(1.6%)
Dizziness	3	(1.2%)	0	–	0	–
Nausea	2	(0.8%)	1	(0.8%)	0	–
Pulmonary arterial hypertension	1	(0.4%)	2	(1.6%)	1	(1.6%)
Renal failure acute	2	(0.8%)	0	–	0	–
Right ventricular failure	0	–	0	–	2	(3.2%)

Once again, hemoptysis as a serious TEAE only occurred in the riociguat-IDT arm, as shown below:

Table 86: PATENT-1 serious TEAEs occurring in >1 subject in any treatment group (safety set, FSR table 10-12 pg 153)

MedDRA system organ class/ preferred term	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
ANY EVENT	29	(11.4%)	23	(18.3%)	11	(17.5%)
Cardiac disorders	5	(2.0%)	2	(1.6%)	3	(4.8%)
Right ventricular failure	2	(0.8%)	1	(0.8%)	3	(4.8%)
General disorders and administration site conditions	4	(1.6%)	2	(1.6%)	0	–
Chest pain	2	(0.8%)	1	(0.8%)	0	–
Infections and infestations	6	(2.4%)	4	(3.2%)	3	(4.8%)
Pneumonia	2	(0.8%)	0	–	1	(1.6%)
Nervous system disorders	5	(2.0%)	7	(5.6%)	0	–
Syncope	3	(1.2%)	5	(4.0%)	0	–
Renal and urinary disorders	2	(0.8%)	0	–	0	–
Renal failure acute	2	(0.8%)	0	–	0	–
Respiratory, thoracic and mediastinal disorders	7	(2.8%)	6	(4.8%)	1	(1.6%)
Haemoptysis	2	(0.8%)	0	–	0	–
Pulmonary arterial hypertension	1	(0.4%)	2	(1.6%)	1	(1.6%)

7.4.2 Laboratory Findings

Arterial Blood Gases

CTEPH

Given the fact that the pathology in Group IV PH-CTEPH is confined to the pulmonary arterial tree and does not extend to the gas exchange unit in the alveolus, desaturation with riociguat therapy would not be expected. After systematic evaluation, this was not demonstrated in the CTEPH population as can be seen below in the descriptive statistics of by-visit PaO2 and PaCO2 analyses from CHEST-1:

Table 87: CHEST-1 PaO2 (mmHg) summary statistics (safety set, FSR table 14.3.5/7 pg 1273)

		Value at Visit						Change from Baseline					
Treatment group	Analysis Visit	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
BAY 63-2521 Individual Titration (N=173)	Baseline	172	69.84	11.71	51.0	67.00	113.0						
	Visit 2 (Day 14)	1	70.00	.	70.0	70.00	70.0	1	-3.00	.	-3.0	-3.00	-3.0
	Visit 4 (Day 42)	1	68.00	.	68.0	68.00	68.0	1	0.00	.	0.0	0.00	0.0
	Visit 6 (Day 84)	2	56.00	18.38	43.0	56.00	69.0	2	-26.00	36.77	-52.0	-26.00	0.0
	Visit 7 (Day 112)	150	66.30	14.07	39.0	64.00	121.0	149	-2.70	14.24	-41.0	-2.00	66.0
	Last Visit	152	66.16	14.10	39.0	64.00	121.0	151	-3.01	14.71	-52.0	-2.00	66.0
	Safety Follow-up Visit	5	62.80	19.31	44.0	55.00	92.0	5	-8.60	26.58	-51.0	-3.00	22.0
Placebo (N=88)	Baseline	87	69.22	11.03	55.0	66.00	110.0						
	Visit 6 (Day 84)	1	60.00	.	60.0	60.00	60.0	1	1.00	.	1.0	1.00	1.0
	Visit 7 (Day 112)	80	64.26	13.76	25.0	63.00	108.0	79	-5.03	12.11	-36.0	-3.00	27.0
	Last Visit	81	64.21	13.69	25.0	63.00	108.0	80	-4.95	12.05	-36.0	-2.50	27.0
	Safety Follow-up Visit	2	65.00	19.80	51.0	65.00	79.0	2	-5.50	3.54	-8.0	-5.50	-3.0

Table 88: CHEST-1 PaCO2 (mm Hg) summary statistics (safety set, FSR Table 14.3.5/6 pg 1272)

		Value at Visit						Change from Baseline					
Treatment group	Analysis Visit	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
BAY 63-2521 Individual Titration (N=173)	Baseline	172	33.24	4.63	17.0	33.00	47.0						
	Visit 2 (Day 14)	1	31.00	.	31.0	31.00	31.0	1	0.00	.	0.0	0.00	0.0
	Visit 4 (Day 42)	1	30.00	.	30.0	30.00	30.0	1	2.00	.	2.0	2.00	2.0
	Visit 6 (Day 84)	2	38.50	0.71	38.0	38.50	39.0	2	0.50	0.71	0.0	0.50	1.0
	Visit 7 (Day 112)	150	33.66	4.26	21.0	33.00	48.0	149	0.34	4.08	-11.0	0.00	15.0
	Last Visit	152	33.72	4.27	21.0	33.00	48.0	151	0.34	4.05	-11.0	0.00	15.0
	Safety Follow-up Visit	5	34.00	4.18	29.0	33.00	40.0	5	1.40	3.36	-2.0	1.00	7.0
Placebo (N=88)	Baseline	87	33.38	4.54	24.0	33.00	47.0						
	Visit 6 (Day 84)	1	28.00	.	28.0	28.00	28.0	1	-2.00	.	-2.0	-2.00	-2.0
	Visit 7 (Day 112)	80	34.00	5.60	21.0	35.00	48.0	79	0.59	4.54	-10.0	0.00	18.0
	Last Visit	81	33.93	5.61	21.0	35.00	48.0	80	0.56	4.52	-10.0	0.00	18.0
	Safety Follow-up Visit	2	27.50	0.71	27.0	27.50	28.0	2	-3.00	0.00	-3.0	-3.00	-3.0

PAH

Given the fact that the pathology in Group I PAH is confined to the pulmonary arterial tree and does not extend to the gas exchange unit in the alveolus, desaturation with riociguat therapy would not be expected. After systematic evaluation, this was not demonstrated in the PAH population as can be seen below in the descriptive statistics of by-visit PaO2 and PaCO2 analyses from PATENT-1:

Table 89: PATENT-1 PaO_2 (mmHg) summary statistics (safety set, FSR table 14.3.5/7 pg 1726)

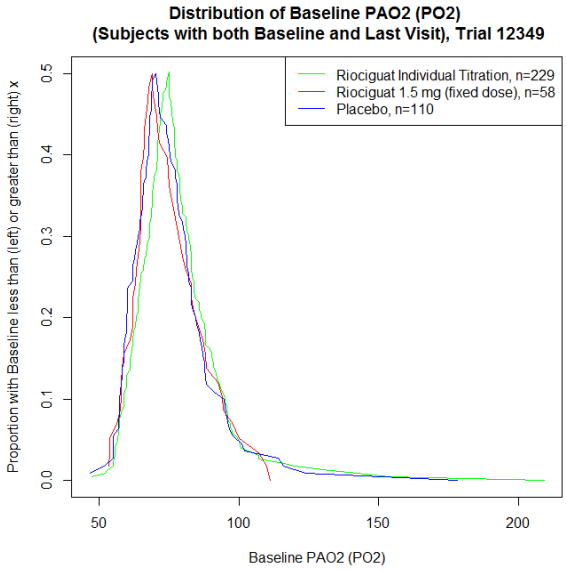
		Value at Visit						Change from Baseline					
Treatment group	Analysis Visit	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
BAY 63-2521 Individual Titration (N=254)	Pre Treatment	1	86.70	.	86.7	86.70	86.7						
	Baseline	249	76.66	17.68	47.5	74.00	209.0						
	Visit 3 (Day 28)	2	71.50	14.85	61.0	71.50	82.0	2	0.50	6.36	-4.0	0.50	5.0
	Visit 4 (Day 42)	2	73.20	3.82	70.5	73.20	75.9	2	-0.50	7.07	-5.5	-0.50	4.5
	Visit 5 (Day 56)	2	56.60	19.66	42.7	56.60	70.5	2	-12.00	14.00	-21.9	-12.00	-2.1
	Visit 6 (Day 84)	226	74.68	21.32	34.6	71.45	213.0	221	-2.04	21.55	-100.0	-3.20	144.4
	Last Visit	229	74.13	21.53	34.6	71.25	213.0	224	-2.43	21.77	-100.0	-3.55	144.4
	Safety Follow-up Visit	8	64.25	13.05	43.3	62.50	86.0	8	-0.25	14.15	-21.3	2.40	24.0
Placebo (N=126)	Baseline	126	73.57	17.04	46.8	69.00	178.0						
	Visit 3 (Day 28)	1	53.25	.	53.3	53.25	53.3	1	-12.75	.	-12.8	-12.75	-12.8
	Visit 4 (Day 42)	1	54.00	.	54.0	54.00	54.0	1	-11.60	.	-11.6	-11.60	-11.6
	Visit 5 (Day 56)	1	56.90	.	56.9	56.90	56.9	1	-10.90	.	-10.9	-10.90	-10.9
	Visit 6 (Day 84)	107	73.04	19.33	22.3	69.00	168.0	107	-1.26	19.00	-92.0	-1.00	70.0
	Last Visit	109	72.72	19.24	22.3	68.40	168.0	109	-1.35	18.88	-92.0	-1.00	70.0
	Safety Follow-up Visit	9	65.88	13.38	47.1	65.00	90.0	9	-2.96	11.92	-17.0	-4.00	22.2
BAY 63-2521 1.5 mg (fixed dose) (N=63)	Baseline	63	72.12	14.08	53.7	68.10	111.1						
	Visit 2 (Day 14)	1	85.00	.	85.0	85.00	85.0	1	15.00	.	15.0	15.00	15.0
	Visit 3 (Day 28)	2	83.10	29.84	62.0	83.10	104.2	2	-6.40	2.26	-8.0	-6.40	-4.8
	Visit 4 (Day 42)	1	78.10	.	78.1	78.10	78.1	1	23.10	.	23.1	23.10	23.1
	Visit 6 (Day 84)	54	72.52	20.42	44.0	70.30	133.0	54	0.66	15.40	-27.0	-0.90	56.0
	Last Visit	54	72.52	20.42	44.0	70.30	133.0	54	0.66	15.40	-27.0	-0.90	56.0
	Safety Follow-up Visit	5	73.16	15.96	53.0	72.00	90.0	5	6.76	8.58	-3.0	7.00	20.0

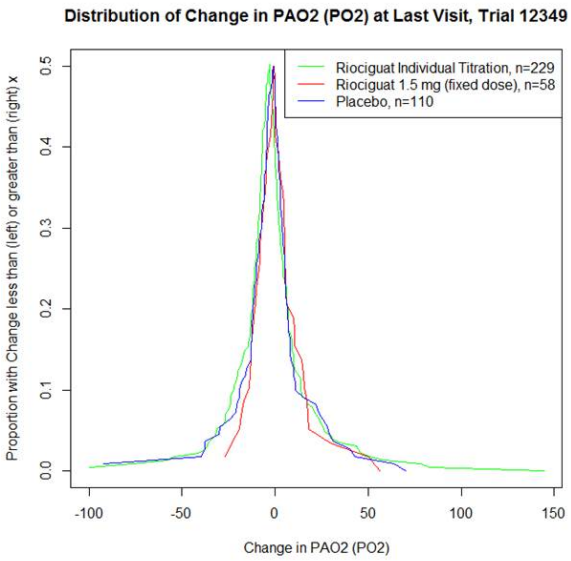
)

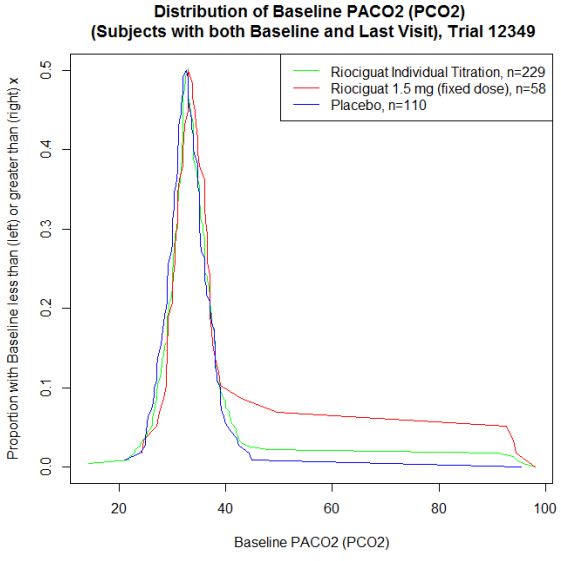
Table 90: PATENT-1 $PaCO_2$ (mmHg) summary statistics (safety set, FSR table 14.3.5/6 pg 1725)

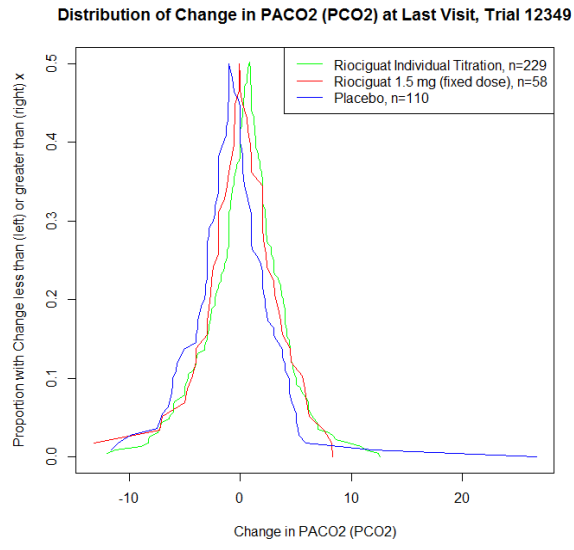
		Value at Visit						Change from Baseline					
Treatment group	Analysis Visit	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
BAY 63-2521 Individual Titration (N=254)	Pre Treatment	1	31.00	.	31.0	31.00	31.0						
	Baseline	249	32.95	4.57	14.3	32.40	47.9						
	Visit 3 (Day 28)	2	32.50	3.54	30.0	32.50	35.0	2	0.00	2.83	-2.0	0.00	2.0
	Visit 4 (Day 42)	2	33.05	0.07	33.0	33.05	33.1	2	0.85	1.48	-0.2	0.85	1.9
	Visit 5 (Day 56)	2	38.13	10.78	30.5	38.13	45.8	2	-0.03	1.24	-0.9	-0.03	0.9
	Visit 6 (Day 84)	226	33.59	4.60	15.8	33.45	50.0	221	0.60	4.00	-12.0	0.80	12.6
	Last Visit	229	33.60	4.61	15.8	33.40	50.0	224	0.64	3.99	-12.0	0.85	12.6
	Safety Follow-up Visit	8	35.98	4.10	30.7	34.85	43.5	8	1.35	3.06	-2.0	1.15	7.0
Placebo (N=126)	Baseline	126	32.55	4.79	21.0	32.05	44.9						
	Visit 3 (Day 28)	1	31.50	.	31.5	31.50	31.5	1	2.25	.	2.3	2.25	2.3
	Visit 4 (Day 42)	1	39.00	.	39.0	39.00	39.0	1	2.70	.	2.7	2.70	2.7
	Visit 5 (Day 56)	1	32.20	.	32.2	32.20	32.2	1	-5.80	.	-5.8	-5.80	-5.8
	Visit 6 (Day 84)	107	32.19	5.51	20.4	32.00	58.0	107	-0.52	4.59	-11.6	-1.00	26.7
	Last Visit	109	32.18	5.48	20.4	32.00	58.0	109	-0.55	4.60	-11.6	-1.00	26.7
	Safety Follow-up Visit	9	36.92	5.27	27.8	38.20	43.5	9	1.19	3.12	-3.4	0.00	5.5
BAY 63-2521 1.5 mg (fixed dose) (N=63)	Baseline	63	33.51	4.43	24.0	33.70	49.6						
	Visit 2 (Day 14)	1	37.30	.	37.3	37.30	37.3	1	0.60	.	0.6	0.60	0.6
	Visit 3 (Day 28)	2	36.00	0.00	36.0	36.00	36.0	2	-0.38	0.53	-0.8	-0.38	0.0
	Visit 4 (Day 42)	1	27.00	.	27.0	27.00	27.0	1	3.00	.	3.0	3.00	3.0
	Visit 6 (Day 84)	54	33.42	4.21	26.7	33.45	43.2	54	0.13	4.07	-13.2	-0.10	8.3
	Last Visit	54	33.42	4.21	26.7	33.45	43.2	54	0.13	4.07	-13.2	-0.10	8.3
	Safety Follow-up Visit	5	34.56	4.52	27.8	36.00	40.0	5	0.22	3.36	-4.0	0.00	3.8

In order to assure that the dose groups that were assessed in the PAH trial were equivalent at baseline, and that there indeed was no dose effect of the drug on gas exchange, mountain plots (cumulative function analyses) were constructed from every blood gas result from every patient in PATENT-1 to rule out a drug induced "leftward shift" as well as a drug-induced leftward "tail" in these plots. As can be seen from the plots below, all dose groups demonstrated equivalent gas exchange at baseline and there was no drug-induced deterioration of gas exchange:









Reviewer's conclusions:

- *The three PATENT-1dose arms are similar with respect to baseline PaO2 and PaCO2*
- *There is no drug-induced intrapulmonary shunting evident with respect to drug-induced hypercarbia and/or hypoxia relative to placebo*
- *There is no dose effect.*

Renal Function

Events of renal failure

There were 6 serious TEAEs of renal failure in CHEST-1 and PATENT-1 combined. All four patients had been treated with riociguat IDT. One of these subjects was a 46 year old female CTEPH patient who also suffered right heart failure/deterioration on day 54 of the study. Three days later, she developed anemia and a hemodialysis catheter hemorrhage. This patient died. Causes of death were reported as renal impairment, bleeding, and anemia.

In following up on this potential safety signal, the sponsor noted the following from their integrated safety analysis:

> *The treatment difference observed in Pool 1 was also apparent in Pool 3. Serious TEAEs of renal failure (renal failure, renal failure acute, renal failure chronic, renal impairment) were observed in 10 subjects (1.3%) in the pooled riociguat group in the main studies in Pool 3, and in 1 subject (0.3%) in the pooled placebo group (Technical Report PH-37089 in Module 5.3.5.3, Tables 3.2.2.1/6). Most TEAEs of renal failure had the outcome "recovered/resolved", but 2 were not resolved and 1 had a fatal outcome (Technical Report PH-37089 in Module 5.3.5.3, Tables 3.2.2.1/20).*

Certainly, this could be the play of chance in small numbers in patients with many co-morbidities (or the unusual case of M1 metabolite renal effects). However, two specific possibilities were of concern to this reviewer:

1. Is riociguat a direct nephrotoxin, and
2. Were these renal failure events associated with drug-induced hypotension (an indirect nephrotoxicity as it were that might emerge from population GFR/creatinine analysis).

CTEPH

Renal failure (acute, chronic or unspecified) was reported as a serious TEAE for a total of 4 subjects in the riociguat IDT group (100068005, 380018013, 380018017, 470028004) but for no subjects in the placebo group. One placebo subject (100018003)

had a serious TEAE of renal impairment (see Table 14.3.1/9). While one of the riociguat patients had a history of an SBP <90 event, his SBP was baseline at the time of his renal failure event. All three of the other subjects suffered deterioration of their right heart failure, one developed lung cancer, another developed new onset atrial fibrillation that antedated her RV decompensation.

Mountain plot analysis demonstrated that riociguat patients and placebo patients had almost identical renal function as groups before drug (absolute creatinine), and that there was no evidence of a clinically important, drug-induced increase in serum creatinine (change from baseline), as can be seen in the following two mountain plots:

Figure 49: CHEST-1 baseline serum creatinine

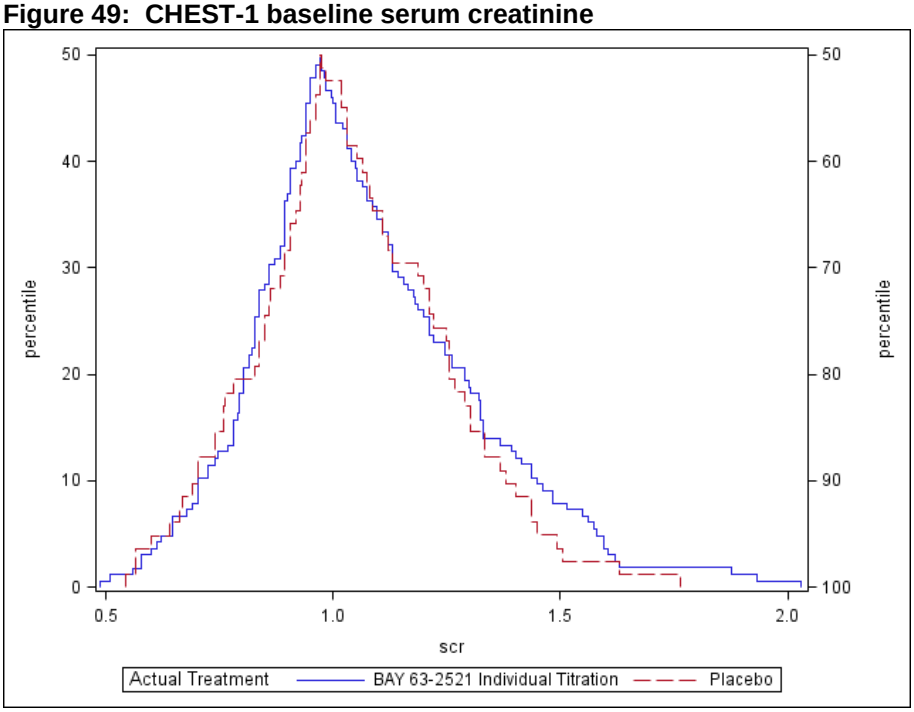
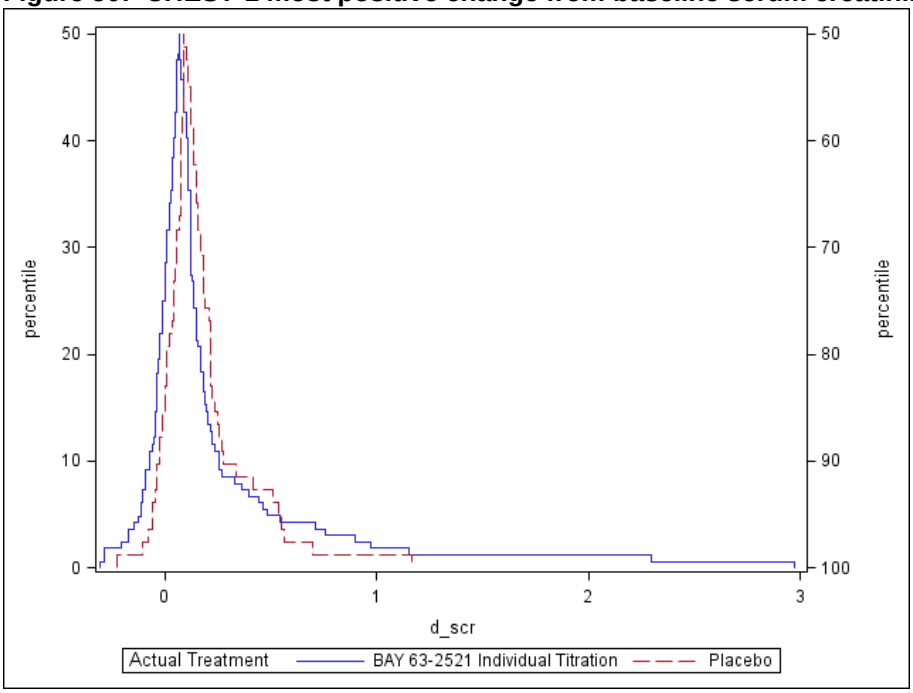


Figure 50: CHEST-1 most positive change from baseline serum creatinine



PAH

In the PATENT-1, one TEAE of renal failure led to discontinuation of the drug. This patient also was suffering from MRSA sepsis, and had severe RV systolic dysfuction by echo that did not recover and the patient died. A second case was not felt to be drug related, the patient continued drug therapy and completed PATENT-1. Other renal TEAEs of "Renal impairment" were not dose responsive.

Mountain plot analysis of serum creatinine by dose in PATENT-1 demonstrated similarity between the arms with respect to baseline serum creatinine. Drug therapy did not show important separations of the change from baseline peaks, but did demonstrate a rightward (upward) shift in the creatinine "tail" of the change from baseline plot in the riociguat-IDT arm, as opposed to a leftward (downward) shift in the higher creatinine values for the riociguate-capped dose arm. These findings are shown in the two mountain plots below:

Figure 51: PATENT-1 baseline serum creatinine

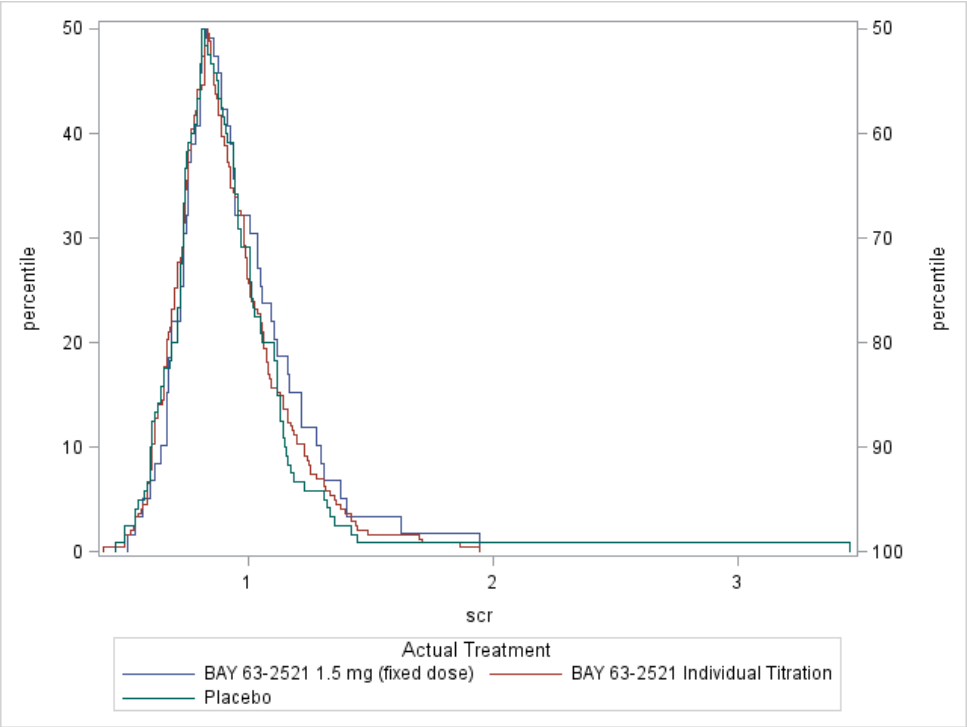
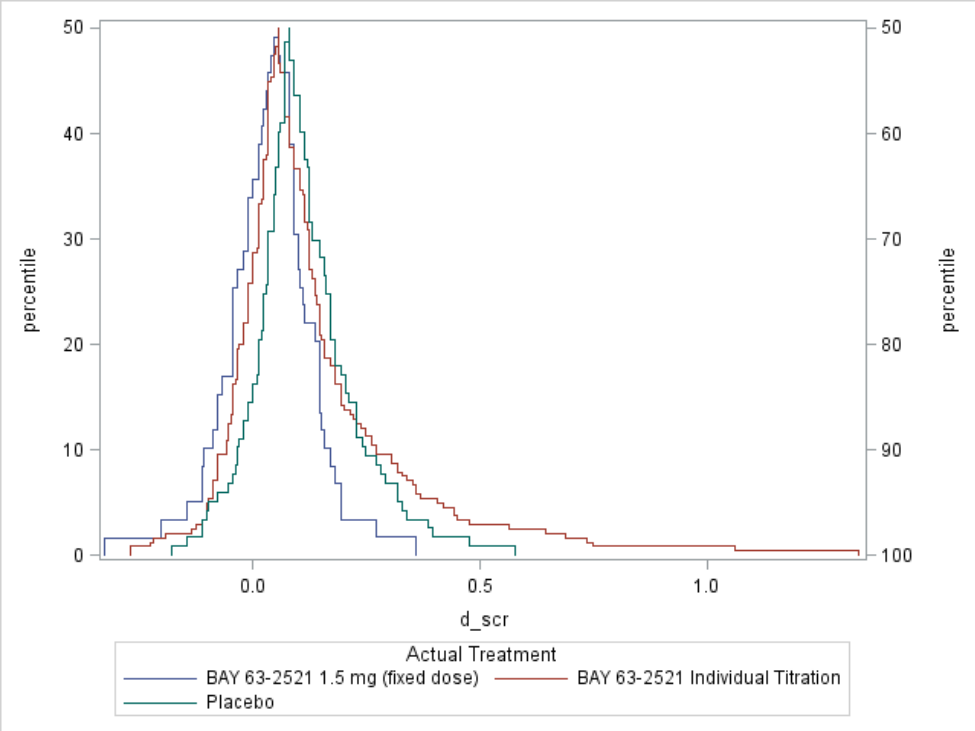


Figure 52: PATENT-1 most positive change from baseline serum creatinine



This analysis suggests that there may in fact be a dose-related negative impact on serum creatinine connetrations in the unusual vulnerable patient receiving the higher dose of riociguat, but the mechanism of this, and its clinical significance if real, is unclear.

Liver Function Tests

No evidence of DILI was seen in either CHEST-1 or PATENT-1, as shown in the two figures below:

Figure 53: CHEST-1 liver function tests

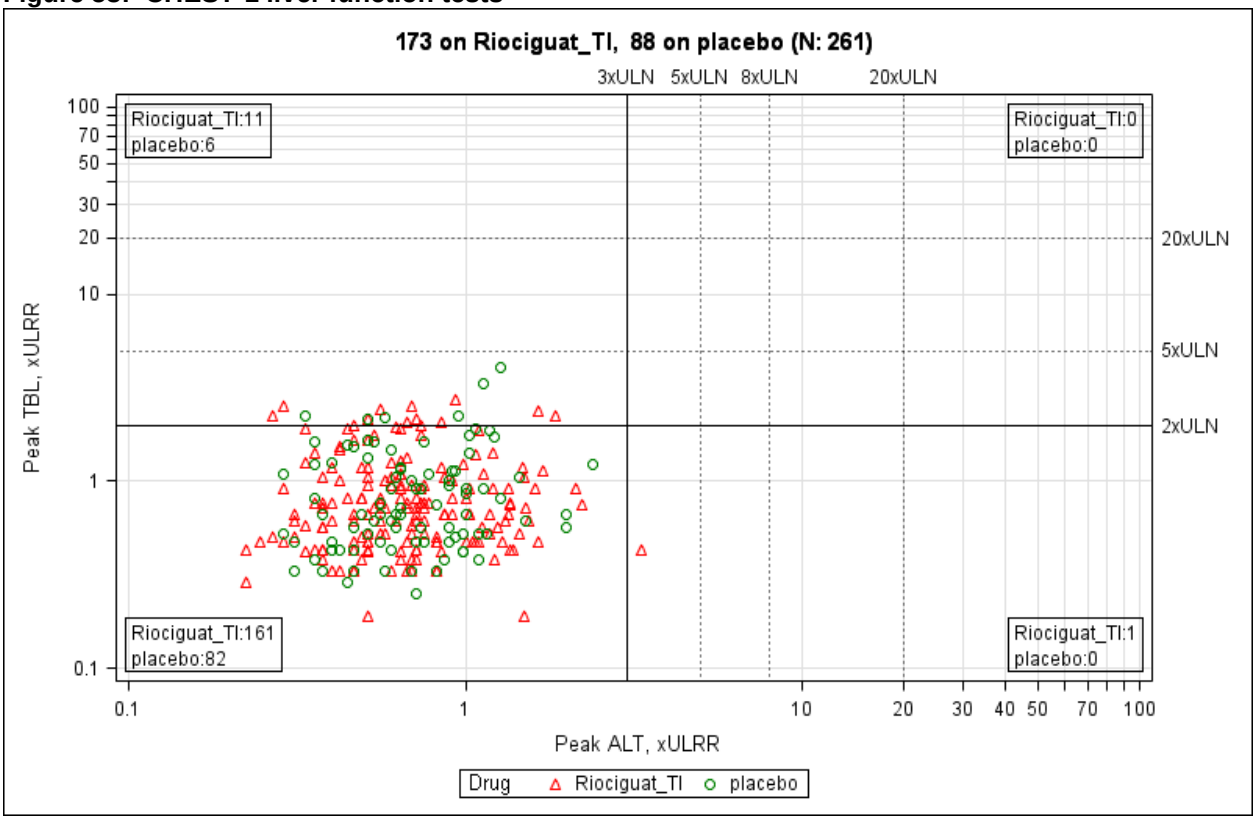
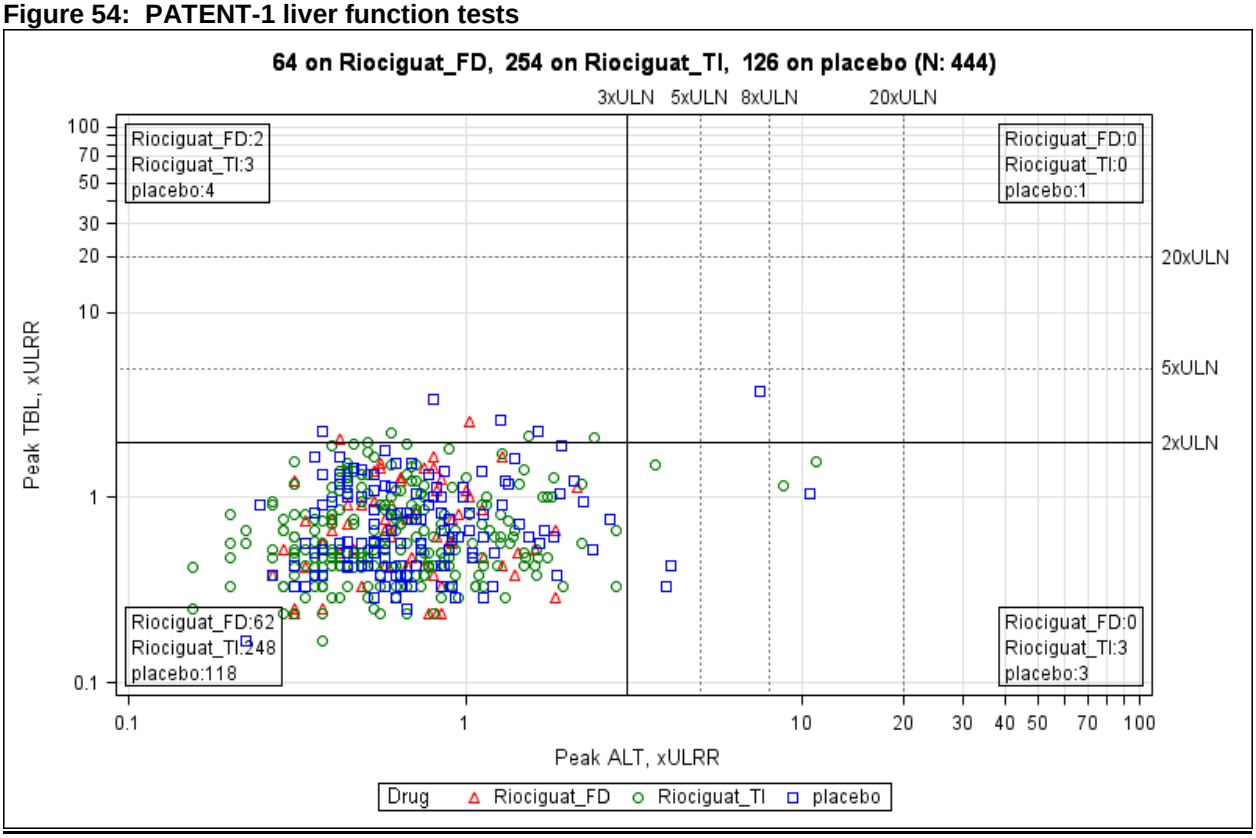


Figure 54: PATENT-1 liver function tests

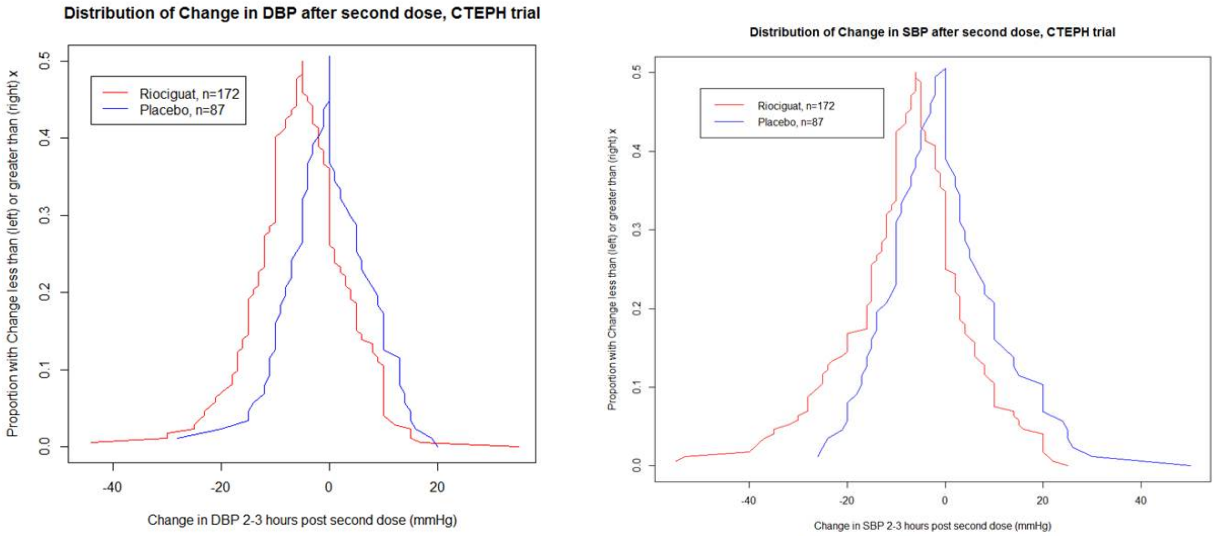


7.4.3 Vital Signs

Blood Pressure – CHEST-1

As would be expected from the phase I and phase II data that were presented in section 5.3 and the PATENT-PLUS trial discussed in section 4.4.2 (pharmacodynamics), riociguat caused a notable downward shift in both diastolic and systolic blood pressure for the entire CHEST-1 trial population, as seen by the mountain plots (cumulative function analysis) below:

Figure 55: CHEST-1 mountain plots of population blood pressure shifts



In addition to a downward shift of the median population values for DBP and SBP (the peak of the mountain) there was a visible enlargement of the left sided tail of the systolic blood pressure curve on therapy, indicating large blood pressure decreases in some individual patients.

Coordinate with these observations from the raw data was the marked imbalance in both hypotension adverse events (symptomatic) and SBP <90 mmHg events (symptomatic and asymptomatic) that were documented in CHEST-1, as seen in the two following tables:

Figure 56: CHEST-1 hypotension adverse events (safety set, FSR table 10-14 pg 144)

MedDRA system organ class/ preferred term	Riociguat 1.0–2.5 mg N=173 (100%)		Placebo N=88 (100%)	
ANY EVENT	24	(13.9%)	7	(8.0%)
Investigations	3	(1.7%)	1	(1.1%)
Blood pressure decreased	3	(1.7%)	1	(1.1%)
Nervous system disorders	6	(3.5%)	3	(3.4%)
Presyncope	2	(1.2%)	0	–
Syncope	4	(2.3%)	3	(3.4%)
Vascular disorders	17	(9.8%)	3	(3.4%)
Hypotension	16	(9.2%)	3	(3.4%)
Orthostatic hypotension	1	(0.6%)	0	–

Table 91: CHEST-1 subjects with SBP < 90 mmHg Events (safety set)

CHEST-1	n/N (%)
Rio IDT	31/173 (17.9%)
Placebo	6/88 (6.8%)

Mean decreases in systolic blood pressure 2-3 hours after dosing at all visits was of a larger magnitude for the riociguat IDT treated patients as compared to placebo, and dramatically more patients experienced low SBP events (SBP <95 mmHg) 2-3 hours after dosing at all visits compared to placebo, as seen in the following two tables:

Table 92: CHEST-1 SBP change from baseline to visit (safety set, FSR table 10-20 pg 153)

Timepoint	Riociguat 1.0–2.5 mg N=173			Placebo N=88		
	n	Mean	(SD)	n	Mean	(SD)
Baseline	173	119.1	(14.76)	88	123.3	(16.12)
Change from baseline to:						
Visit 1, 2-3 h after 1st dose	173	–8.29	(11.86)	86	–6.16	(12.09)
Visit 1, 1-0 h before 2nd dose	171	–5.65	(11.80)	87	–2.70	(13.15)
Visit 1, 2-3 h after 2nd dose	172	–6.84	(14.02)	87	–0.79	(13.89)
Visit 1, 1-0 h before 3rd dose	47	–7.98	(15.59)	20	–3.25	(13.54)
Visit 1, 1-0 h before 4th dose	46	–8.65	(13.43)	20	–3.95	(14.25)
Visit 1, 2-3 h after 4th dose	47	–10.19	(13.80)	19	–4.42	(14.08)
Visit 2, 1-0 h before 1st dose	168	–1.57	(13.61)	88	2.26	(17.18)
Visit 2, 2-3 h after 1st dose	169	–8.07	(13.54)	87	–1.90	(14.42)
Visit 3, 1-0 h before 1st dose	168	–2.60	(13.58)	87	0.57	(17.04)
Visit 3, 2-3 h after 1st dose	168	–9.36	(13.81)	85	–3.56	(13.64)
Visit 4, 1-0 h before 1st dose	164	–4.75	(14.06)	87	3.06	(13.84)
Visit 4, 2-3 h after 1st dose	163	–9.64	(14.72)	87	–2.93	(13.77)
Visit 5, 1-0 h before 1st dose	164	–5.01	(14.21)	87	0.97	(12.45)
Visit 5, 2-3 h after 1st dose	164	–11.05	(14.34)	87	–2.24	(12.69)
Visit 6, 1-0 h before 1st dose	161	–4.40	(13.77)	84	0.11	(15.25)
Visit 6, 2-3 h after 1st dose	160	–9.49	(14.01)	83	–5.42	(14.77)
Visit 7, 1-0 h before 1st dose	159	–4.62	(13.71)	82	–3.11	(15.74)
Visit 7, 2-3 h after 1st dose	159	–10.45	(13.90)	82	–5.26	(15.05)
Last visit	173	–10.49	(14.17)	88	–5.28	14.61

Table 93: CHEST-1 subjects with low SBP events (safety set, FSR table 10-21 pg 155)

Timepoint	Riociguat 1.0–2.5 mg N=173			Placebo N=88		
	n	Low n	Low (%)	n	Low n	Low (%)
Visit 1, 2-3 h after 1st dose	173	19	(11.0%)	86	4	(4.7%)
Visit 1, 1-0 h before 2nd dose	171	12	(7.0%)	87	5	(5.7%)
Visit 1, 2-3 h after 2nd dose	172	17	(9.9%)	87	2	(2.3%)
Visit 1, 1-0 h before 3rd dose	47	5	(10.6%)	20	0	–
Visit 1, 1-0 h before 4th dose	46	3	(6.5%)	20	0	–
Visit 1, 2-3 h after 4th dose	47	6	(12.8%)	19	2	(10.5%)
Visit 2, 1-0 h before 1st dose	168	7	(4.2%)	88	1	(1.1%)
Visit 2, 2-3 h after 1st dose	169	20	(11.8%)	87	4	(4.6%)
Visit 3, 1-0 h before 1st dose	168	8	(4.8%)	87	3	(3.4%)
Visit 3, 2-3 h after 1st dose	168	22	(13.1%)	85	3	(3.5%)
Visit 4, 1-0 h before 1st dose	164	10	(6.1%)	87	1	(1.1%)
Visit 4, 2-3 h after 1st dose	163	17	(10.4%)	87	5	(5.7%)
Visit 5, 1-0 h before 1st dose	164	12	(7.3%)	87	2	(2.3%)
Visit 5, 2-3 h after 1st dose	164	26	(15.9%)	87	1	(1.1%)
Visit 6, 1-0 h before 1st dose	161	10	(6.2%)	84	2	(2.4%)
Visit 6, 2-3 h after 1st dose	160	21	(13.1%)	83	4	(4.8%)
Visit 7, 1-0 h before 1st dose	159	8	(5.0%)	82	1	(1.2%)
Visit 7, 2-3 h after 1st dose	159	20	(12.6%)	82	4	(4.9%)
Last visit	173	22	(12.7%)	88	4	(4.5%)

From FDA's analysis of the timing of SBP <90 mmHg events with riociguat, it is known that these events are front loaded in the first two days of therapy (see figure 57 below). So for the CHEST-1 data, excluding all events occurring within the first 2 days, calculation of the occurrence rates of SBP < 90 mmHg events and hypotension adverse events during the dose escalation confirms that these events continue to occur even in patients who have tolerated lower doses, as seen in the two following tables:

Table 94: CHEST-1 SBP <90 mmHg events (safety set, FDA analysis)

Hypotension SBP <90*	2.5 mg Ind. Titration Dose Arm		
Dose	1.5 mg	2 mg	2.5 mg
Events (n)	7	5	6
Patients (N)	162	155	135
Exposure in Weeks	2	2	10
Events per 100 person-year	**112**	**84**	**23**

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

Table 95: CHEST-1 hypotension adverse events (safety set, FDA analysis)

Hypotension AE*	2.5 mg Ind. Titration Dose Arm		
Dose	1.5 mg	2 mg	2.5 mg
Events (n)	3	4	6
Patients (N)	162	155	135
Exposure in Weeks	2	2	10
Events per 100 person-year	**48**	**67**	**30**

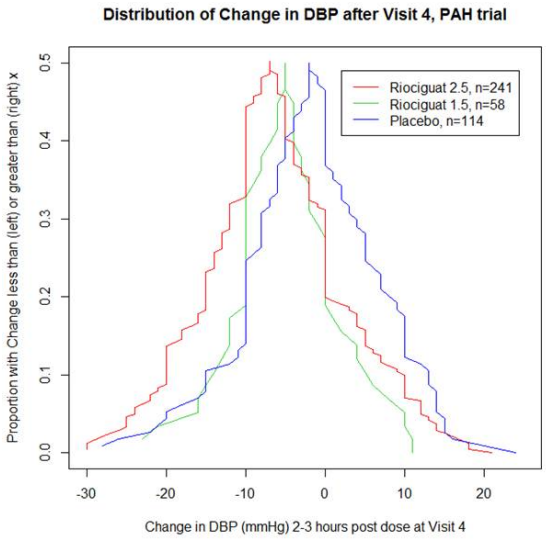
*Only events after 2 days from start of treatment are considered here

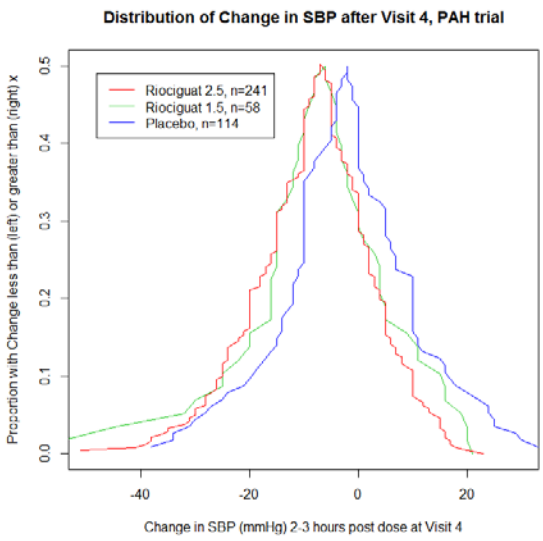
These findings are of particular concern in the CHEST-1 population, where 40% of the enrolled population was ≥ age 65, and therefore at risk for harboring occult but

important coronary artery disease, cerebral vascular disease, and peripheral vascular disease that would likely make some of these patients tolerate systemic hypotension poorly. The exclusion criteria for CHEST-1 had the effect of removing patients with important coronary artery disease from the trial population. Thus, a post-market unselected population could be expected to tolerate these events less well than was seen in clinical trials.

Blood Pressure – PATENT-1

As would be expected from the phase I and phase II data that were presented in section 5.3 the PATENT-PLUS trial discussed in section 4.4.2 (pharmacodynamics), and the CHEST-1 data above, riociguat caused a notable downward shift in both diastolic and systolic blood pressure for the entire PATENT-1 trial population, as seen by the mountain plots (cumulative function analysis) below:





However, because of the presence of the 1.5 mg TID capped arm in green, we have much more information here for the PAH population. With respect to the DBP, there are elements of a dose-responsive effect, with positive/upward changes from baseline being blunted to an equal degree by the IDT and 1.5 mg TID riociguat dosing regimens as compared to placebo, but notable excess in the larger negative changes from baseline induced by the IDT doing strategy as compared to either placebo or 1.5 mg TID riociguat. Effects on change from baseline in SBP are much uniform between the two riociguat dosing strategies as compared to placebo. These dose-dependent differences in blood pressure effects are evident in the tabular data showing an approximately 3-

fold increase of adverse events coded as hypotension with IDT dosing as opposed to fixed/capped 1.5 mg TID dosing in PATENT-1, as shown in the following table:

Table 96: PATENT-1 hypotension adverse events (safety set, FSR table 10-14 pg 157)

MedDRA system organ class/ preferred term	Riociguat 1.0–2.5 mg N=254 (100%)		Placebo N=126 (100%)		Riociguat 1.0–1.5 mg N=63 (100%)	
ANY EVENT	34	(13.4%)	11	(8.7%)	4	(6.3%)
Investigations	1	(0.4%)	1	(0.8%)	1	(1.6%)
Blood pressure decreased	1	(0.4%)	1	(0.8%)	1	(1.6%)
Nervous system disorders	8	(3.1%)	7	(5.6%)	2	(3.2%)
Loss of consciousness	0	–	1	(0.8%)	0	–
Presyncope	5	(2.0%)	1	(0.8%)	2	(3.2%)
Syncope	3	(1.2%)	5	(4.0%)	0	–
Vascular disorders	25	(9.8%)	3	(2.4%)	2	(3.2%)
Hypotension	25	(9.8%)	3	(2.4%)	2	(3.2%)

SBP <90 mmHg event (symptomatic and asymptomatic) also increased in a dose-dependent fashion, as seen in the table below:

Table 97: PATENT-1 subjects with SBP < 90 mmHg Events (safety set)

	n/N (%)
Rio IDT	49/254 (19.3%)
Rio Capped	10/63 (15.9%)
Placebo	15/126 (11.9%)

Mean decreases in systolic blood pressure 2-3 hours after dosing at all visits were of a larger magnitude for the riociguat IDT treated patients as compared to riociguat 1.5 mg capped arm patients, which in turn were of a larger negative magnitude as compared with placebo-treated patients, as shown in the following table:

Table 98: PATENT-1 SBP change from baseline to visit (safety set, FSR table 10-20 pg 168)

Timepoint	Riociguat 1.0–2.5 mg N=254			Placebo N=126			Riociguat 1.0–1.5 mg N=63		
	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
Baseline	254	115.07	(14.95)	126	114.37	(13.54)	63	111.65	(13.11)
Change from baseline to:									
Visit 1, 2-3 h after 1st dose	251	–6.24	(10.04)	124	–2.36	(10.48)	63	–6.41	(9.12)
Visit 1, 1-0 h before 2nd dose	250	–4.85	(10.72)	124	–1.32	(11.75)	63	–4.06	(10.52)
Visit 1, 2-3 h after 2nd dose	246	–5.59	(11.02)	122	–0.59	(11.81)	63	–5.19	(11.72)
Visit 1, 1-0 h before 3rd dose	100	–7.18	(12.28)	49	–0.51	(13.54)	27	–9.11	(12.07)
Visit 1, 1-0 h before 4th dose	108	–5.14	(10.62)	49	–1.98	(13.00)	26	–4.31	(11.89)
Visit 1, 2-3 h after 4th dose	108	–8.06	(10.77)	48	–2.81	(11.32)	27	–5.37	(10.36)
Visit 2, 1-0 h before 1st dose	250	–0.79	(14.27)	119	0.29	(13.44)	61	1.66	(14.90)
Visit 2, 2-3 h after 1st dose	247	–6.61	(14.14)	119	–2.10	(13.02)	61	–3.38	(12.50)
Visit 3, 1-0 h before 1st dose	246	–2.16	(13.95)	118	1.38	(13.48)	59	–1.73	(14.36)
Visit 3, 2-3 h after 1st dose	245	–7.34	(13.41)	118	–1.72	(13.97)	58	–5.95	(11.32)
Visit 4, 1-0 h before 1st dose	241	–3.91	(13.57)	115	0.90	(14.62)	58	–2.78	(13.19)
Visit 4, 2-3 h after 1st dose	241	–7.49	(13.33)	114	–1.88	(14.67)	58	–6.41	(15.22)
Visit 5, 1-0 h before 1st dose	238	–3.97	(14.51)	114	0.49	(13.28)	57	–1.23	(11.99)
Visit 5, 2-3 h after 1st dose	237	–7.95	(15.06)	114	–0.69	(14.55)	57	–1.49	(13.65)
Visit 6, 1-0 h before 1st dose	236	–5.53	(13.81)	111	0.05	(14.62)	57	–0.23	(12.55)
Visit 6, 2-3 h after 1st dose	234	–10.31	(13.89)	109	–2.45	(14.04)	56	–4.32	(14.67)
Last visit	253	–9.70	(14.16)	126	–3.40	(13.83)	63	–4.19	(15.62)

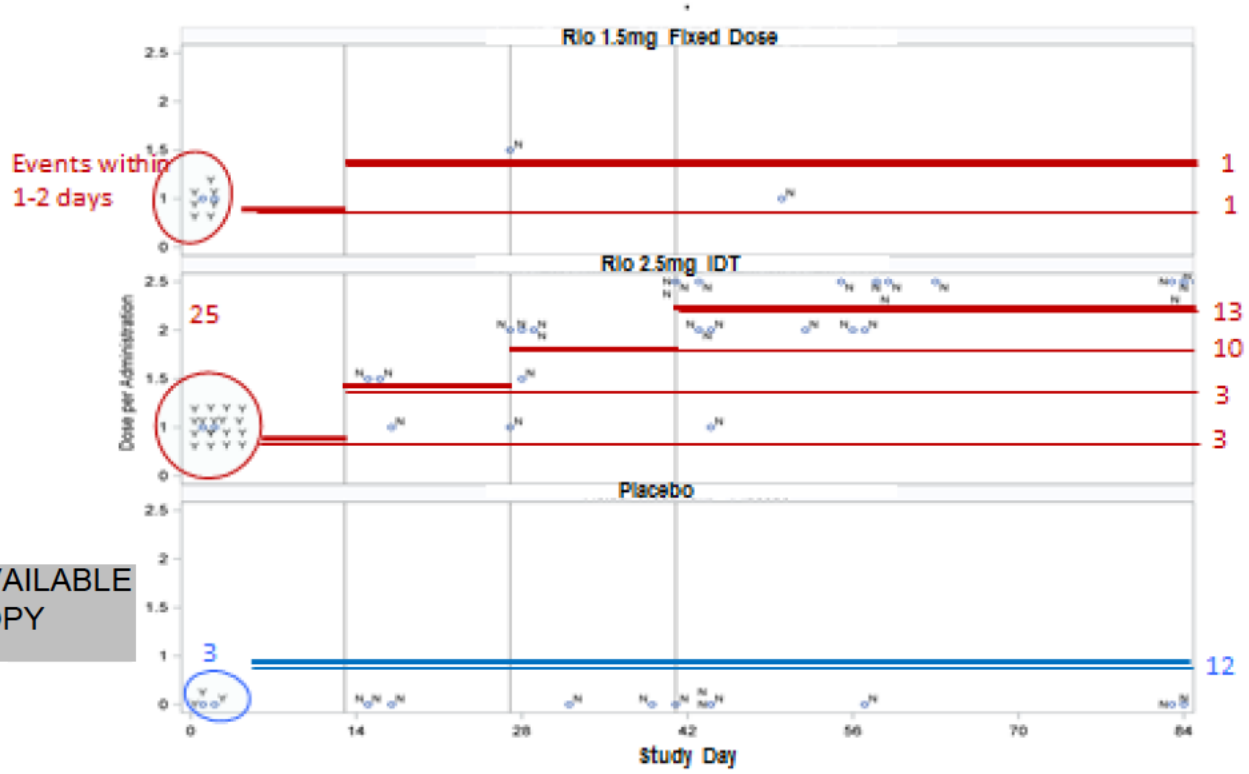
The percentage of patients having low SBP events (SBP <95 mmHg) 2-3 hours after dosing at most of the scheduled follow-up visits was higher for riociguat patients than for placebo patients, but the difference between the two riociguat arms in this comparison was less evident, as shown by the following table:

Table 99: PATENT-1 subjects with low SBP events (safety set, FSR table 10-21 pg 170)

Timepoint	Riociguat 1.0–2.5 mg N=254			Placebo N=126			Riociguat 1.0–1.5 mg N=63		
	n	Low n	Low (%)	n	Low n	Low (%)	n	Low n	Low (%)
Visit 1, 2-3 h after 1st dose	251	26	(10.4%)	124	12	(9.7%)	63	10	(15.9%)
Visit 1, 1-0 h before 2nd dose	250	20	(8.0%)	124	11	(8.9%)	63	9	(14.3%)
Visit 1, 2-3 h after 2nd dose	246	26	(10.6%)	122	7	(5.7%)	63	7	(11.1%)
Visit 1, 1-0 h before 3rd dose	100	17	(17.0%)	49	1	(2.0%)	27	6	(22.2%)
Visit 1, 1-0 h before 4th dose	108	9	(8.3%)	49	4	(8.2%)	26	3	(11.1%)
Visit 1, 2-3 h after 4th dose	108	12	(11.1%)	48	2	(4.2%)	27	1	(3.7%)
Visit 2, 1-0 h before 1st dose	250	12	(4.8%)	119	8	(6.7%)	61	1	(1.6%)
Visit 2, 2-3 h after 1st dose	247	32	(13.0%)	119	12	(10.1%)	61	6	(9.8%)
Visit 3, 1-0 h before 1st dose	246	10	(4.1%)	118	4	(3.4%)	59	5	(8.5%)
Visit 3, 2-3 h after 1st dose	245	30	(12.2%)	118	14	(11.9%)	58	8	(13.8%)
Visit 4, 1-0 h before 1st dose	241	15	(6.2%)	115	8	(7.0%)	58	7	(12.1%)
Visit 4, 2-3 h after 1st dose	241	28	(11.6%)	114	17	(14.9%)	58	11	(19.0%)
Visit 5, 1-0 h before 1st dose	238	21	(8.8%)	114	7	(6.1%)	57	3	(5.3%)
Visit 5, 2-3 h after 1st dose	237	41	(17.3%)	114	12	(10.5%)	57	8	(14.0%)
Visit 6, 1-0 h before 1st dose	236	21	(8.9%)	111	7	(6.3%)	57	3	(5.3%)
Visit 6, 2-3 h after 1st dose	234	47	(20.1%)	109	13	(11.9%)	56	10	(17.9%)
Last visit	253	47	(18.6%)	126	17	(13.5%)	63	9	(14.3%)

In PATENT-1, FDA examined the timing of all SBP <90 events, by dose. For the IDT dosing arm 36% of these events occurred within two days of dosing. For the 1.5 mg TID capped arm, 78% of these events happened within the first two days. Placebo events happened randomly throughout the dosing period. This result suggests a very strong dose-dependent effect for the occurrence of SBP <90 mmHg events throughout the later trial period, as seen in the figure below:

Figure 57: PATENT-1 timing of SBP < 90 mmHg events (safety set, FDA analysis)



7.4.4 Electrocardiograms (ECGs)

On 3 May 2013, the TQT IRT assessed the ECG data from the following two trials:

- Study 13796 – 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 – 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 TID) in patients with symptomatic pulmonary arterial hypertension (PAH) (PATENT-1)

This approach to assessing the QT effects of riociguat was used given that the potential for drug-induced repolarization effects and/or conduction system abnormalities in patients with various degrees of RV pressure overload and failure was of interest. The TQT IRT concluded the following:

> *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 Tmax*
>
> *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.*

7.4.5 Special Safety Studies/Clinical Trials

See review of animal bone toxicity studies (toxicology review), as well as the sponsor's repeat review of the histology slides from those studies in response to FDA IR-19 and IR-21 (attachments 2 and 3 in section 9.4).

7.4.6 Immunogenicity

No new studies submitted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

- Hypotension - see section 7.4.3 (Vital Signs)
- Bone toxicity at high doses in animal studies – see sections 7.3.5 (Submission Specific Primary Safety Concerns) and 7.6.3 (Pediatrics and Assessment of Effects on Growth)

7.5.2 Time Dependency for Adverse Events

- Bone toxicity at high doses in animal studies – see sections 7.3.5 (Submission Specific Primary Safety Concerns) and 7.6.3 (Pediatrics and Assessment of Effects on Growth)

7.5.3 Drug-Demographic Interactions

See section 4.4.3 (PK)

7.5.4 Drug-Disease Interactions

- Approximately 3-fold increased exposure in PH patients as compared to normal healthy subjects
- Approximately 1.5 to 2-fold increased exposure in any degree of renal insufficiency
- Approximately 1.5-fold increased exposure in Child's B hepatic insufficiency
- 2 to 3-fold decreased exposure in smokers
- See clinical pharmacology review and section 4.4.3 (PK) of this review

7.5.5 Drug-Drug Interactions

See section 4.4.3 (PK)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Mouse and rat carcinogenicity studies were presented to the Executive CAC on April 16, 2013 and concurred that there were no drug-related neoplasms in these studies.

Human neoplasms during therapy with riociguat (benign or **malignant**) have been infrequent, and are enumerated below:

Trial	Riociguat	Placebo
Phase II trial 12166 LTE	**1/68 (1.5%) hepatocellular CA of liver – subject with h/o liver cirrhosis, splenomegaly, ascites, and alcohol abuse, diagnosed with hepatocellular carcinoma after 3 years and 5 moths of riociguat therapy. Felt not related to study drug by investigator. Subject died.**	N/A
CHEST-1	: Benign + **Malignant** • 4/173 (2.3%) benign GI neoplasms • 1/173 (0.6%) – seborrhoeic keratosis • 1/173 (0.6%) – thyroid neoplasm (nodule) • **1/173 (0.6%) – malignant lung neoplasm. Subject died.**	2/88 (2.3%) benign GI neoplasms
CHEST-2	Benign + **Malignant** • 1/194 (0.5%) benign neoplasm of skin • 1/194 (0.5%) neoplasm skin	N/A

	• 1/194 (0.5%) neoplasm skin bleeding • 1/194 (0.5%) seborrhoeic keratosis • 1/194 (0.5%) tongue neoplasm • 1/194 (0.5%) uterine leiomyoma • 2/194 (1.0%) benign GI neoplasms • 2/194 (1.0%) benign prostatic hypertrophy • 1/194 (0.5%) thyroid neoplasm (enlarged nodule) • **2/194 (1.0%) breast cancers** • **1/194 (0.5%) lung neoplasm malignant**	
PATENT-1	Benign + **Malignant** • **2/317 (0.6%) benign GI neoplasms** • **1/317 (0.3%) papilloma** • **1/317 (0.3%) uterine leiomyoma**	• **1/126 (0.8%) metastatic melanoma**
PATENT-2	Benign + **Malignant** • 1/363 (0.3%) Basal cell carcinoma • 1/363 (0.3%) Bladder neoplasm • 1/363 (0.3%) Bone neoplasm (gonyoncus in right knee) • 2/363 (0.6%) Colon adenoma • 1/363 (0.3%) Fibroadenoma of breast • 1/363 (0.3%) Lipoma • 2/363 (0.6%)Skin papilloma • 3/363 (0.8%) Uterine leiomyoma • 6/363 (1.7%) Benign GI neoplasms • **1/363 (0.3%) Thyroid neoplasm (cold nodule)** • **1/363 (0.3%) Squamous cell carcinoma of skin** • **1/363 (0.3%) Hepatic neoplasm malignant recurrent (h/o chronic HepC and cirrhosis)** • **1/363 (0.3%) Lung neoplasm** • **1/363 (0.3%) Lung adenocarcinoma** • **1/363 (0.3%) non-small cell lung cancer resulted in death** • **1/363 (0.3%) malignant melanoma** • **1/363 (0.3%) Metastatic malignant melanoma** • **1/363 (0.3%) Rectal Cancer**	N/A

7.6.2 Human Reproduction and Pregnancy Data

Cardiac and skeletal teratogenicity. See maternal-fetal health evaluation and REMS.

7.6.3 Pediatrics and Assessment of Effects on Growth

Bones

The NO-sGC-cGMP pathway is known to be involved in the regulation of bone metabolism. FDA requested that the sponsor review their bone histopathology information from the animal toxicology studies in detail, the results of those reviews are imbedded in section 9.4 of this review (Appendices A and B, responses to FDA IR-19 and FDA IR-21). The following drug-induced bone abnormalities were noted in those preclinical toxicology animal studies:

- Pilot Juvenile Rat study (PH-36257) demonstrated dose-related bone findings, including Grade 1 disorganized bone/bone marrow cavity and reduced epiphyseal bone marrow cells at the low dose. Intermediate doses demonstrated Grade 2 (slight) irregularities of bone trabeculae and increased formation of compact bone. High doses demonstrated Grade 4(severe) hyperostosis and enlarged mesenchymal cells (including osteoclasts), as well as Grade 5 (extensive/massive) findings including disorganized bone/bone marrow cavity, absence of hematopoietic cells and marrow adipocytes, and reduced epiphyseal bone marrow cells

- Adolescent rates demonstrated marked hypertrophy of growth plate cartilage and thickening of primary and secondary spongiosa in the metaphysis and diaphyseal funnel, called hyperostosis in the respective reports, of long bones were seen. At the diaphyseal shaft increased modeling was seen in the subperiosteal zone of lateral bone growth. After 4-week treatment in rats study, growth plate changes started at 15 mg/kg corresponding to systemic exposure in terms of unbound AUC of about 3-fold of human exposure. After 26-week treatment, hyperostosis was seen at 10 mg/kg and above corresponding to margins of exposure of approximately 2.

We do note, however that:

- A definitive juvenile animal study using lower doses than the pilot study showed effects on serum electrolytes but without histologic correlates in bone or any other apparent effects

- A 26-week mechanistic study in adult rats demonstrated no findings in animals surviving to the end of the study, but three died prematurely. In one of the animals that died prematurely, some bone abnormalities were noted to include a patellar fracture with patellar tendon ruptures, marked intra-articular hemorrhage and thrombosis/necrosis of the patellar bone marrow, bone resorption, and cellular infiltration of the tendons. These findings are different in morphology from those described as riociguat-related bone effects, and their significance is unclear.

- In dogs, which were almost full grown at start of treatment, in repeat-dose studies from 2-weeks up to 52-weeks no skeletal findings were observed at an exposure range up to 3.8 times the human exposure at 2.5 mg TID.

Human exposure in phase II/III clinical trials has been limited. However, review of the musculoskeletal adverse event data, and the bone fracture data in the LTEs of the pivotals demonstrates no safety signal in musculoskeletal/fracture outcomes.

To further investigate the potential for riociguat to induce clinical bone disease in humans with chronic/long-term therapy, DCRP consulted DRUP due to their experience with bisphosphonate-induced bone toxicity. The DRUP consult is embedded as Appendix C in section 9.4 of this review. The DRUP consultant reviewed the animal findings and human bone turnover markers from the pivotal trials and came to the following conclusions:

- *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 do not have major concerns about skeletal effects of riociguat in adults, as the studies in rodents provide an adequate safety margin. Adults with PAH/CTEPH tend to have low bone mass, but there is no compelling nonclinical or clinical evidence suggesting that riociguat would increase their fracture risk. The mature skeleton of adults probably makes them less susceptible, compared to children/adolescents, to developing severe hypertrophy of bone. If hyperostosis were to occur in adults, based on the experience with retinoid bone*

toxicity, it may present in a manner similar to the syndrome of diffuse idiopathic skeletal hyperostosis (DISH), with ossification of ligament and tendon insertions, especially the anterior spinal ligament.

- *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.*

- *…it may be appropriate to investigate the possible development of hyperostosis with long term use. In particular, lateral spine X-rays (perhaps even PA/lateral chest X-rays) could readily detect calcification of the anterior spinal ligament in patients in the ongoing extension studies, at least in those with any complaints of back pain or stiffness. However, such calcifications are common in the general population of older adults so such findings may be difficult to interpret without a control group or baseline imaging.*

- *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.*

Unfortunately, the adult fracture data is not helpful in sorting out the long-term risk in either the adult or pediatric population for long-term fractures due to the brief duration of the controlled trials relative to the timing of pathologic fracture occurrence (weeks versus years, respectively). The LTE extensions for the pivotal studies, which contrary to advice from the Division in 2009 did not include a control group, are therefore not interpretable with respect to fracture risk. For the sake of completeness, the cumulative fracture experience across the program is shown in the table below:

Table 100: Treatment emergent fractures by SOC and PT - all pivotal studies and LTEs (safety sets, 4msu-iss table 1.2.2.3/92 pg 252)

Primary system organ class Preferred term MedDRA Version 15.1	BAY 63-2521 (main) N=490 (100%)	Placebo (main) N=214 (100%)	BAY 63-2521 (LTE, main) N=442 (100%)	BAY 63-2521 (LTE, placebo in main) N=191 (100%)	LTE total N=633 (100%)
ANY EVENT	1 (0.2%)	0	18 (4.1%)	11 (5.8%)	29 (4.6%)
Injury, poisoning and procedural complications	0	0	17 (3.8%)	11 (5.8%)	28 (4.4%)
Facial bones fracture	0	0	1 (0.2%)	0	1 (0.2%)
Femur fracture	0	0	1 (0.2%)	1 (0.5%)	2 (0.3%)
Foot fracture	0	0	3 (0.7%)	2 (1.0%)	5 (0.8%)
Hand fracture	0	0	1 (0.2%)	1 (0.5%)	2 (0.3%)
Humerus fracture	0	0	2 (0.5%)	3 (1.6%)	5 (0.8%)
Lumbar vertebral fracture	0	0	1 (0.2%)	0	1 (0.2%)
Radius fracture	0	0	2 (0.5%)	0	2 (0.3%)
Rib fracture	0	0	3 (0.7%)	3 (1.6%)	6 (0.9%)
Spinal compression fracture	0	0	0	2 (1.0%)	2 (0.3%)
Spinal fracture	0	0	1 (0.2%)	0	1 (0.2%)
Sternal fracture	0	0	1 (0.2%)	0	1 (0.2%)
Thoracic vertebral fracture	0	0	1 (0.2%)	0	1 (0.2%)
Ulna fracture	0	0	1 (0.2%)	0	1 (0.2%)
Upper limb fracture	0	0	3 (0.7%)	0	3 (0.5%)
Musculoskeletal and connective tissue disorders	1 (0.2%)	0	1 (0.2%)	0	1 (0.2%)
Osteoporotic fracture	0	0	1 (0.2%)	0	1 (0.2%)
Pathological fracture	1 (0.2%)	0	0	0	0

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The most prominent concern for overdose is drug-induced hypotension, which was seen in the overdose experience in trial12166 (core)….

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

None. Riociguat is neither approved nor marketed in any jurisdiction world-wide.

9 Appendices

9.1 Literature Review/References

Source references are embedded in table headers.

9.2 Labeling Recommendations

- Reduce the dose (see section 9.3)
- Contraindicate PDE inhibitors
- Contraindicate NO Donors
- Contraindicate use in coronary artery disease patients who may need to take sublingual nitroglycerin to abort attacks of angina pectoris
- Double the targeted dose for 1.5 mg TID to 3.0 TID in smokers (> 10 cigarettes per day)
- Intermittent assessment of complete blood counts, serum creatinine, TFTs
- Modify REMS to align with other teratogens used to treat pulmonary hypertension

9.3 Advisory Committee Meeting

Scheduled August 6, 2013. This is first-in-class NME for a fatal disease. For the CTEPH indication, no other drugs are approved. No external consultants have been engaged. DRUP consulted internally on the potential bone toxicity question and its impact on the request for a pediatric waiver for PAH (Appendix C in section 9.4).

It is the opinion of this reviewer that riociguat causes dose-related decreases in blood pressure that can be profound. However, these hemodynamic shifts have been well tolerated in the clinical program when riociguat is not used with either NO donors or PDE5 inhibitors, possibly due to its concomitant vasodilatory effects on peripheral vascular beds. It is also the opinion of this review that efficacy in CTEPH and PAH have been demonstrated. Therefore, I think that this drug is approvable so long as its dosing algorithm is modified to reflect the flat E-R curves in the current IDT dosing scheme and the higher incidence of hypotension with the higher dose as compared to fixed/capped dosing at 1.5 mg TID. Thus,

- For the PAH indication, I would like to propose a modified dosing algorithm to the advisory committee, initiating therapy at 0.5 mg TID, increasing by 0.5 mg TID no sooner than every two weeks to a maximal dose of 1.5 mg TID

- For the CTEPH indication, I would like to propose the same reduced dosing algorithm
- For both indications, the question remains regarding allowing up-titration to the 2.5 mg TID dose for patients demonstrating an inadequate efficacy response so long as their baseline SBP was ≥ 110 mmHg systolic (the level above which hypotensive events were not seen above the placebo background rate in CHEST-1).

This reviewer would like to ask the committee's opinion of this approach in light of the fact that 40% of the patients enrolled in the CTEPH trial were ≥ 65 years of age, and will therefore have a higher incidence of occult and symptomatic coronary artery disease, cerebral vascular disease, and peripheral vascular disease which will like cause at least some of them to tolerate drug-induced hypotension poorly.

9.4 Bone Toxicity Evaluations by Sponsor and Internal FDA Consultant

Introduction

In an e-mail from May 10, 2013, additional information on riociguat-related bone lesions were requested:
'From Study A43289, 26 week mechanistic study in rats:
Please provide detailed descriptions of the findings in the vertebrae, costae and humerus as well as an assessment of the findings from a veterinary pathologist with expertise in bone histopathology. Also provide photomicrographs of the findings to illustrate what you are describing and to show the spectrum of lesions from mild to severe. If Bayer feels that these findings are not relevant to the clinical situation, a detailed explanation of that position should be provided.'

The responses attached are divided into 4 different sections

1. Morphological changes seen in the skeleton of an isolated animal in the 26-week mechanistic study and their interpretation in the context of riociguat-related bone lesions.

2. Compilation of photomicrographs from the pilot study in juvenile animals illustrating the lesions observed with regard to their morphological features as well as with regard to their severity spectrum.

3. Compilation of photomicrographs from the repeat-dose studies in adolescent animals illustrating the lesions observed with regard to their morphological features as well as with regard to their severity spectrum.

4. Considerations on human relevance of bone findings in adolescent and juvenile rats.

Section 1

Riociguat
26-week Mechanistic Rat Study in Adult Rats (A43289)

Documentation of Morphological Bone Lesions

As riociguat induces treatment-related findings in the long bones of adolescent, growing rats, a chronic study in full-grown rats with treatment duration of up to 26 weeks was performed. The animals were treated at 0, 15 and 25 mg/kg riociguat. The high dose group was initially started at 50 mg/kg however, due to clinical symptoms and especially body weight gain effects which could interfere with bone metabolism, the dose was reduced to 25 mg/kg after 9 days of treatment. 10 animals each were sacrificed at day 1 (to obtain base line values for bone marrow density measurement) as well as after 4, 8, 13 and 26 weeks of treatment (named interim sacrifices K1 to K5 in the Pathology Report).

The following bones were fixed for histopathological examination:

- Femur (incl. proximal tibia and knee joint)
- Humerus
- Sternum
- Vertebrae
- Costae

Of note, erroneously, in the original report, a restricted panel of bones examined histopathologically was mentioned to be examined. However, all bone samples of all animals were investigated.

Histopathology was performed on the bone specimen according to the following schedule

	0 mg/kg					15 mg/kg				25 mg/kg			
Interim Sacrifice	**1**	**2**	**3**	**4**	**5**	**2**	**3**	**4**	**5**	**2**	**3**	**4**	**5**
Sternum	X	X	X	X	X	X	X	X	X	X	X	X	X
Femur	X	X	X	X	X	X	X	X	X	X	X	X	X
Humerus	X	X	X	X	X	X	X	X	X	X	X	X	X
Vertebra	X	X	X	X	X	X	X	X	X	X	X	X	X
Costa	X	X	X	X	X	X	X	X	X	X	X	X	X

Primary histopathological examination was performed by an ESVP board-certified veterinary pathologist with long-standing history (> 10 years) in toxicological pathology.

In consequence of the information request by the Agency, animal 221 showing morphological bone changes, was reviewed by Dr. Matthias Rinke, Head of Pathology, Bayer HealthCare AG and member of the INHAND (**IN**ternational **HA**rmonization of **N**omenclature and **D**iagnostic criteria) Skeletal (bone, cartilage, tooth) working group. The INHAND task force formed by members of international STPs is currently establishing controlled terminology for neoplastic and non-neoplastic histopathological findings to support the FDA SEND initiative.

Thus, both the study pathologist and the reviewing pathologist have deep knowledge on bone morphology and bone-associated pathology.

As outlined in the original report, none of the animals surviving until the end of their scheduled treatment duration showed any bone-related findings.

Three high dose animals died or were sacrificed prematurely during the course of the study. Animal 225 showed a purulent pleuritis, indicating a gavage error as cause of death on day 9 of the study.

Animal 203 was found dead on day 21. This animal was emaciated but no obvious cause of death was discernible.

Whereas animal 225 (Figure 10) and 203 showed no bone lesions at all, animal 221 revealed alterations of the bone in samples all investigated which were described as bone resorption, increased osteoclasts, fibrosis/osteosclerosis and inflammation in the narrative of the pathology report.

As can be seen from the individual data sheets, the main feature in the knee joint was a fracture/rupture of the patella from the patellar tendons (Figure 1 and Figure 2) with marked subsequent intra-articular hemorrhage and thrombosis/necrosis of the patellar bone marrow. As evidence that this lesion occurred in-life and not post mortem, a moderate mixed cellular infiltration of the tendons (Figure 2) and the surrounding musculature (Figure 6) was seen. Bone resorption characterized by numerous osteoclasts and reduced bone matrix occurred especially in the subcartilage zone of the epiphysis of the femur (Figure 3 and Figure 5) but way less in the tibia where they were restricted to the region of the activated synovialis (Figure 5). In contrast to the lesions seen after treatment with riociguat, no hyperostosis of cancellous or diaphyseal bone was observed. Furthermore, growth plates were normal (Figure 2, Figure 3, Figure 4, Figure 5, Figure 6).

In the epiphysis of the humerus, a wide zone of bone marrow necrosis was observed, most likely due to the presence of a thrombotic event while the bone marrow of the shaft was completely normal. The reported moderately increased number of osteoclasts, bone resorption and fibrosis could not be verified and were restricted to the area of necrosis in the epiphysis (Figure 7). Also the findings reported for sternum, costae (Figure 8), and vertebrae (Figure 9) appear to be less pronounced when compared to the massive local lesions in the injured knee joint.

In conclusion, the lesions described for animal 221 differ distinctly from the treatment-related lesions described in adolescent riociguat-treated animals. In contrast to animal 221, in riociguat-treated, adolescent animals, an increase of bone mass with hyperostosis in cancellous as well as in diaphyseal bone is seen.

In addition to the fact that the findings are morphologically different to those described as riociguat-related, that they were isolated, restricted to a single animal and not seen in animals sacrificed in close temporal relationship to the respective animal they are considered not to be treatment-related.

Overall, the primary origin of the lesions seen exclusively in the deceased animal 221 has to remain open; a treatment-relationship can be excluded since the findings are clearly different in morphology from those described as riociguat-related bone effect.

Figure 1: Animal No.221, male (50 mg/kg, 8 days on treatment): Knee joint with femur (left) and tibia (right) and fracture/rupture of patella from tendons and massive hemorrhage, normal appearance of growth plates, metaphysis and diaphysis

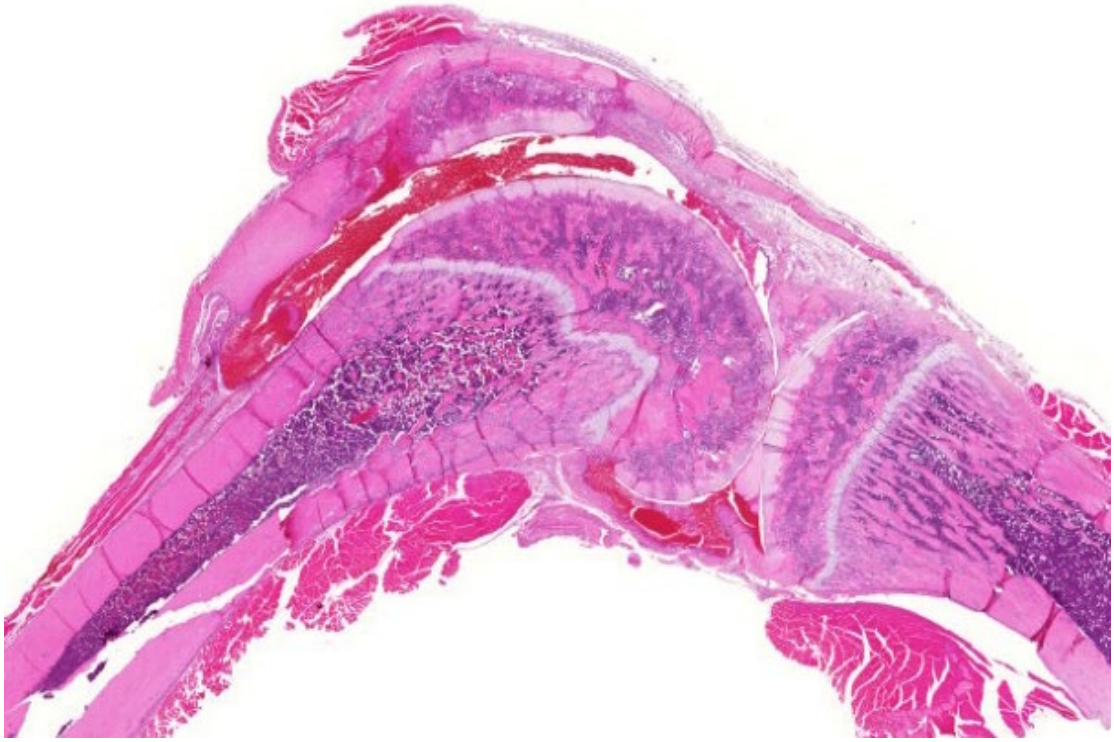


Figure 2: Animal No.221, male (50 mg/kg, 8 days on treatment): Higher magnification of knee joint with fracture/rupture of patella from tendons and massive hemorrhage and inflammatory cells on the right side.

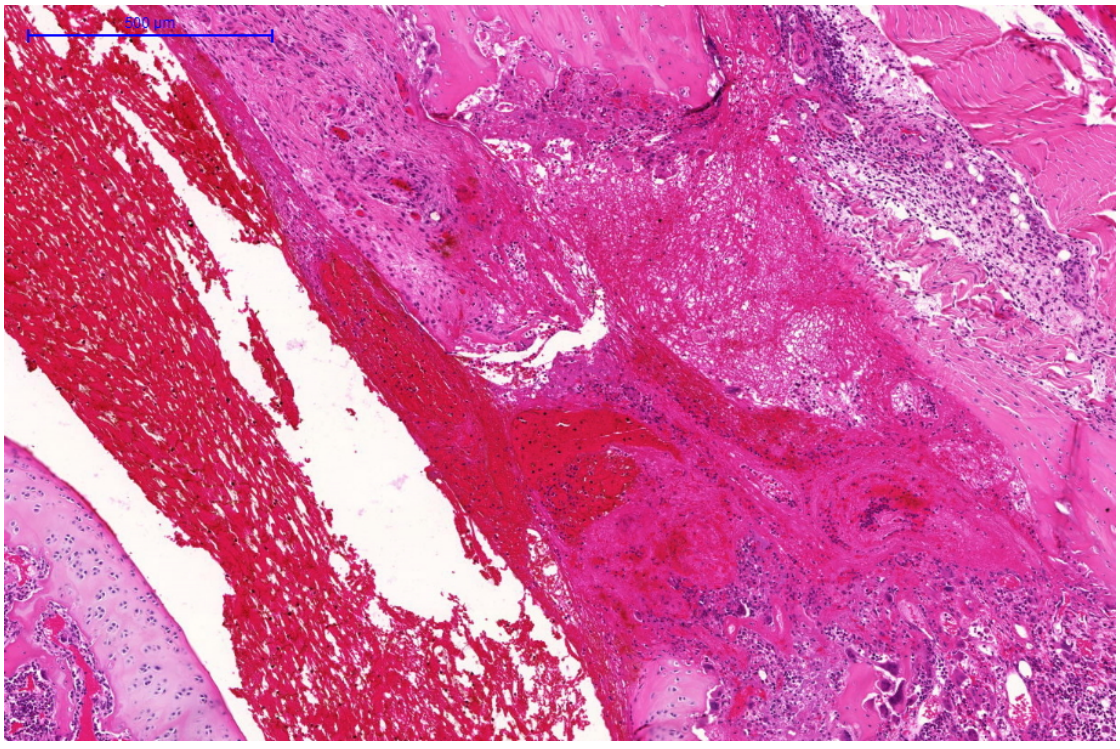


Figure 3: Animal No.221, male (50 mg/kg, 8 days on treatment): Epiphysis of the femur showing necrotic bone marrow, bone resorption with numerous osteoclasts. Note normal appearance of epiphysis, growth plate and metaphysis in the tibia

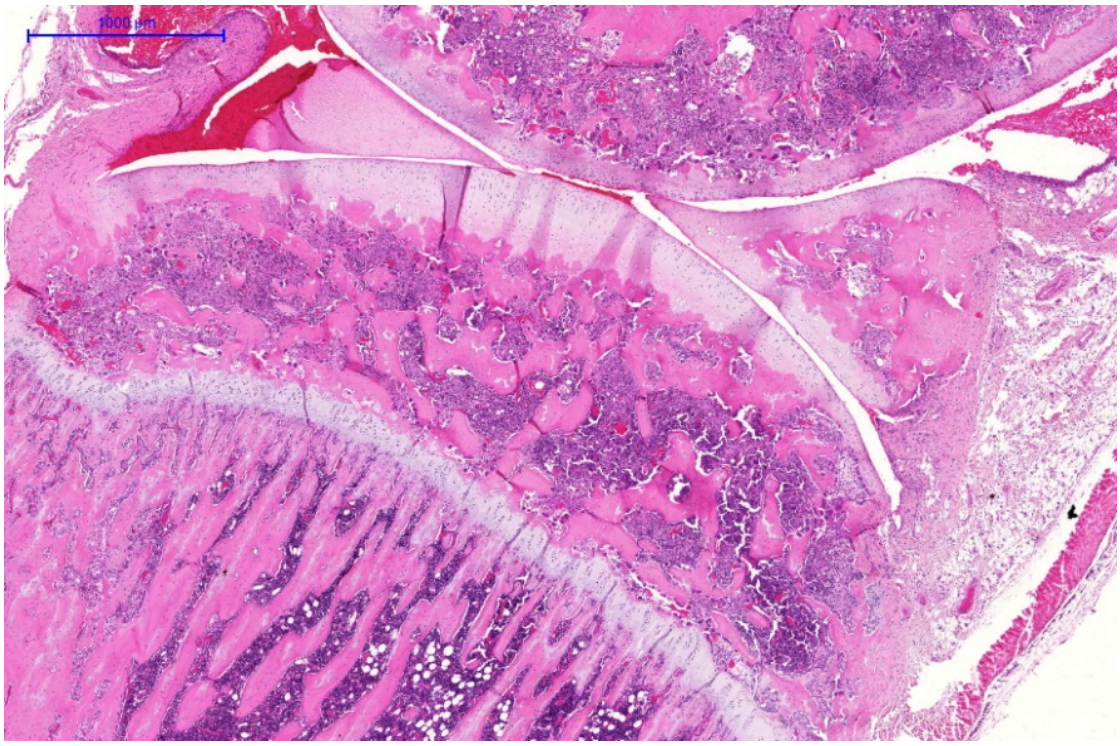


Figure 4: Animal No.221, male (50 mg/kg, 8 days on treatment): Higher magnification of the epiphysis of the femur with necrotic bone marrow and numerous osteoclasts, bone resorption and partial fibrosis. Note normal appearance of growth plate, subepiphyseal metaphysis and bone marrow.

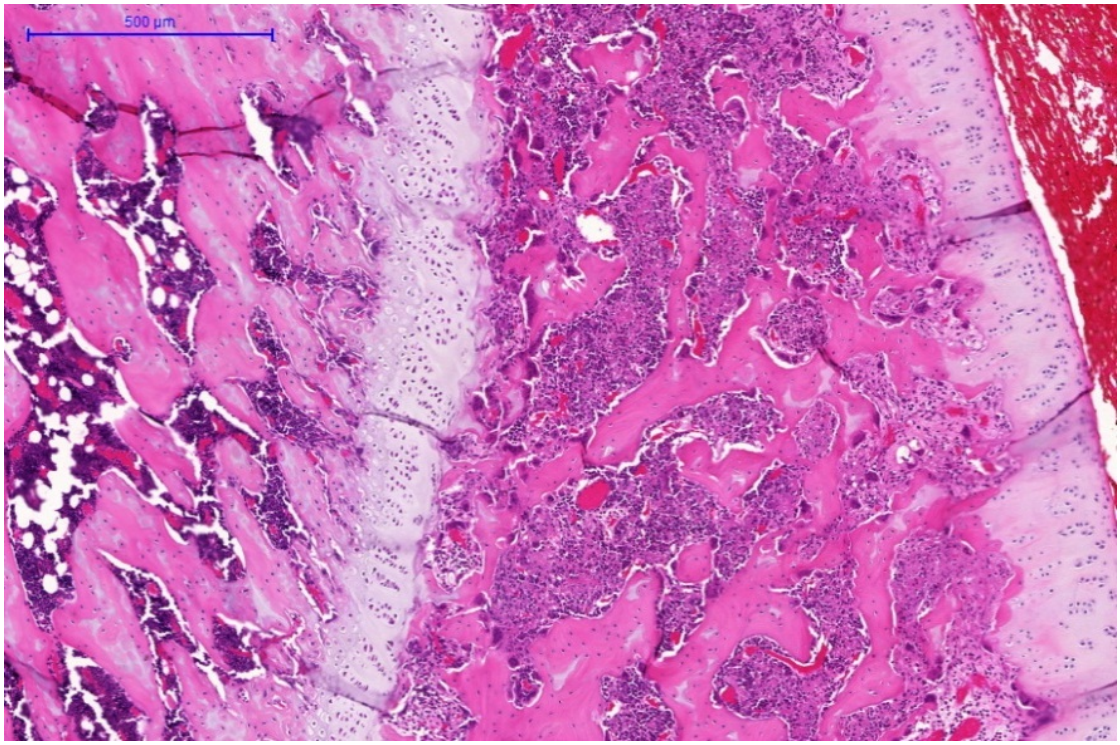


Figure 5: Animal No.221, male (50 mg/kg, 8 days on treatment): Higher magnification of the epiphysis of the tibia with necrotic bone marrow and focal activation of osteoclasts, close to the activated synovialis

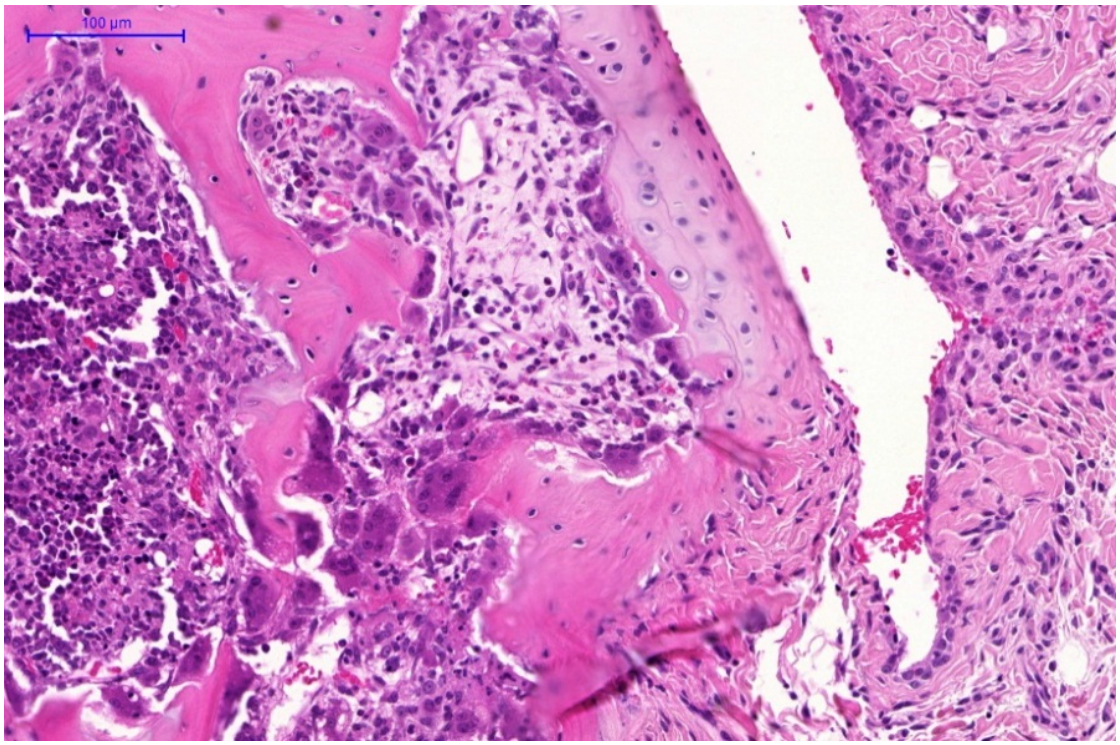


Figure 6: Animal no.221, male (50 mg/kg, 8 days on treatment): Normal diaphysis, Note inflammatory infiltration of the surrounding musculature.

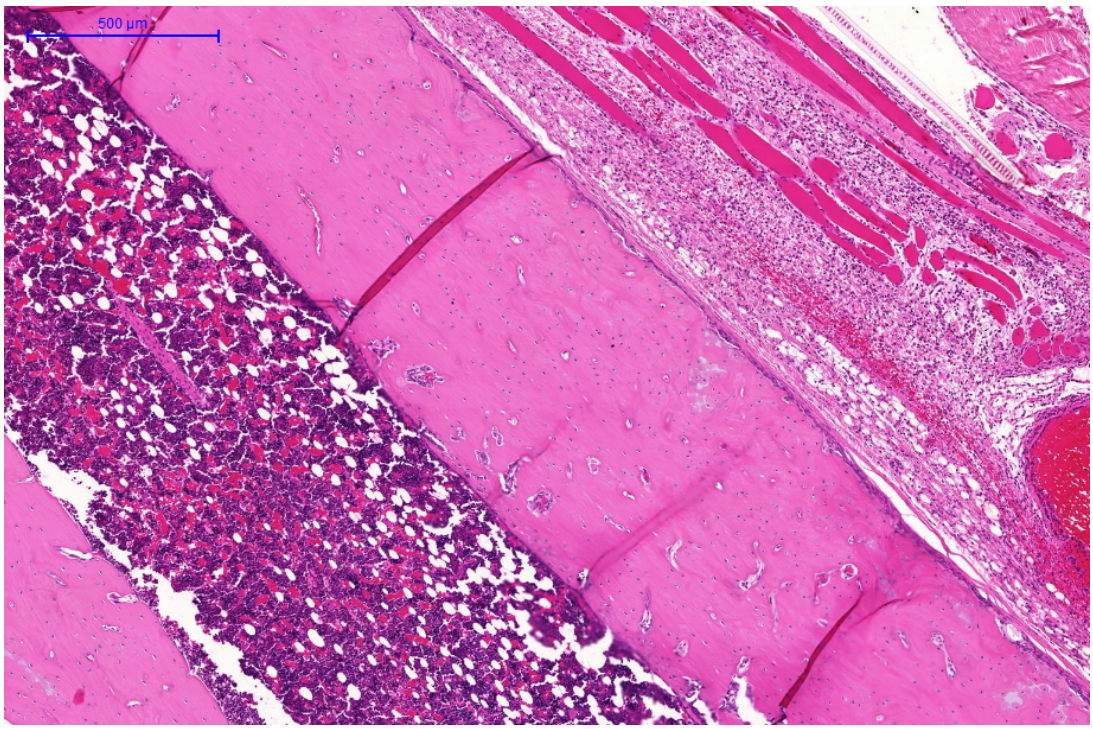
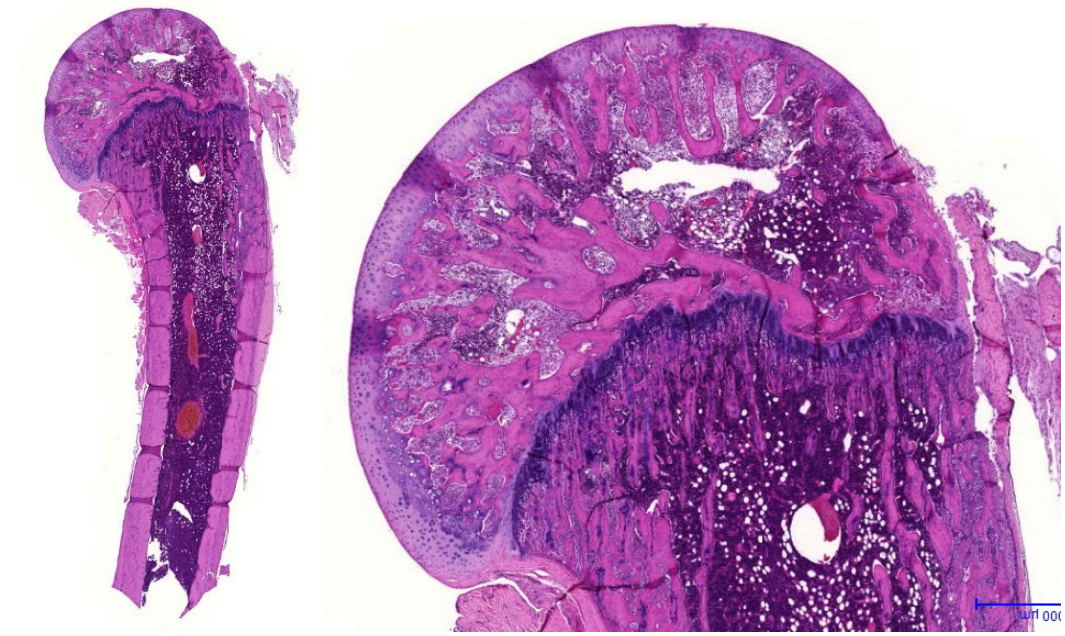


Figure 7: Animal No.221, male (50 mg/kg, 8 days on treatment): Humerus: Bone marrow necrosis in the epiphysis. Note normal appearance of epiphyseal bone, growth plate, subepiphyseal metaphysis, diaphysis and bone marrow.



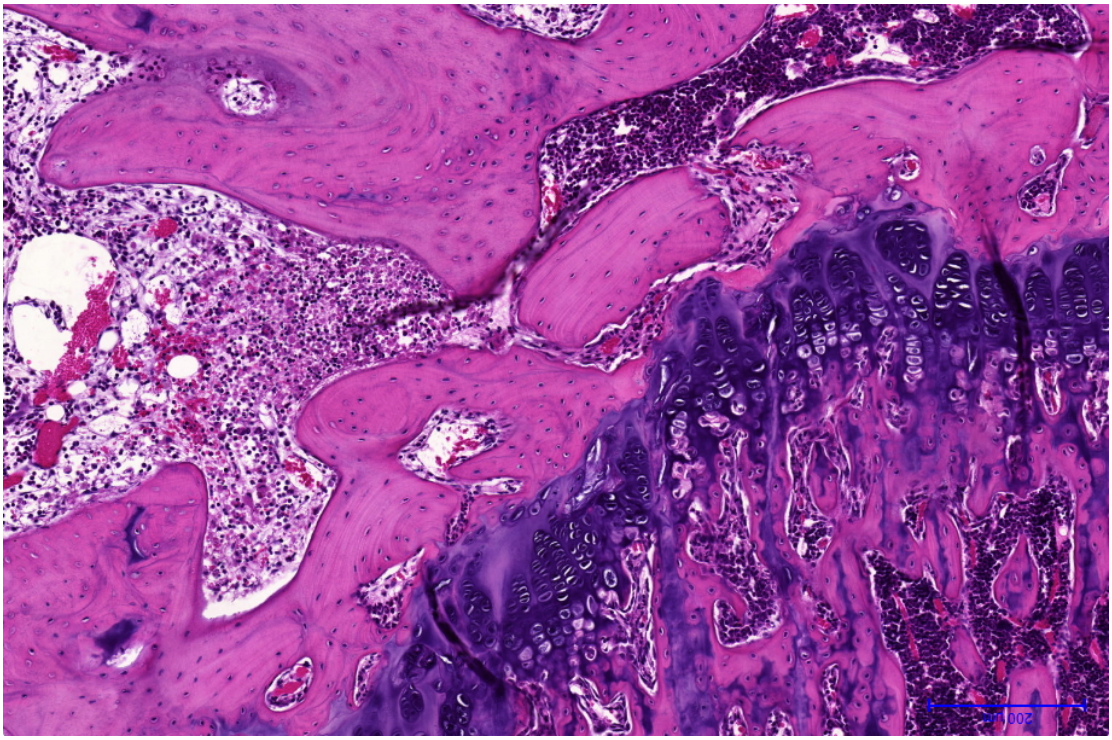


Figure 8: Animal No.221, male (50 mg/kg, 8days on treatment): Rib, normal bone morphology with increased myelopoiesis of the bone marrow.

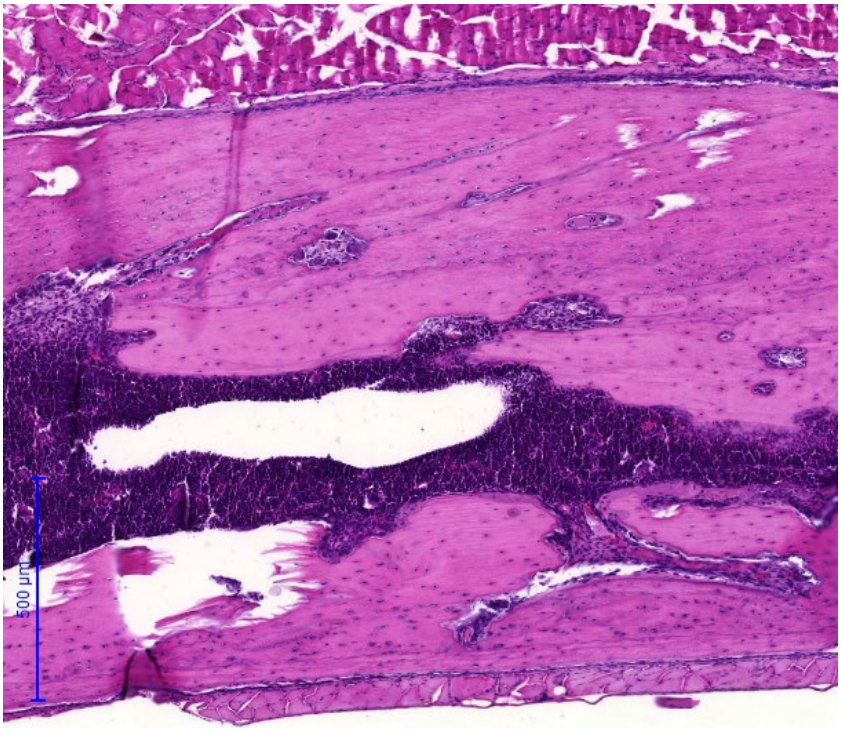


Figure 9: Animal No.221, male (50 mg/kg, 8 days on treatment): Vertebra, increased multifocal myelofibrosis, osteoclasts with slight bone resorption. Note slight myodegeneration in adjacent skeletal muscle.

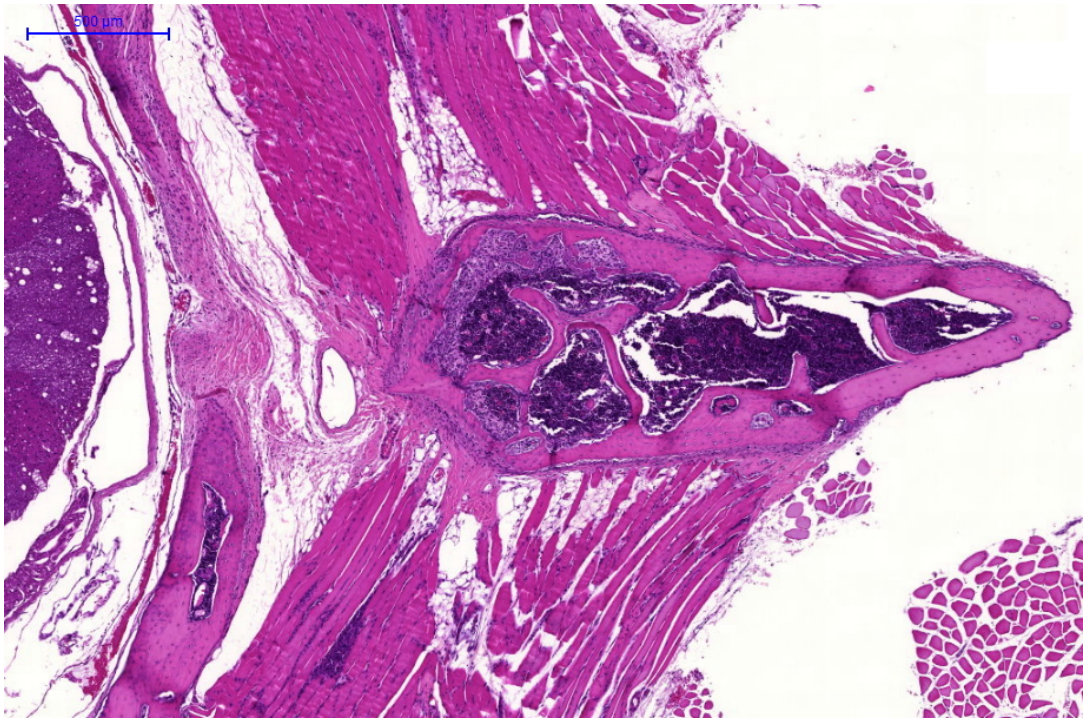
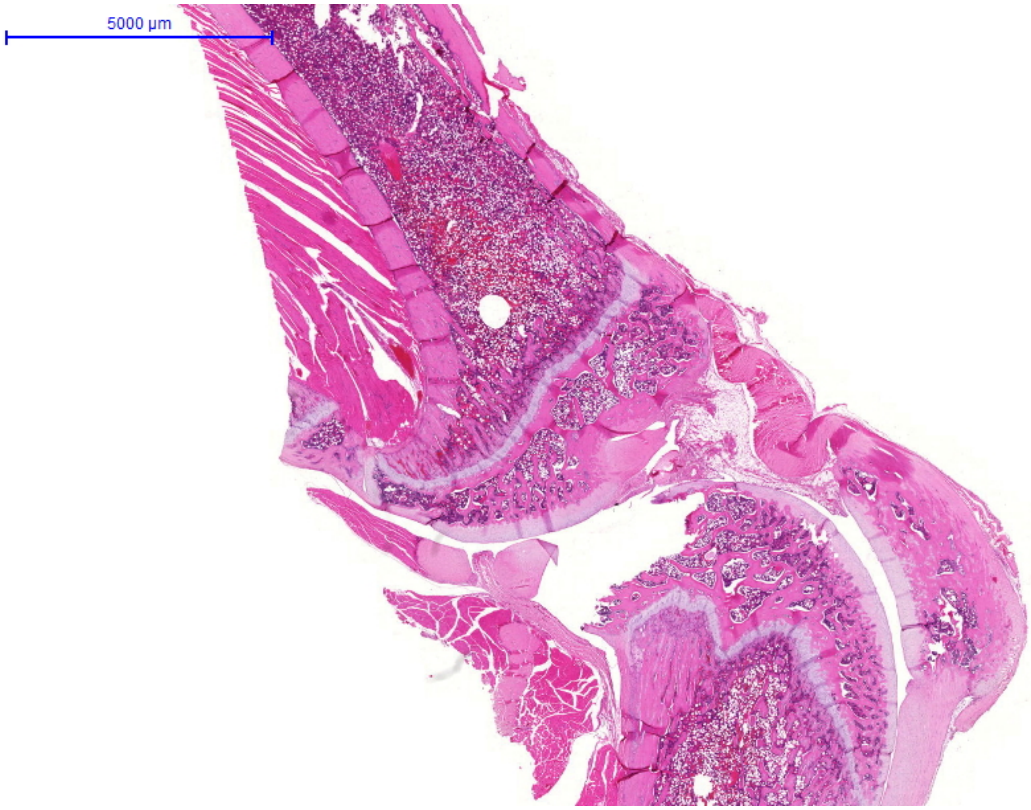


Figure 10: Animal No.225, male (50 mg/kg, 9 days on treatment): Knee joint with femur (left) and tibia (right) and patella with tendons: normal appearance of all parts with the exception of reduced cellularity of the bone marrow.

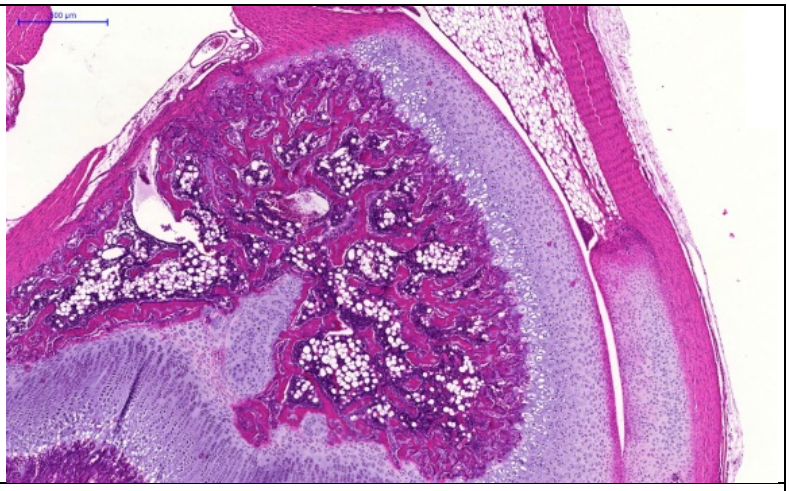
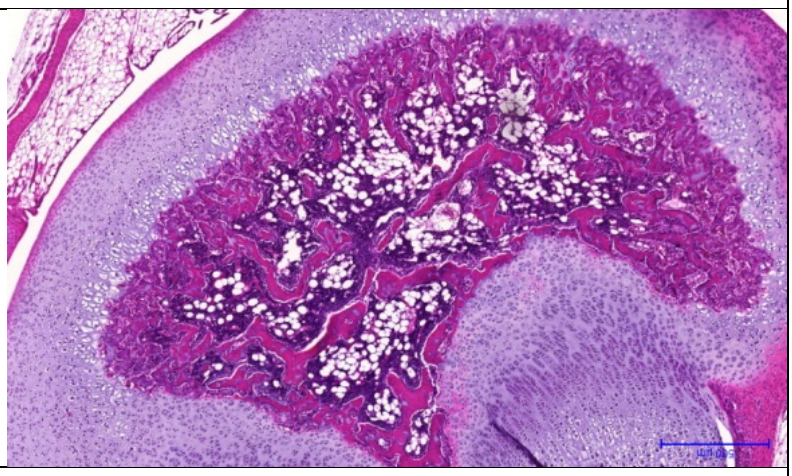
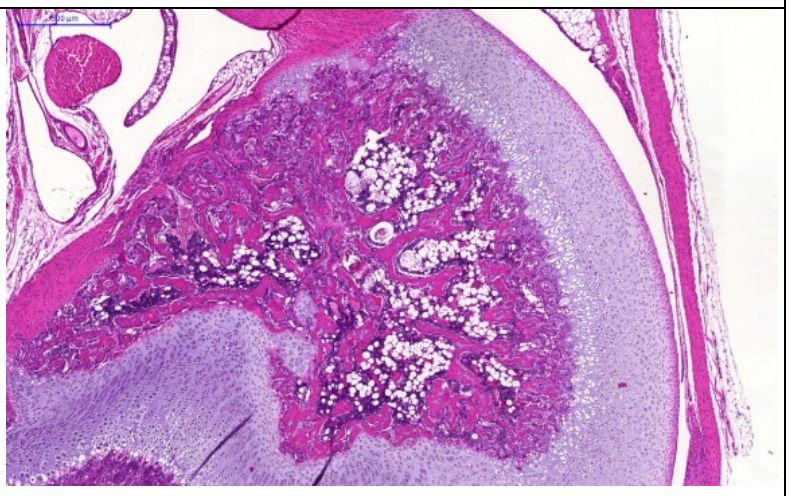


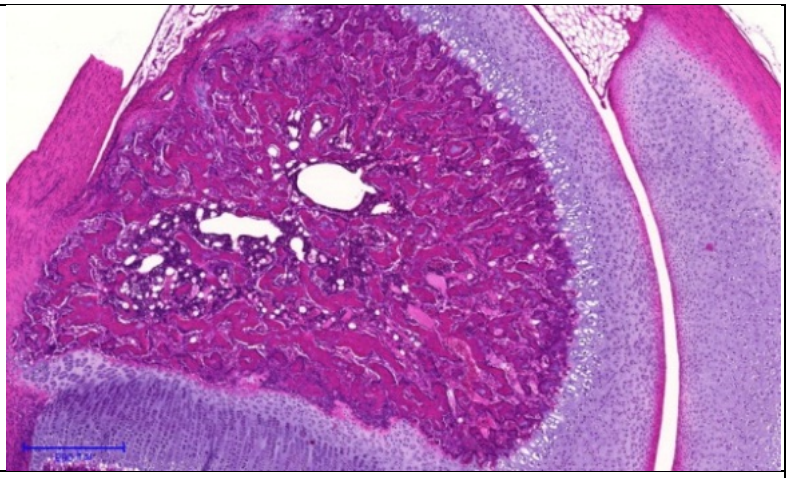
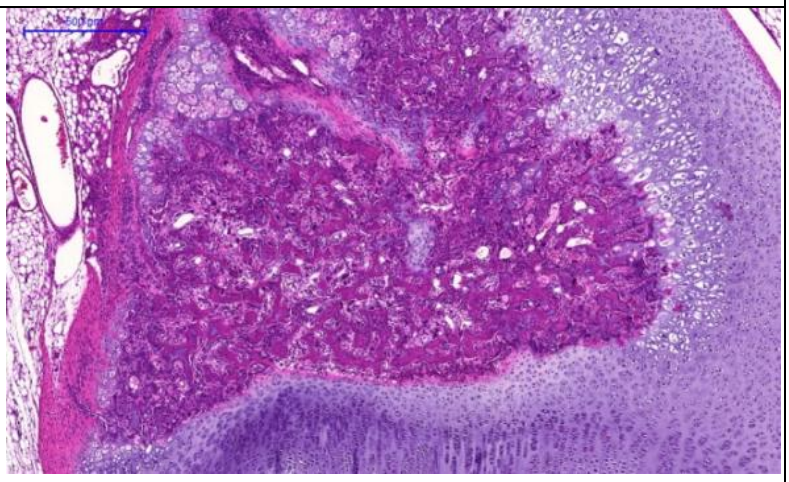
Section 2

Riociguat
Pilot Juvenile Rat Study (PH-36257)
Documentation of Morphological Bone Lesions

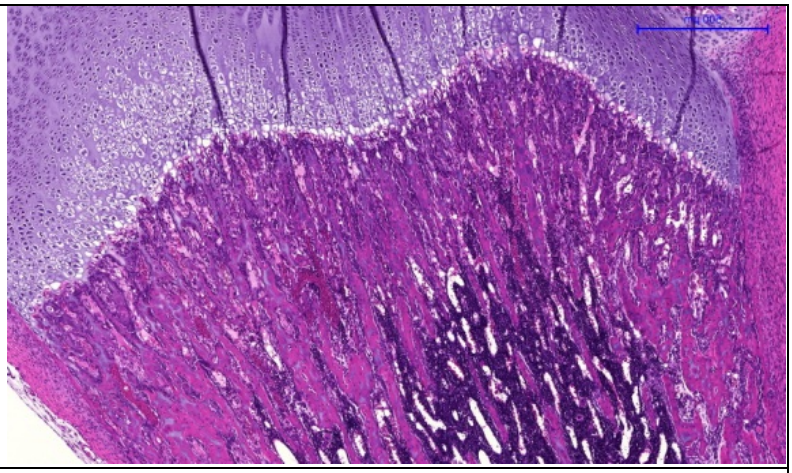
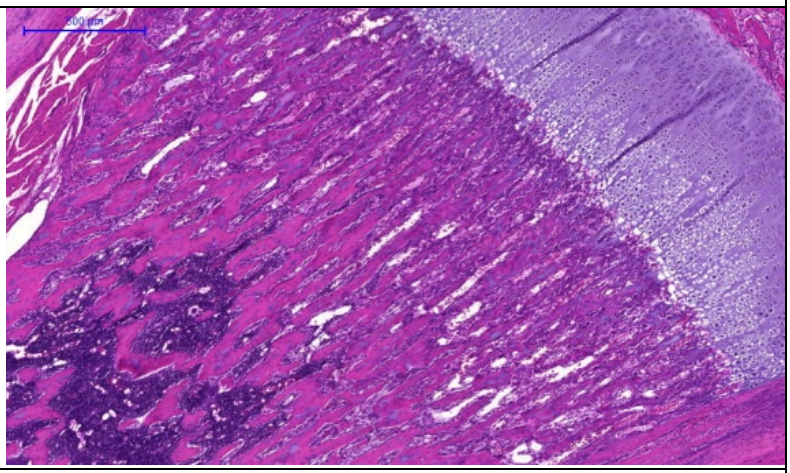
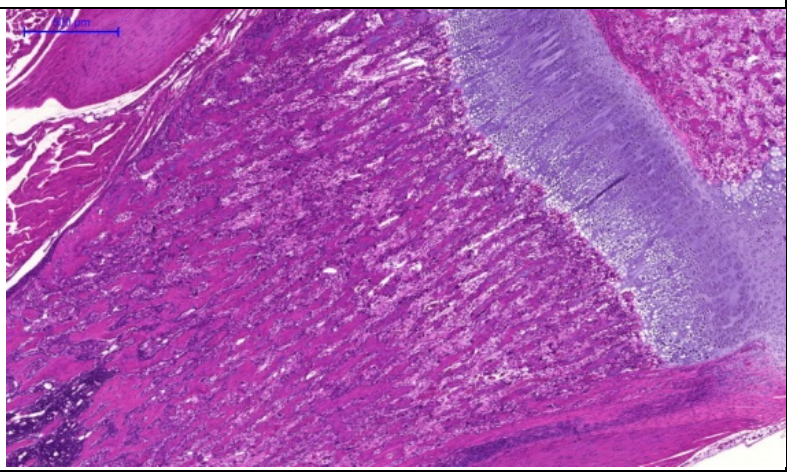
- Qualitative Description of Findings
- Description of Severity Gradings

Images of the femur epiphysis illustrating the morphology and severity scores applied for the histopathological findings "disorganized bone and bone marrow cavity, epiphysis" and "reduced bone marrow cells, epiphysis".

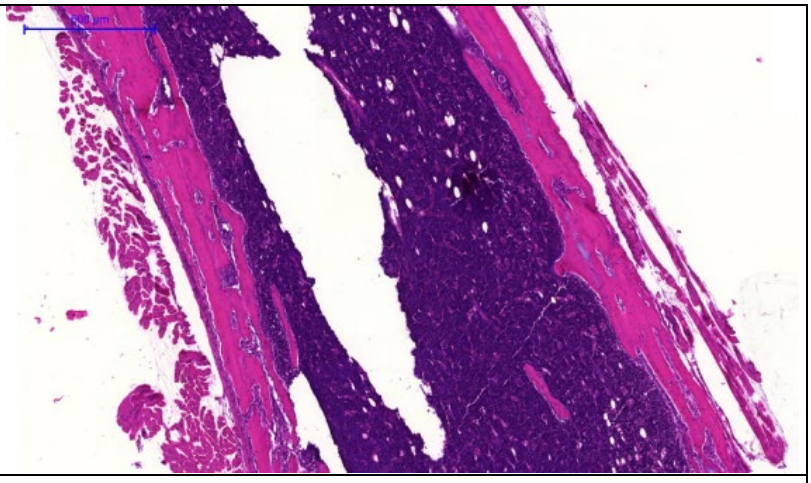
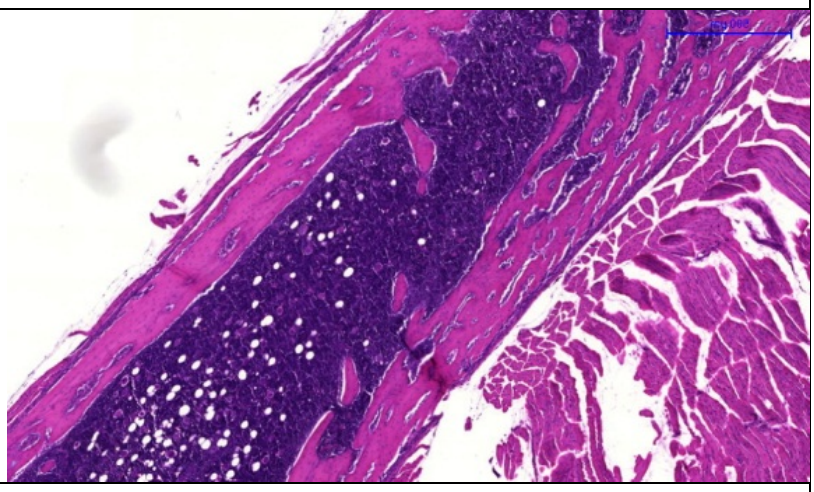
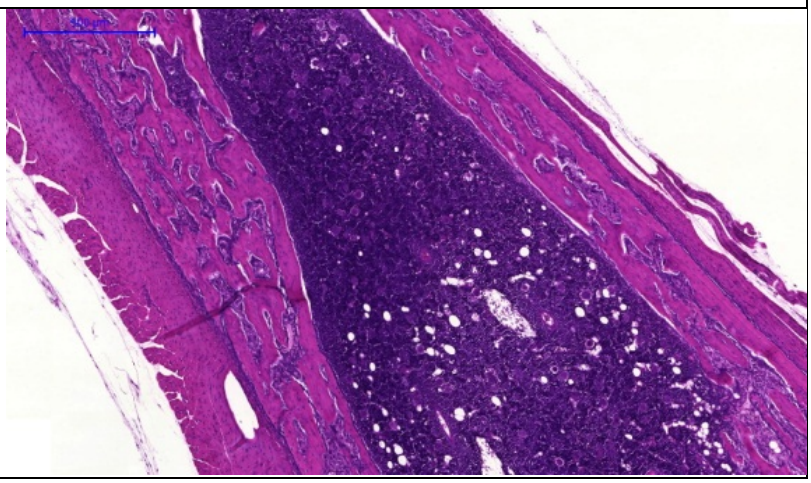
Animal no.1, male (0 mg/kg) Physiologic appearance of the epiphysis at that age with a rather narrow zone of spongiosa adjacent to the prominent articular cartilage. Bone marrow cavity with abundant hematopoietic cells and bone marrow adipocytes.	
Animal no 7, male (3 mg/kg) Comparable morphology to animal no. 1. **No microscopic findings.**	
Animal no 6, male (3 mg/kg) At the insertion site of the cruciate ligament a small area of disorganized bone with increased undifferentiated intercellular matrix, increase of bone formation and reduced bone marrow cells. **Grade 1 (minimal) disorganized bone/bone marrow cavity.** Since also the plane of section either more peripherally or centrally under the insertion of the ligaments has an impact with more bone and less hematopoiesis, the observations in this rat are equivocal. **Grade 1 (minimal) reduced epiphyseal bone marrow cells**	

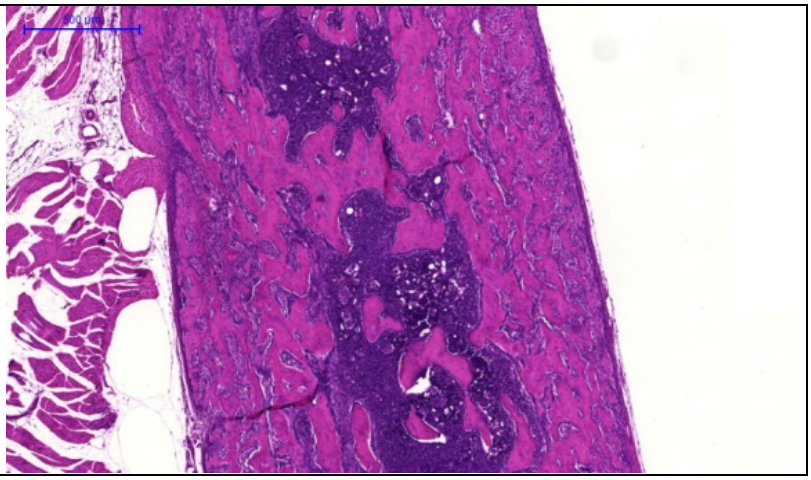
Animal no. 15, male (10 mg/kg) Further increase of plump and radially orientated bone trabeculae and increase of intertrabecular cells. **Grade 2 (slight) disorganized bone/bone marrow cavity.** Further reduction of the area with hematopoietic cells. **Grade 3 (moderate) reduced epiphyseal bone marrow cells.**	
Animal no. 20, male (30 mg/kg) Epiphyseal bone marrow cavity. completely replaced by bone trabeculae, osteoblasts/ mesenchymal cell **Grade 5 (extensive/massive) disorganized bone/bone marrow cavity.** Hematopoietic cells and bone marrow adipocytes are absent. **Gade 5 (extensive/massive) reduced epiphyseal bone marrow cells**	

Images of the tibia metaphysis illustrating the morphology and severity scores applied for the histopathological finding "hyperostosis metaphysis".

Animal no. 21, female (0 mg/kg) Physiologically wide zone of primary and secondary spongiosa, rather slim trabeculae.	
Animal no. 33, female (10 mg/kg) Sponigosa zone expanded further into the metaphyseal cone, more plump and irregular bone trabeculae. **Grade 2 (slight)**	
Animal no 16, male, (30 mg/kg) Further progression of hyperostosis towards the diaphysis, proportion of plump trabeculae and intertrabecular mesenchymal cells (including osteoclasts) enlarged. **Grade 4 (severe)**	

Images of the femur diaphysis illustrating the severity scores applied for the histopathological finding "hyperostosis diaphysis".

Animal no.2, male (0 mg/kg) Normal appearance and thickness of the cortical bone of the diaphyseal shaft.	
Animal no 34, female (10 mg/kg) Increased formation of compact bone, most pronounced at the posterior/ rear side of the femur shaft. **Grade 2 (slight)**	
Animal no. 17, male (30 mg/kg) Further increase of diaphyseal bone formation at the anterior and posterior (stronger) femur shaft **Grade 3 (moderate) hyperostosis diaphysis**	

Animal no 16, male (30 mg/kg) Advanced example of hyperostosis with distinct narrowing of the bone marrow cavity and a high number of lacunae with abundant osteoblasts /mesenchymal cells, close to the proximal end of the femur. **Grade 4 (severe) hyperostosis diaphysis**	

Section 3

Riociguat/BAY 60-4552

Repeat-dose Study in Adolecent Rats

Documentation of Morphological Bone Lesions

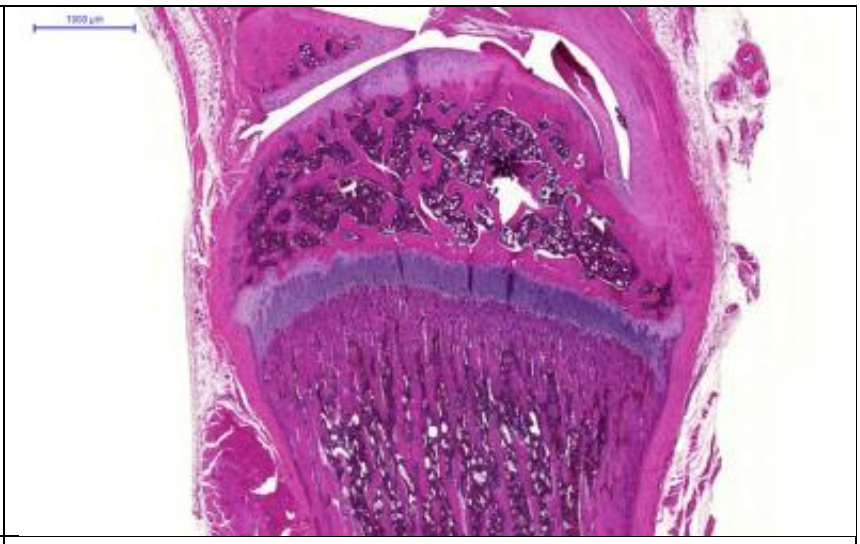
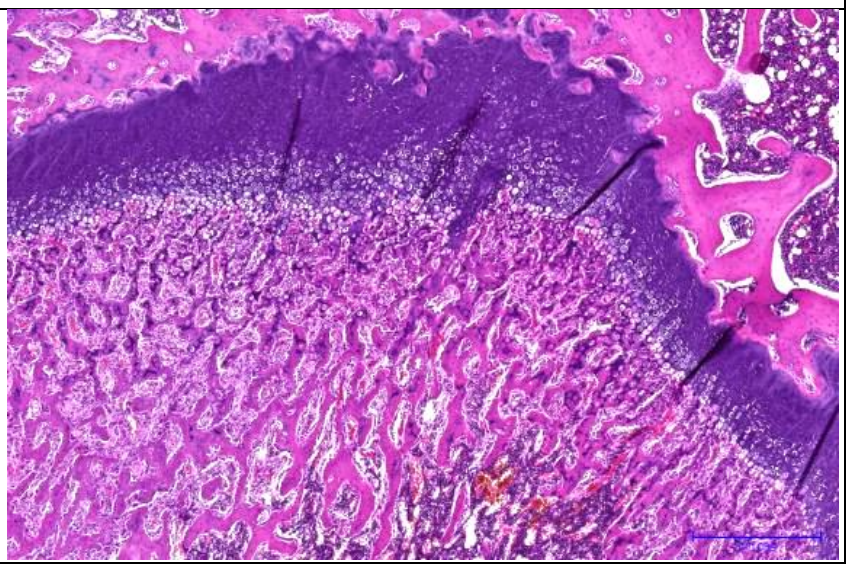
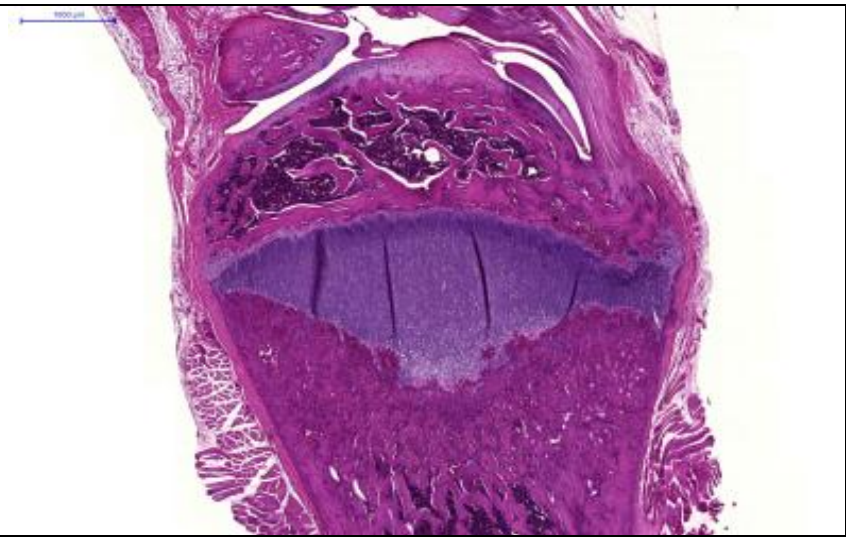
- Qualitative Description of Findings
- Description of Severity Gradings

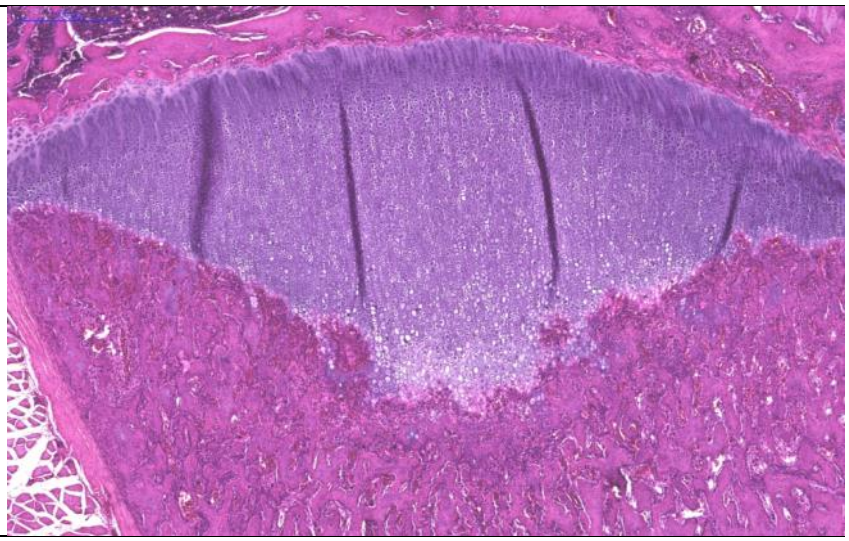
In this document, a compilation of the different lesions observed in riociguat-treated adolescent rats is presented.

For some lesions (e.g. growth plate thickening) only a limited spread of severity was recorded in riociguat-treated rats.

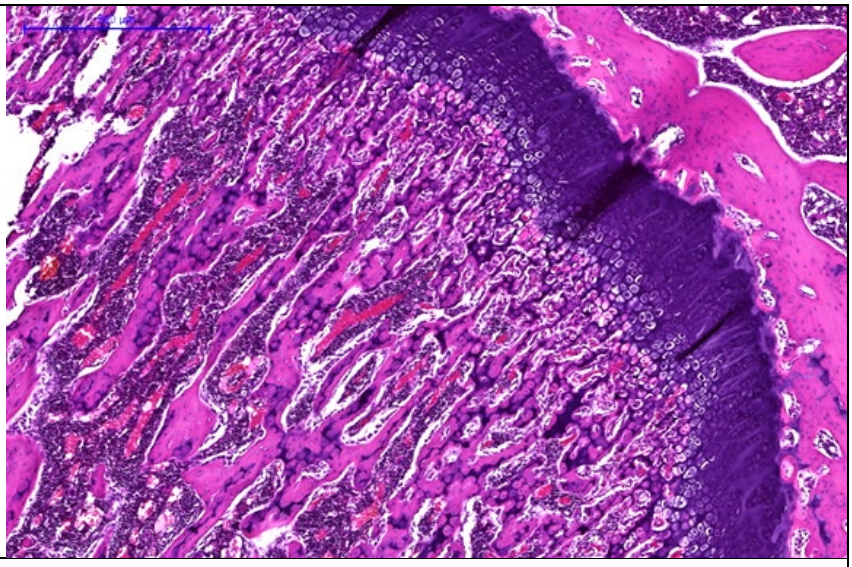
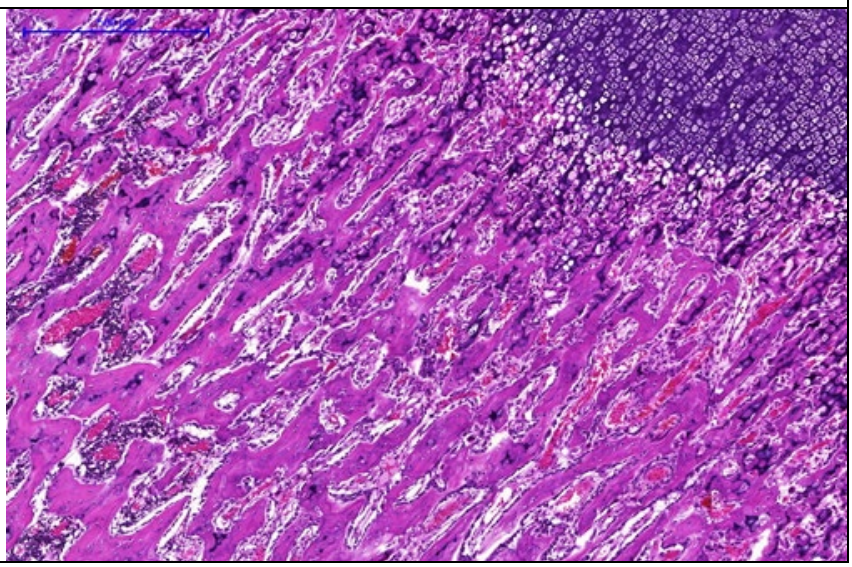
In order to give a full overview on the complete spectrum of the morphological changes also slides taken from BAY 60-4552 (M1 of riociguat) studies were included.

Images of femur and tibia illustrating the severity scores applied for the histopathological finding "thickened growth plate"

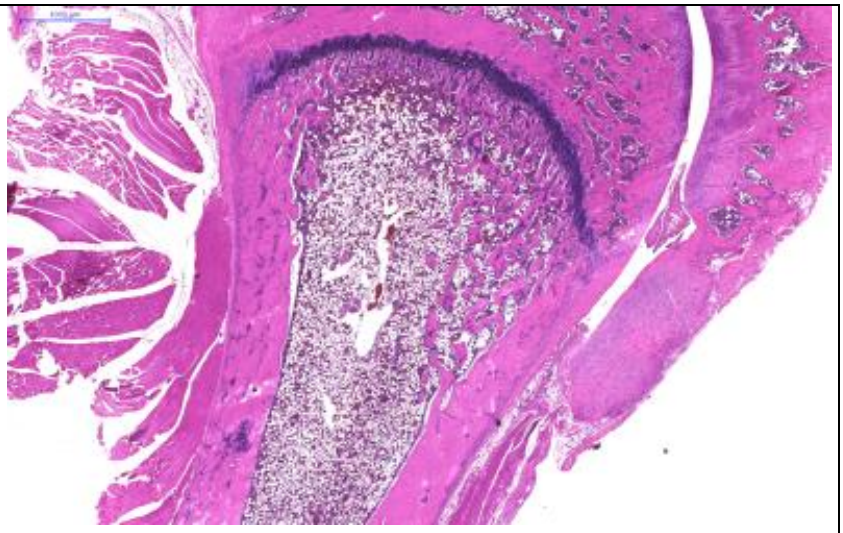
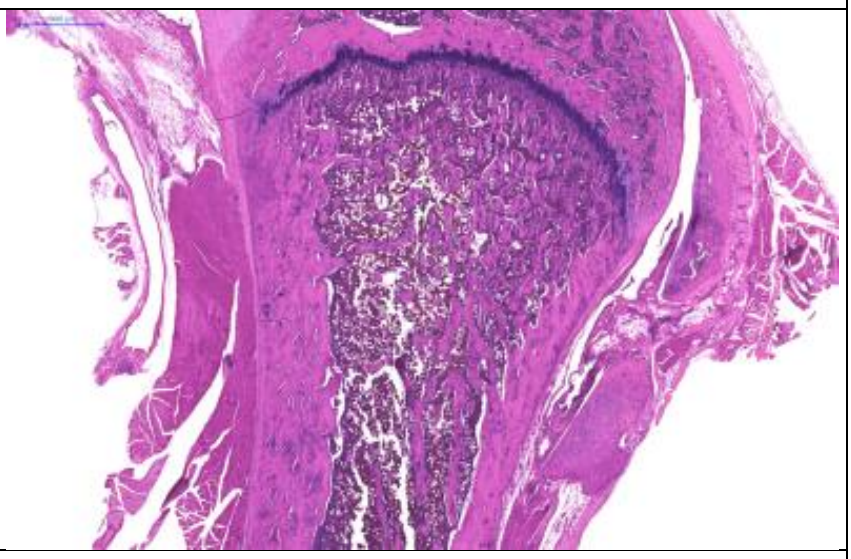
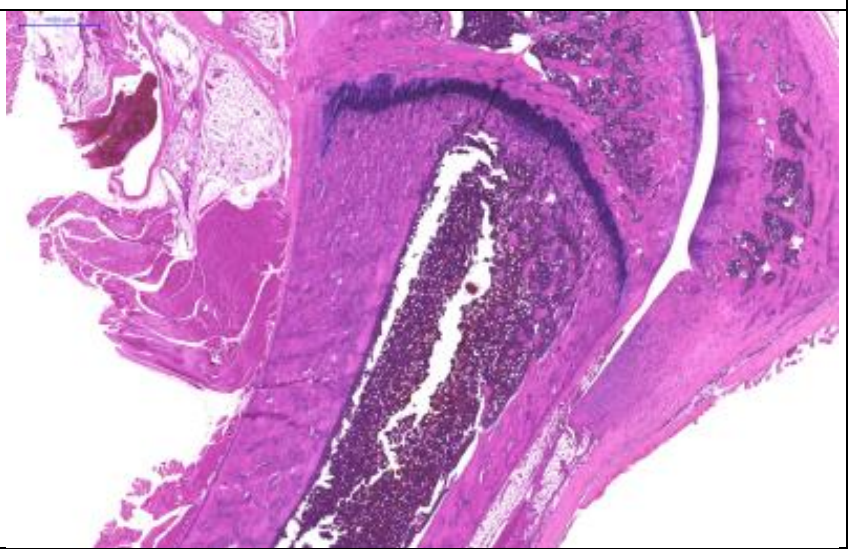
Animal no. 1, male, tibia (0 mg/kg riociguat, 4-week treatment) Normal growth plate: thin line of growth plate cartilage merging into slim trabeculae of primary and secondary spongiosa **No microscopic findings.**	
Animal no. 75, female, femur (100 mg/kg BAY 60-4552, 4-week treatment) Increased thickness of the growth plate with abundant hypertrophic chondrocytes at the border to the metaphysis and an irregular demarcation to epi- and metaphysis. **Grade 1 (minimal) thickening of the growth plate**	
Animal no. 41, male, tibia (30 mg/kg riociguat, 4-week treatment) Thickened growth plate showing hyperplastic cartilage and underlying blunt trabeculae of primary and secondary spongiosa, grade 3 **Grade 3 (moderate) thickening of the growth plate**	

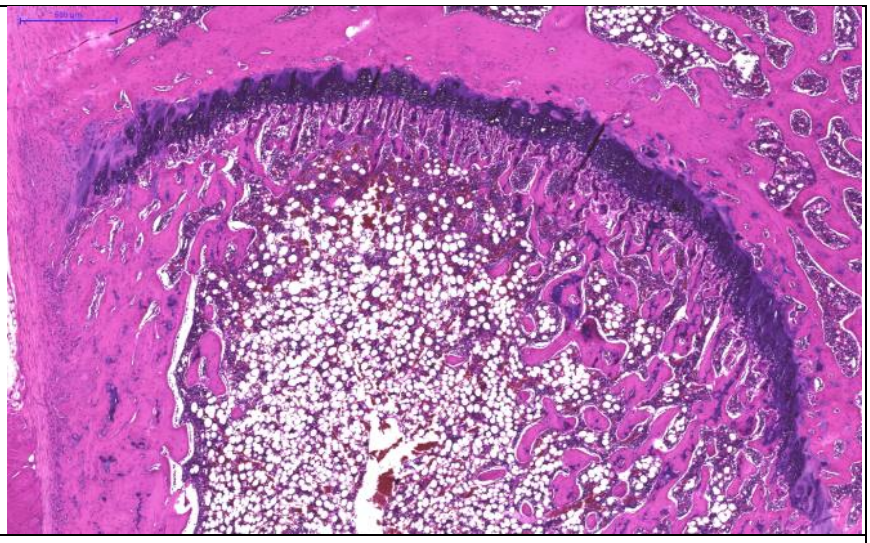
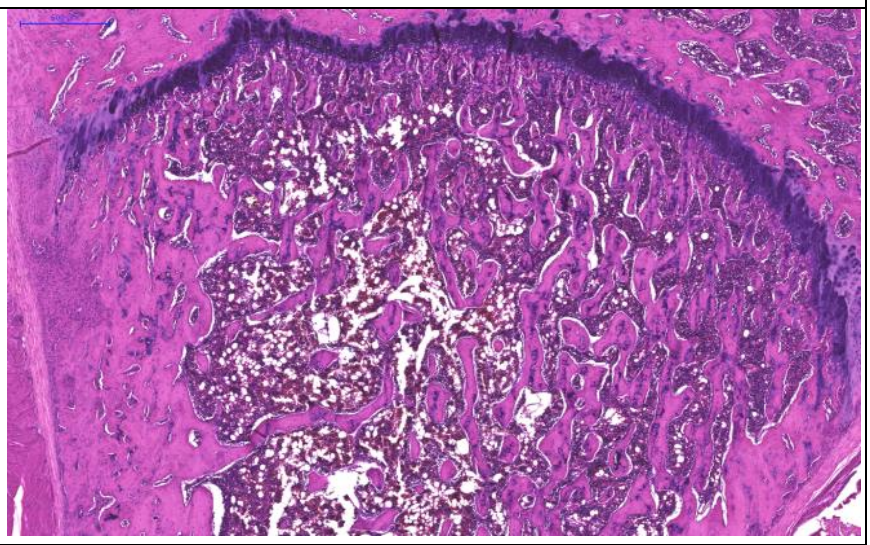
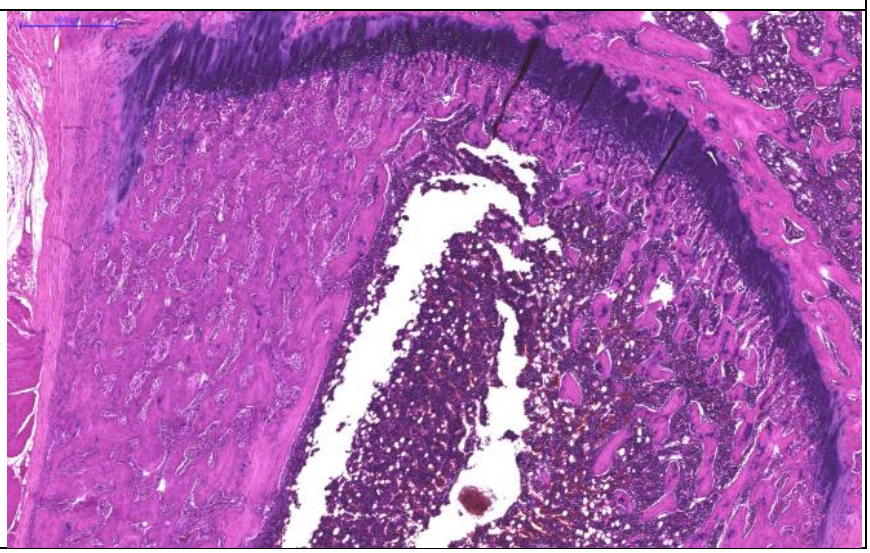
Animal no. 41, male, tibia (30 mg/kg riociguat, 4-week treatment) Thickened growth plate showing hyperplastic cartilage and underlying blunt trabeculae of primary and secondary spongiosa, grade 3 **Grade 3 (moderate) thickening of the growth plate**	

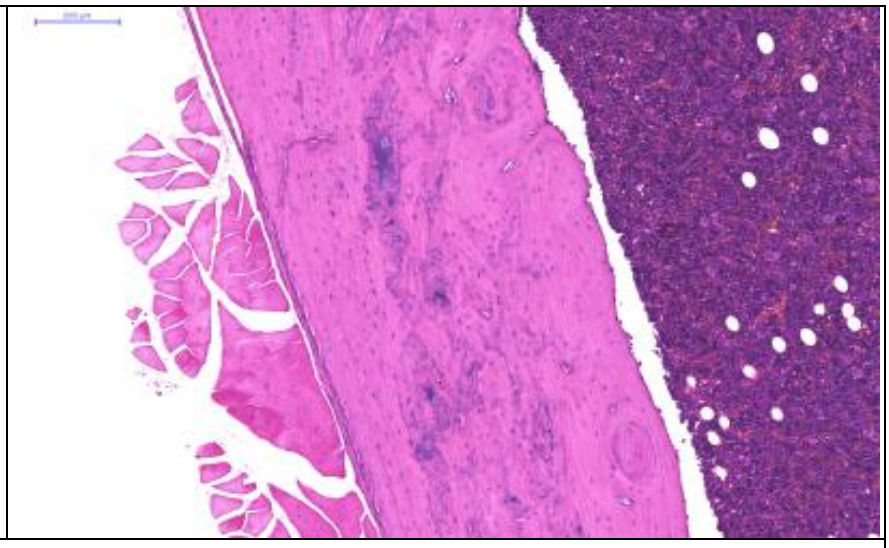
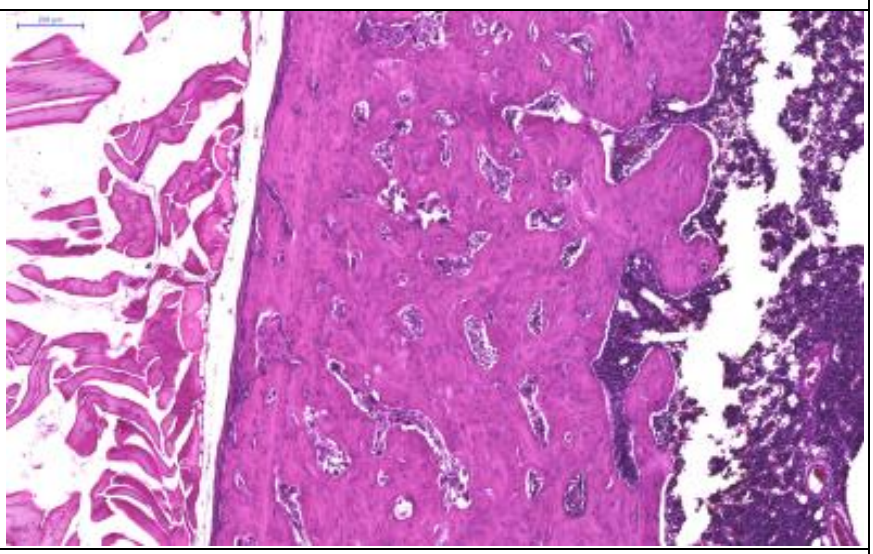
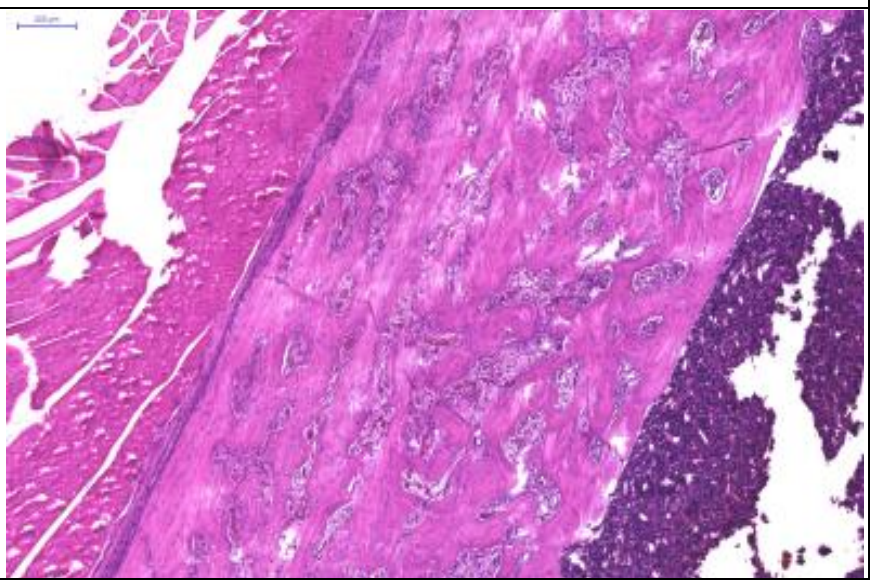
Images of femur and tibia illustrating the severity scores applied for the histopathological finding "increased remodeling/ hyperostosis" after 4-week treatment with BAY 60-4552 (In the 4-week study on riociguat; no cancellous bone changes were diagnosed)

Animal no. 1, male (0 mg/kg, BAY 60-4552): Normal appearance and thickness of the primary and secondary spongiosa **No microscopic findings.**	
Animal no. 39, male (100 mg/kg BAY 60-4552, 4-week treatment): Sponigosa zone expands into the metaphyseal cone, more plump and irregular bone trabeculae, hyperostosis, increase of intertrabecular cells. **Grade 2 (slight) disorganized trabecular bone**	

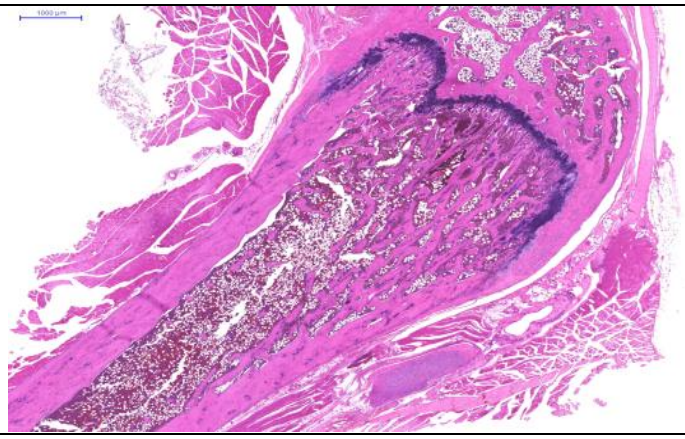
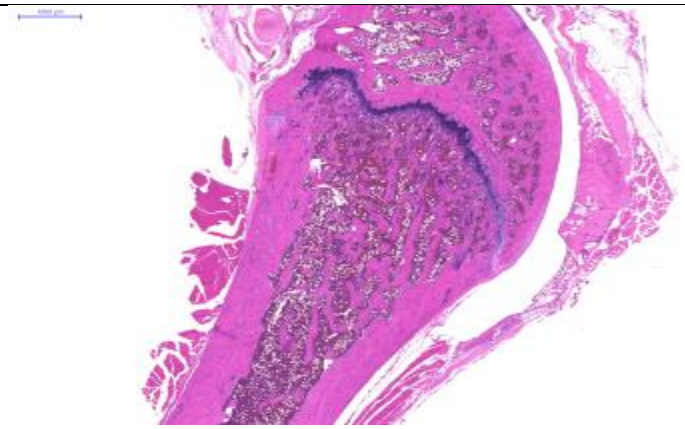
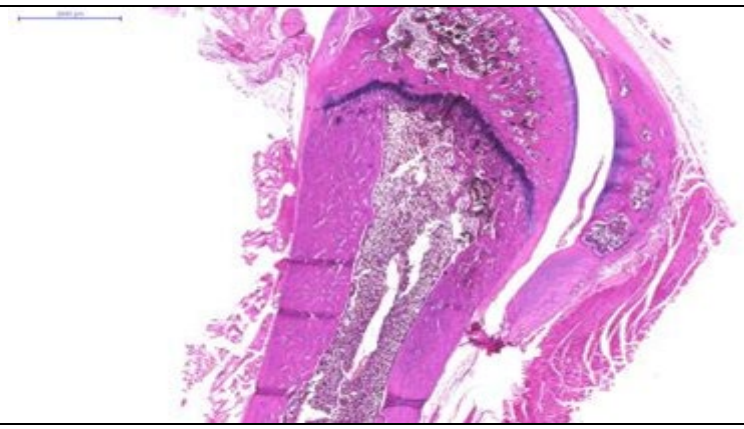
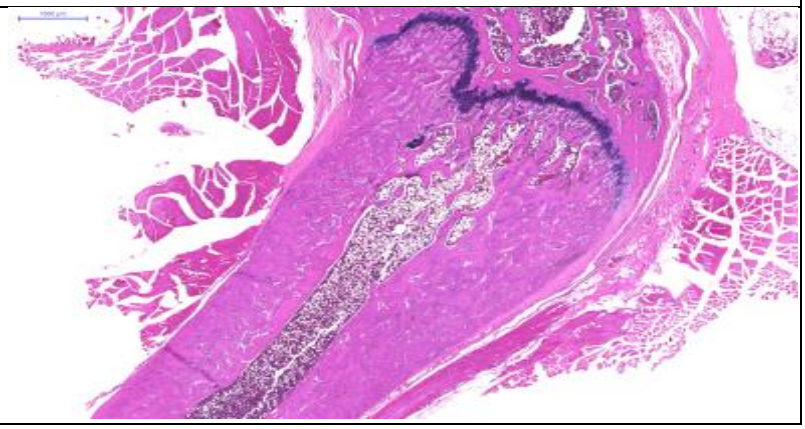
Images of femur and tibia illustrating the severity scores applied for the histopathological finding "increased remodeling/ hyperostosis" after 13-week treatment with riociguat

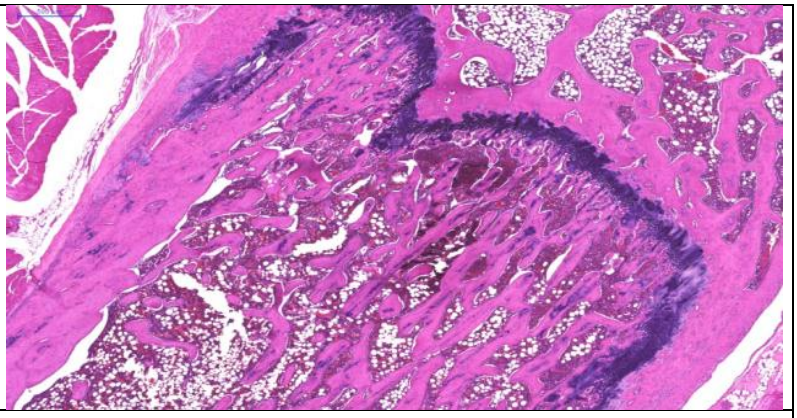
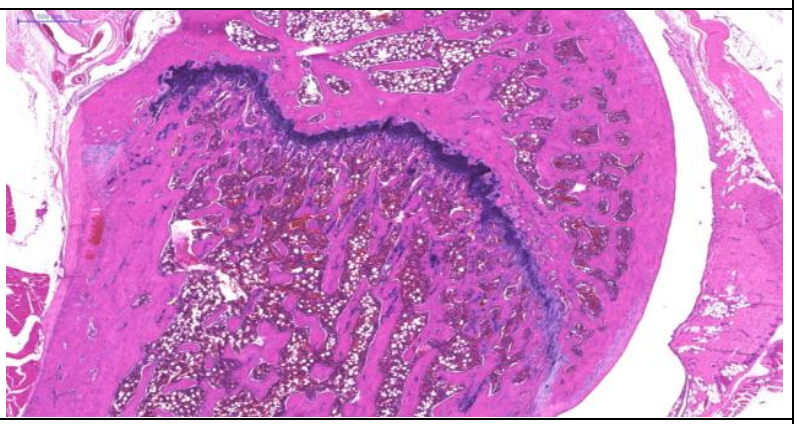
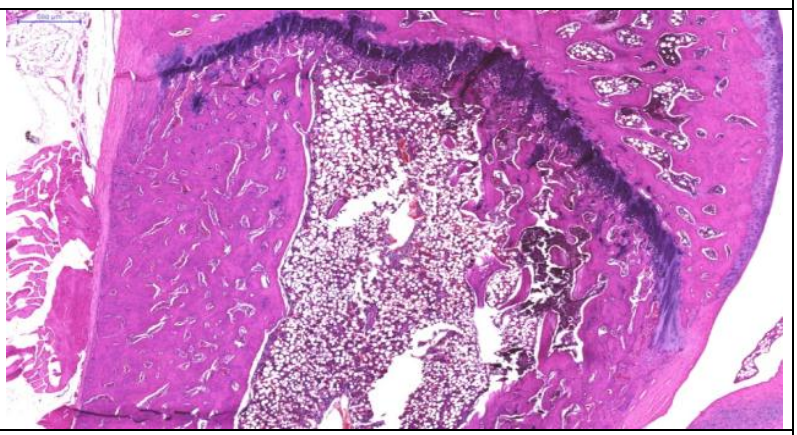
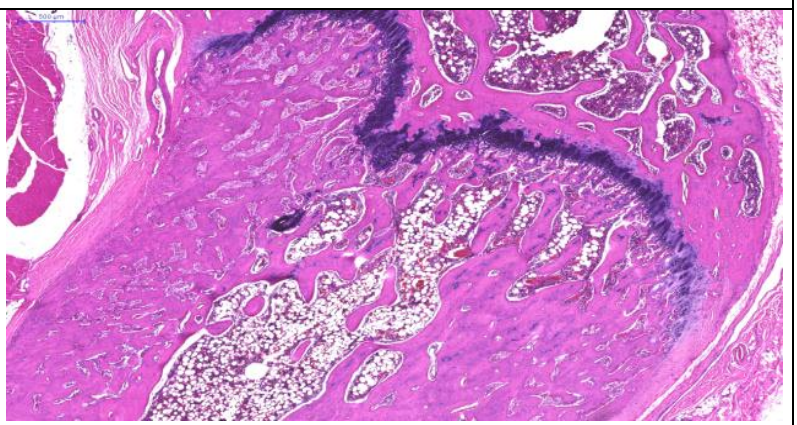
Animal no. 6, male, femur (0 mg/kg riociguat, 13-week treatment) Normal meta-/diaphysal cone: slim line of growth plate cartilage merging into thin plate of metaphyseal spongiosa, equal thickness of diaphyseal corticalis on front and rear side of the femur Higher magnification on next page	
Animal no. 39, male, femur (100 mg/kg riociguat, 13-week treatment, diet admixture) Slim line of growth plate cartilage, slight thickening of metaphyseal spongiosa and rear side corticalis in the meta-/diaphysal cone, **Grade 2** Higher magnification on next page	
Animal no. 38, male, femur (100 mg/kg riociguat, 13-week treatment, , diet admixture) Slim line of growth plate cartilage, hyperostotic thickening of metaphyseal spongiosa plate and corticalis on rear side of the femur, **Grade 3**, Higher magnification on next page	

Animal no. 6, male, femur (0 mg/kg riociguat, 13-week treatment, diet admixture) Normal meta-/diaphyseal cone: slim line of growth plate cartilage merging into thin plate of metaphyseal spongiosa	
Animal no. 39, male, femur (100 mg/kg riociguat 13-week treatment, diet admixture) slim line of growth plate cartilage, slight thickening of metaphyseal spongiosa and rear side corticalis in the meta-/diaphysal cone, cell rich lacunae in rear side corticalis, **Grade 2**	
Animal no. 38, male, femur (100 mg/kg riociguat, 13-week treatment, diet admixture) slim line of growth plate cartilage, hyperostotic thickening of metaphyseal spongiosa plate and corticalis on rear side of the femur containing cell rich lacunae, **Grade 3**	

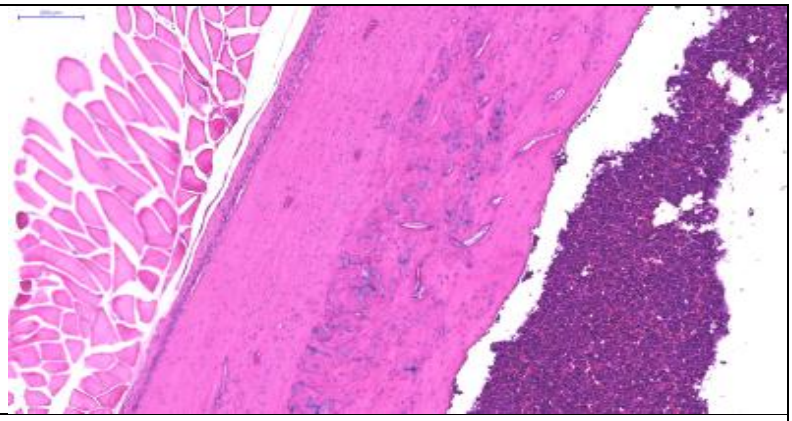
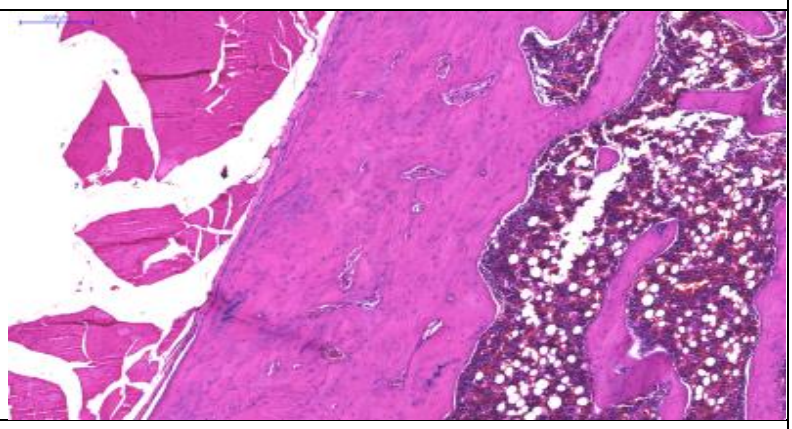
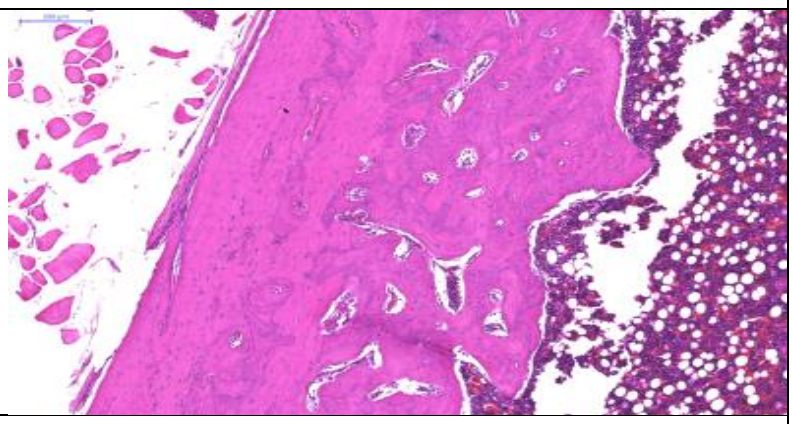
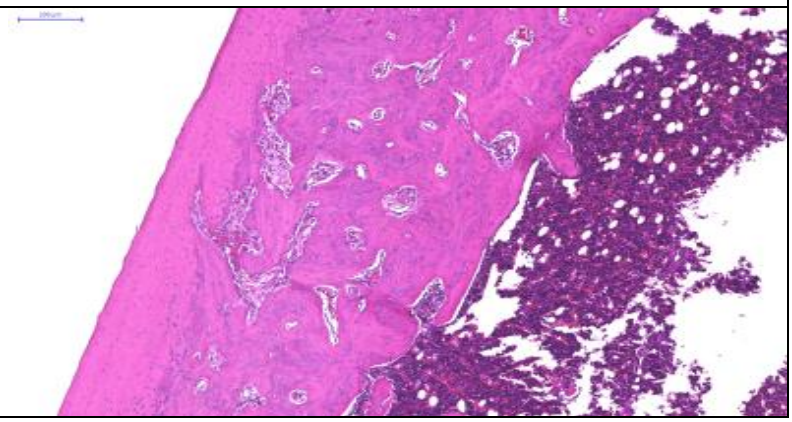
Animal no. 1, male, femur (0 mg/kg riociguat, 13-week treatment, diet admixture) diaphyseal shaft with normal corticalis on the rear side of the femur	
Animal no. 39, male, femur (100 mg/kg riociguat, 13-week treatment, diet admixture) Bone remodeling in diaphyseal shaft showing cell rich lacunae on the rear side of the femur **Grade 2**	
Animal no. 38, male, femur (100 mg/kg riociguat, 13-week treatment, diet admixture) Bone remodeling in diaphyseal shaft, cell rich lacunae containing spindle-shaped tissue on the rear side of the femur **Grade 3**	

Images of femur and tibia illustrating the severity scores applied for the histopathological finding "increased remodeling/ hyperostosis" in the metaphysis after 26-week treatment

Animal no. 4, male, femur (0 mg/kg riociguat, 26-week treatment) Normal morphology with slim line of growth plate cartilage and thin trabeculae of primary and secondary spongiosa in the metahysis, equal thickness of corticalis on front and rear side of the femur Higher magnification on next page	
Animal no. 148, female, femur (40 mg/kg, riociguat, 26-week treatment) Minimal hyperostotic thickening of metaphyseal spongiosa and corticalis on rear side of the femur **Grade 1** Higher magnification on next page	
Animal no. 80, male, femur (40 mg/kg riociguat, 26-week treatment) slight hyperostotic thickening of the metaphyseal spongiosa plate on the rear side and minimally on the front side of femur **Grade 2** Higher magnification on next page	
Animal no. 77, male, femur (40 mg/kg riociguat, 26-week treatment) Moderate hyperostotic thickening of the metaphyseal spongiosa plate and corticalis on the rear and front side of femur, **Grade 3** Higher magnification on next page	

Animal no. 4, male, femur (0 mg/kg riociguat, 26-week treatment) normal morphology: metaphysis showing slim line of growth plate cartilage and metaphyseal ossification zone consisting of thin trabeculae with primary and secondary spongiosa	
Animal no.148, female, femur (40 mg/kg riociguat, 26-week treatment) Minimal hyperostosis in metaphyseal spongiosa plate and rear side corticalis, few cell rich lacunae in rear side corticalis, **Grade 1**	
Animal no. 80, male, femur (40 mg/kg riociguat, 26-week treatment) slight hyperostosis of metaphyseal spongiosa plate and corticalis, multiple cell rich lacunae on the rear side of the femur, **Grade 2**	
Animal no. 77, male, femur (40 mg/kg riociguat, 26-week treatment) moderate hyperostosis in the metaphyseal spongiosa plate and corticalis on rear and front side of femur, corticalis containing multiple cell rich lacunae, **Grade 3**	

Images of femur and tibia illustrating the severity scores applied for the histopathological finding "increased remodeling/ hyperostosis" in the diaphysis after 26-week treatment

Animal no. 5, male, femur (0 mg/kg riociguat, 26-week treatment) Normal morphology of diaphyseal shaft, outer lamellar bone and inner woven bone containing bluish cartilage islands	
Animal no. 148, female, femur (40 mg/kg riociguat, 26-week treatment) Diaphyseal shaft with few cell rich lacunae in rear side corticalis **Grade 1**	
Animal no. 80, male, femur (40 mg/kg riociguat, 26-week treatment) Diaphyseal shaft on rear side of femur showing outer lamellar bone and inner woven bone containing several cell rich lacunae, **Grade 2**	
Animal no. 78, male, femur (40 mg/kg riociguat, 26-week treatment) Diaphyseal shaft on rear side of femur showing outer lamellar bone and inner woven bone containing several lacunae with spindle-shaped cells, **Grade 3**	

Section 4

Considerations on Human Relevance of Bone Findings in Adolescent and Juvenile Rats

1 Short summary of toxicological data

Riociguat was tested in juvenile, adolescent and full grown rat as well as in full grown mice and dogs with regard potential changes of bone morphology. The bone findings in experimental animals were dependent on the life stage of the animals at initiation of treatment. Riociguat-related changes were only seen in juvenile and adolescent fast growing animals, whereas the bones of full grown animals remained unchanged. A short summary of the findings is given below.

In adolescent mice, only in a 2-week pilot feeding study (Module 4.2.3.2, PH-34519), at lethal doses minimal thickening of the growth plates were seen.

Longer-term treatment of mice which where full grown over almost the whole treatment period did not reveal any morphological bone effects at exposure levels of 7-fold (Module 2.6.6, Section 10, Table 10-1, 13-week study, Module 4.2.3.2, PH-34865, Module 4.2.3.2, PH-34866) to 11-fold of human exposure (Module 2.6.6, Section 10, Table 10-10, 2-year treatment study, Module 4.2.3.4.1, PH-36818) after 2.5 mg TID.

In adolescent rats, treated during the phase of pronounced body growth marked hypertrophy of growth plate cartilage and thickening of primary and secondary spongiosa in the metaphysis and diaphyseal funnel, called hyperostosis in the respective reports, of long bones were seen. At the diaphyseal shaft increased modeling was seen in the subperiosteal zone of lateral bone growth.

After 4-week treatment in rats study (Module 4.2.3.2, PH-33408), growth plate changes started at 15 mg/kg corresponding to systemic exposure in terms of unbound AUC of about 3-fold of human exposure (Module 2.6.6, Section 10, Table 10-4).

After 13-week treatment (Module 4.2.3.2, PH-34674, Module 4.2.3.2, PH-34877), no cartilage lesions were observed. However, increased bone modelling and remodelling resulting finally in an increased bone mass was seen at 100 mg/kg in the 13-week dose adjusted feeding study corresponding to margins of exposure of 20 to 26 (Module 2.6.6, Section 10, Table 10-4). In the 13-week gavage study up to a daily

dose of 30 mg/kg (MoE ~8) (Module 2.6.6, Section 10, Table 10-4), no bone changes were observed.

After 26-week treatment (Module 4.2.3.2, PH-35002), hyperostosis was seen at 10 mg/kg and above corresponding to margins of exposure of about 2. Of note, the changes observed after chronic treatment indicated more mature bone structure and less pronounced active remodeling.

A life-time bioassayt (Module 4.2.3.4.1, PH-36817) with treatment start during adolescence did not reveal bone findings up to exposure levels about 9-fold of human exposure (Module 2.6.6, Section 10, Table 10-10).

In juvenile rats (Module 4.2.3.5.4, PH-36257), treated from PND 6 for about 3 weeks, starting at 3 mg/kg with clear changes at 10 mg/kg and above, morphological bone changes were observed. They were restricted to osseous structures with fast turnover, whereas the cartilaginous part of the growth plate remains unchanged. It is hypothesized that this is due to the fact that in this young fast growing animals, the cartilage proliferation and turnover is already maximally stimulated and cannot be further influenced by the NO-cGMP pathway.

In full grown rats, treated at daily doses up to 25 mg/(up to 6-fold of human exposure at 2.5 mg TID) over a treatment period of 26 weeks, no morphological bone changes and no changes in bone mineral density and bone-related biomarkers were observed.

In dogs, which were almost full grown at start of treatment, in repeat-dose studies from 2-weeks up to 52-weeks no skeletal findings were observed at an exposure range up to 3.8 times the human exposure at 2.5 mg TID.

2 Interpretation of the bone findings

Riociguat is a stimulator of the soluble guanylate cyclase. As a consequence intracellular cGMP levels increases followed by enhanced activation of Protein Kinase G.

It is generally accepted that the eNOS-NO-sGC-cGMP-PGK pathway is involved in the regulation of bone homeostasis [(1-5)] and the riociguat-related bone findings in growing rats are mode of action-related and do not represent off-target and unexpected toxicity. Furthermore, the morphological findings observed as well as the published data indicate that the above-mentioned pathway results in a stimulation of bone formation and not in increased bone resorption.

As evidenced by the absence of riociguat-associated bone findings in dogs, mice and adult rats, the respective toxicological data demonstrate that activation of this pathway beyond physiological levels induces morphological changes only during the phase of bone growth and pronounced bone modeling. Treatment of riociguat in animals undergoing pronounced bone growth results in skeletal lesions consisting of

growth plate alterations and remodeling of osseous structures, at exposure levels close to therapeutic exposure levels. The absence of comparable lesions in full grown adult animals at comparable exposure supports the hypothesis that individuals undergoing pronounced bone growth and modeling associated with a high turnover rate of the bone mass are more susceptible for these changes than adult individuals.

Thus, the Sponsor concludes that one cannot exclude a risk for children treated chronically with riociguat. Although the clinical relevance of the findings in the bones of rapidly growing young rats is not fully understood, the age-dependency as well as the small therapeutic index shown in preclinical studies along with the physiological mechanism of the NO-sGC-CMP-PKG pathway suggests that children undergoing rapid and pronounced skeletal development may be susceptible for riociguat-related bone effects.

For adult patients the situation is different: data from the chronic rat study showing more mature bone structure and less active remodeling at about 2-fold human exposure and no morphological changes after 2-year treatment at up to 9-fold human exposure suggest that after full cessation of bone growth, remodeling stops, and bone homeostasis normalizes. In this context, it is of particular note that also in the spinal column, bone known to be of major importance in patients suffering from osteoporosis, no morphological were seen.

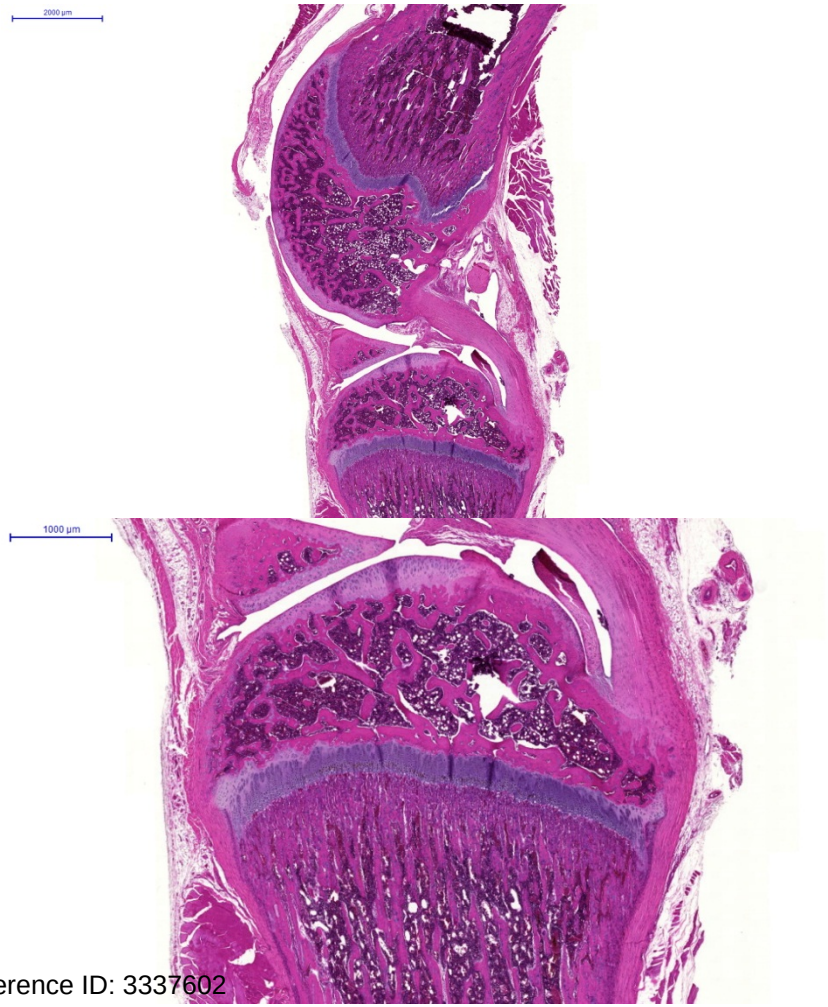
On the basis of these observation and in conjunction with the absence of bone findings in a mechanistic study in adult (full grown) rats as well as in the absence of respective findings in dogs and mice, there is no evidence of risk for adult patients under therapy.

3 References

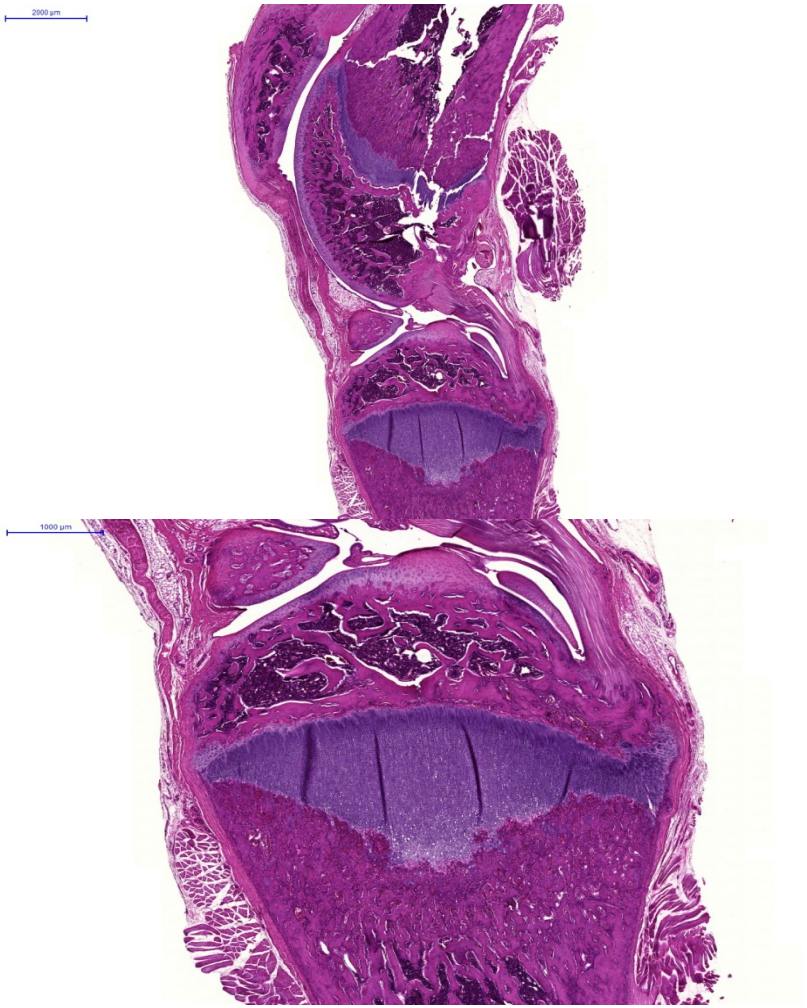
1. Wimalawansa S. Nitric oxide and bone. Ann NY Acad Sci. 2010;1192:391-403.
2. Rangaswami H, Schwappacher R, Tran T, Chan GC, Zhuang S, Boss GR, et al. Protein kinase G and focal adhesion kinase converge on Src/Akt/beta-catenin signaling module in osteoblast mechanotransduction. J Biol Chem. 2012 Jun 15;287(25):21509-19.
3. Rangaswami H, Schwappacher R, Marathe N, Zhuang S, Casteel DE, Haas B, et al. Cyclic GMP and protein kinase G control a Src-containing mechanosome in osteoblasts. Sci Signal. 2010;3(153):ra91.
4. Rangaswami H, Marathe N, Zhuang S, Chen Y, Yeh JC, Frangos JA, et al. Type II cGMP-dependent protein kinase mediates osteoblast mechanotransduction. J Biol Chem. 2009 May 29;284(22):14796-808.
5. Marathe N, Rangaswami H, Zhuang S, Boss GR, Pilz RB. Pro-survival effects of 17beta-estradiol on osteocytes are mediated by nitric oxide/cGMP via differential actions of cGMP-dependent protein kinases I and II. J Biol Chem. 2012 Jan 6;287(2):978-88.

BAY 63-2521, T2072968, P6494, Subacute Oral Study in Rats (4w+2w rec), Doses: 0-1.5-5-15-30 mg/kg Body Weight

Rat no.1, male, control (0 mg/kg), normal femur and tibia with joint



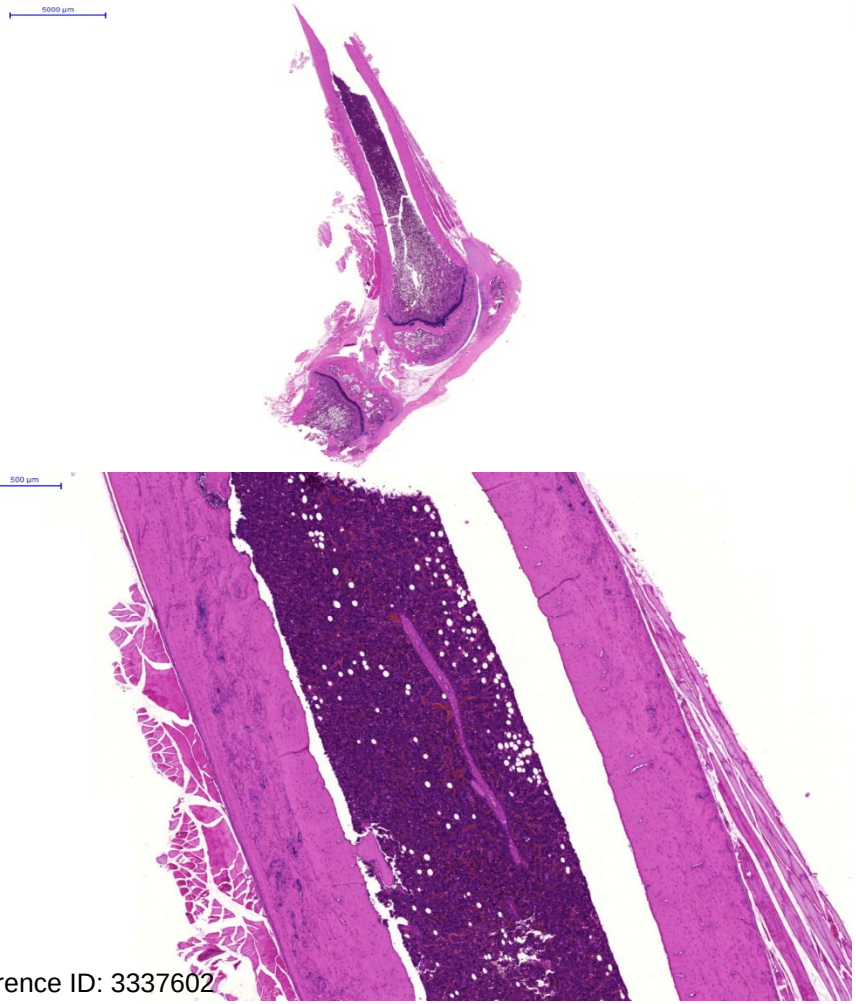
Rat no.41, male, HD (30 mg/kg), femur and tibia with joint, thickened growth plate grade 3



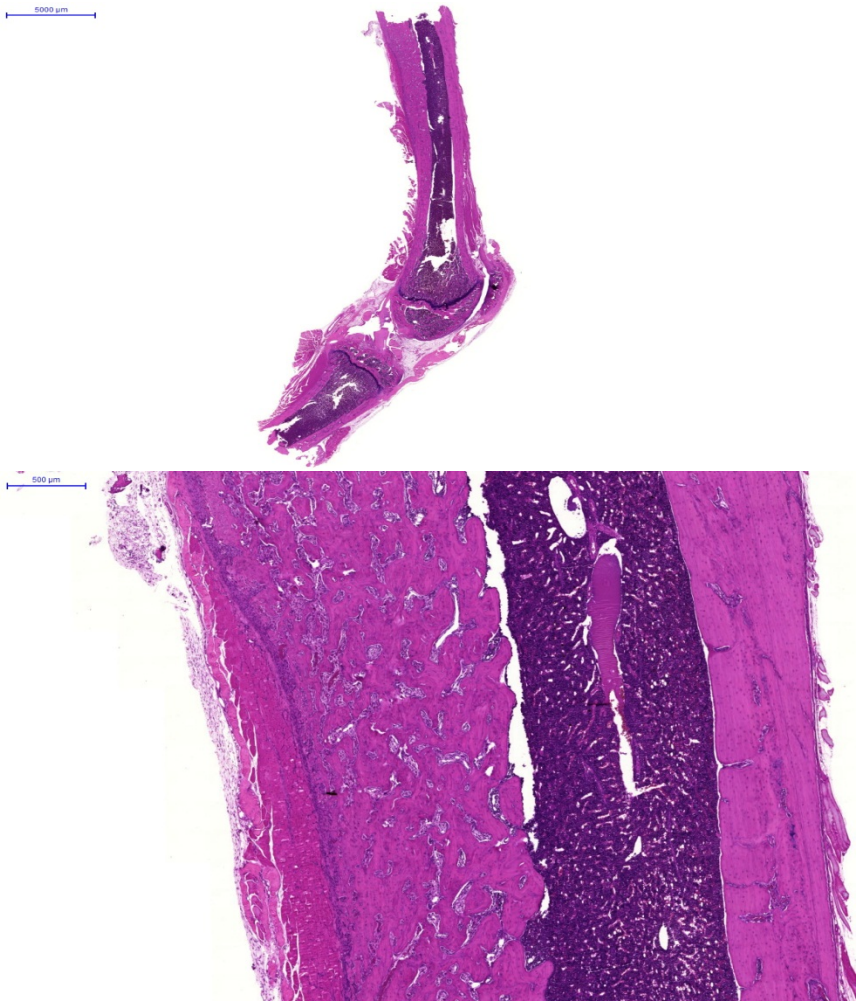
Reference ID: 3337602

BAY 63-2521, T4076731, P7041, Subchronic Toxicity Study (13w via diet), Doses: 0-4-20-100 mg/kg Body Weight

Rat no.1, male, control (0 mg/kg), normal femur and tibia with joint



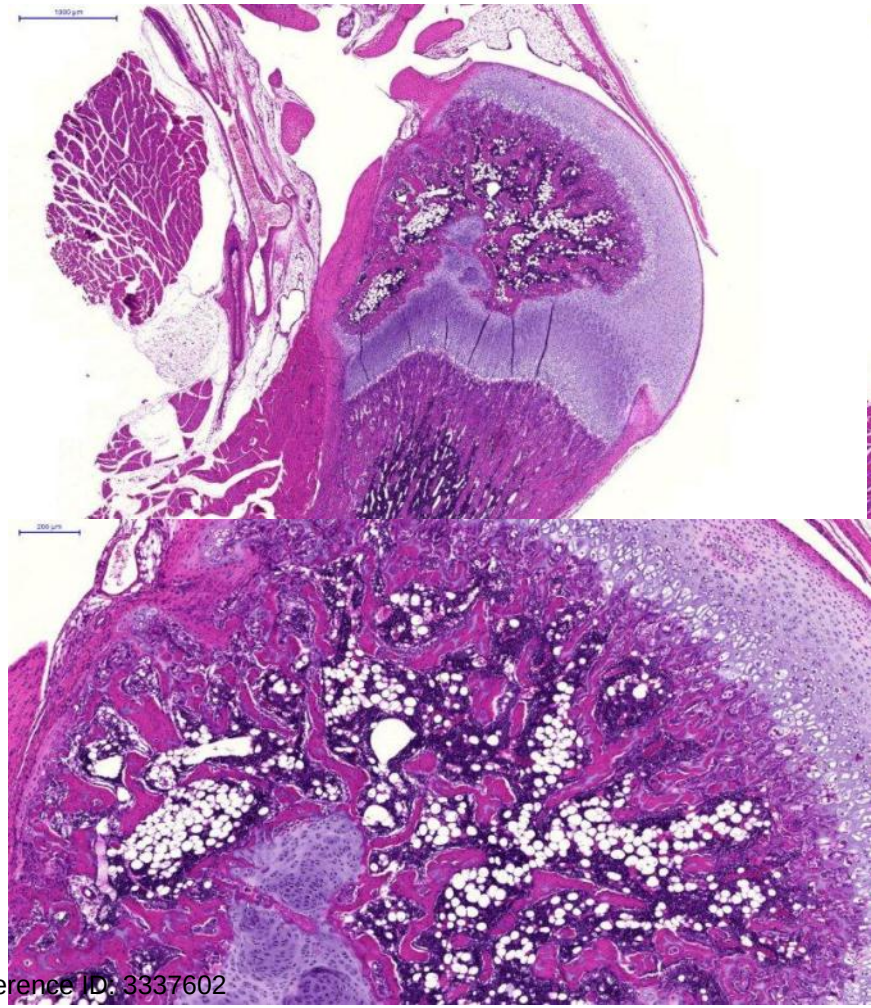
Rat no.36, male, HD (100 mg/kg), increased remodelling/hyperostosis of femur diaphysis grade 3



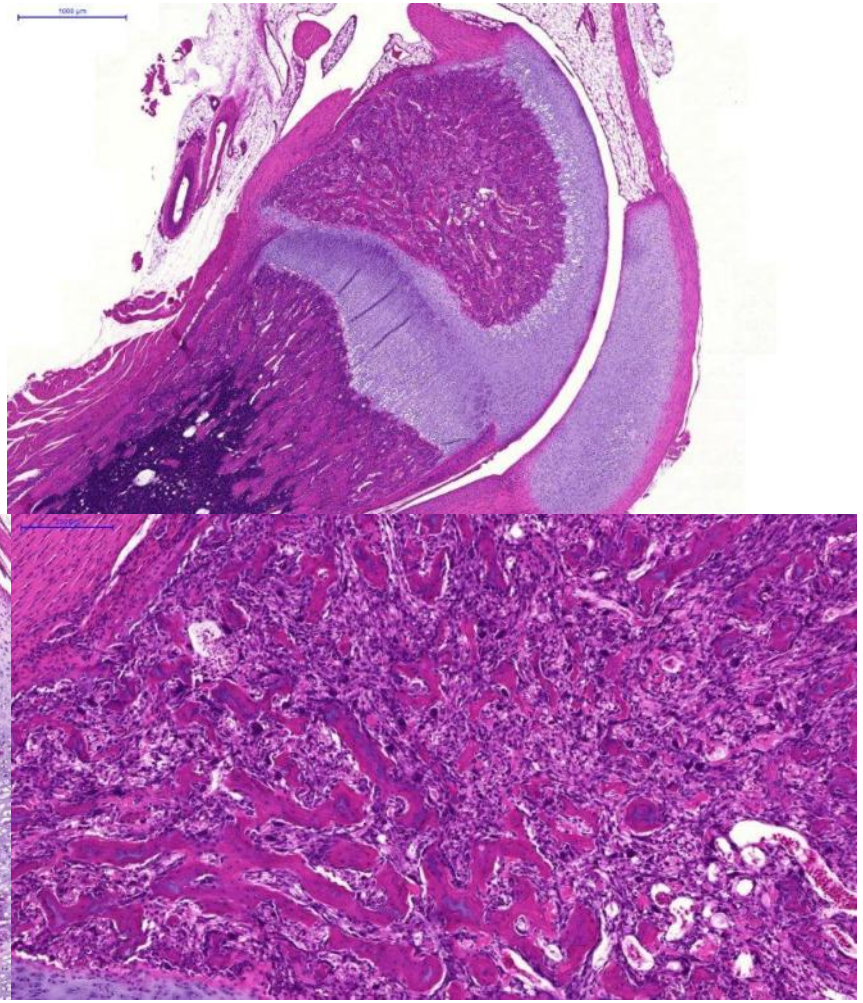
Reference ID: 3337602

BAY 63-2521, T0081434, P7712, Pilot Study in Juvenile Rats (2w gavage), Doses: 0-3-10-30 mg/kg Body Weight

Rat no.21, female, control (0 mg/kg), normal femur



Rat no. 36, female, HD (30 mg/kg), femur with epi-/metaphyseal hyperostosis grade 5



Reference ID: 3337602

19 pages of Appendix C have been withheld in full immediately following this page as a duplicate copy of the “Clinical Consultation, Division of Bone, Reproductive and Urologic Products (DBRUP) Track Correspondence No. 425” dated 4/26/2013 which can be found in this review.

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

/s/

PRESTON M DUNNMON
07/08/2013
Medical NDA 204819 Review

Clinical Consultation

Division of Bone, Reproductive and Urologic Products (DBRUP)
Track Correspondence No. 425

From:	Eric Andreasen PhD, Pharmacology/Toxicology DBRUP Stephen Voss MD, Medical Officer DBRUP
Through:	Theresa Kehoe MD, Medical Team Leader DBRUP Hylton Joffe MD, MMSc, Division Director DBRUP
To:	Edward Fromm, R.Ph., RAC, RPM, DCRP Preston Dunnmon, MD, Medical Officer DCRP
Subject:	**Riociguat tablets (NDA 204819) potential bone toxicity**

Date consult received: March 20, 3013

Overview:
NDA 204819 was submitted on 2/8/13 to DCRP for riociguat (BAY63-2521, Bayer HealthCare AG), a first-in-class soluble guanylate cyclase (sGC) agonist that has been developed for treatment of Group I and Group IV pulmonary hypertension. Mechanistic considerations and rodent toxicology studies suggest a potential for adverse effects of this drug on bone, particularly in pediatric patients. Clinical trials in adults provide limited data relevant to bone metabolism, which the Applicant believes showed no clinically meaningful changes or difference from placebo.

The reviewing division, DCRP, is consulting DBRUP regarding the bone safety issue, as follows:
Understanding that clinical trials in PAH are much shorter than would be needed to assess clinical outcomes for fracture risk, we would like your assistance in understanding the potential risk of this drug dosed chronically in :

- *Pediatric patients – a waiver for Group I PAH may not be justified in the absence of medical risk specific to pediatric patients,*
- *Postmenopausal women, and*
- *Male patients.*

Accordingly, our questions are as follows:
1. Is there evidence of a bone effect in the animal or pivotal trial data that is concerning for human bone health or fractures in adolescents? In postmenopausal women? In men?
2. If a pediatric waiver would otherwise not be granted for PAH, would the animal bone findings described in the above noted pre-clinical studies justify a waiver/ contraindication for this drug in adolescent humans with PAH?
3. If this drug is approved, is there justification for a PMC/R for a BMD study in post-menopausal women? In adolescents? Other bone assessments in adolescents?

4. If the answer to question 2 above is yes, would the answer to the question 2 above be different based on the outcomes of such a PMC/R trial in women/adolescents, or some other sequential imaging study in adolescents?

Background:
This application pertains to two variants of pulmonary hypertension (PH). Pulmonary arterial hypertension (PAH = WHO Group 1) and chronic thromboembolic pulmonary hypertension (CTEPH = WHO Group 4) are rare, progressive and debilitating diseases. PAH encompasses numerous etiologic categories including idiopathic, heritable and associated with connective tissue disease. CTEPH typically presents initially as a symptomatic pulmonary embolus, but is believed to share with PAH a similar pathophysiology of pulmonary microvascular remodeling with increased pulmonary vascular resistance. Prior to the availability of specific therapies, these progressive conditions generally carried a poor prognosis, with high mortality related to right heart failure; a large PAH registry in 1984 showed a mean survival of 2.8 years.

Beginning in 1995, numerous vasodilator drugs have been approved for treatment of PAH in adults:

- endothelin receptor antagonists (ERAs): bosentan (Tracleer), ambrisentan (Letairis)
- phosphodiesterase-5 (PDE-5) inhibitors: sildenafil (Revatio), tadalafil (Adcirca)
- prostacyclin/ analogs (PCAs) for injection or inhalation: epoprostenol (Flolan, Veletri), treprostinil (Tyvaso, Remodulin), iloprost (Ventavis)
- nitric oxide by inhalation (Inomax, approved for PH in neonates)

These therapies, which are frequently used in combinations, improve hemodynamics, symptoms and functional status of patients with PAH; it is unclear to what extent they have improved survival. For CTEPH, the treatment of choice is pulmonary endarterectomy, but many CTEPH patients are not candidates for surgery, or have persistent symptoms and disease progression postoperatively, and are treated off-label with drugs approved for PAH. Other therapies used frequently in these diseases include anticoagulants, diuretics, digoxin, calcium channel blockers and oxygen.

Pulmonary hypertension affects all age groups. Among pediatric patients, the median age at diagnosis in a large registry was 7.0 y/o; 17% were diagnosed between 3-24 months of age, 31% between 2-6 y/o, 25% between 7-11 y/o, and 28% between 12-18 y/o.[1] Children with the disease have similar clinical features as adults and may also manifest growth delay: in the UK registry, mean height and weight Z-scores were -0.71 and -0.66 respectively and did not change with treatment, and lower Z-scores correlated with lower survival.[2] The most common pediatric causes of progressive pulmonary hypertension are idiopathic PAH (35-60% of registry cases), and PAH associated with congenital heart disease (CHD) (24-52%). In the UK registry, the 1-year, 3-year and 5-year survival for children with idiopathic PAH was 89%, 84% and 75%; in the U.S. registry, 5-year survival was also 75% (most patients in these registries were enrolled after 2001, the time period during which time most of the above drugs were approved). Children with PAH are generally treated with the above drugs, none of which are approved for pediatric use in the U.S.

It is not known whether patients with PAH or CTEPH have an increased risk for bone disorders. Patients with advanced stages of other respiratory diseases such as COPD or cystic fibrosis are at increased risk of osteoporotic fractures, due in part to low physical activity and debilitation. A published study reported DXA data on 32 PAH patients (24 idiopathic, 8 scleroderma-associated; WHO/NYHA functional class III (n=22) or IV (n=10); being considered for lung transplantation. There were 27 women and 5 men with a mean age of 49 y/o. Upon testing, a high proportion of the patients (22/32 = 69%) had low bone mass i.e. a T-score (lumbar spine, total hip and/or femoral neck) ≤ -1.0. Trends toward greater risk for low bone mass were seen in the expected subgroups of postmenopausal status, prior history of smoking or glucocorticoid use, and also in those with lower functional status (WHO/NYHA FC IV, lower 6 minute walking distance).[3]

Riociguat is a direct stimulator of the soluble guanylate cyclase (sGC) enzyme. This is similar to the action of endothelial-derived NO (nitric oxide), which binds to sGC and activates the conversion of GTP to cGMP, which in turn regulates vascular tone, proliferation, fibrosis, platelet aggregation and inflammation. This results in a decline in pulmonary (and systemic) vascular resistance and, potentially, an interruption of the progressive vascular remodeling process.

In addition to vascular effects, NO is involved in bone homeostasis[4,5]; other sGS agonists such as riociguat could have a similar effect. Paracrine and/or autocrine regulation of NO production in bone (osteoblasts, osteoclasts, immune cells, and endothelial cells) is involved in bone development, homeostasis, and response to trauma. In vitro and in vivo data suggest that low to medium levels of NO, produced endogenously by endothelial nitric oxide synthase, may increase bone growth by promoting osteoblast proliferation and activity while decreasing bone resorption by osteoclasts. However, in response to cytokine stimulation, inducible nitric oxide synthase produces high levels of NO which may promote bone loss by suppressing osteoblasts while stimulating osteoclasts.

Repression of endogenous NO production or supplemental NO therapy in animals and humans may affect bone morphology. Bone growth is abnormal and inhibited in mice that are genetically deficient in NO synthase, or normal rodents exposed to NO synthase inhibitors. Endogenous NO can be supplemented by therapeutic use of organic nitrates such as nitroglycerin (NTG), which act as NO donors. In animals, organic nitrates have prevented bone loss in several osteoporosis models.

In humans, several published studies have evaluated effects of organic nitrates on bone, including bone mineral density (BMD).[6] A 12-week RCT enrolling 144 healthy postmenopausal women (hip T-score 0 to -2.5) found decreases in urine NTX (a marker of bone resorption) of 36-45% and increases in serum BSAP (a marker of bone formation) of 16-23% with isosorbide mononitrate 5 or 20 mg/d relative to placebo.[7] In another study, 243 postmenopausal women without osteoporosis (mean age 61 y/o, mean T-scores -0.6 to -1.1) were randomized to NTG ointment 15 mg/d or placebo. After 2 years the NTG group showed, relative to placebo, BMD mean increases of 6.7%, 6.2% and 7.0% at spine, total hip, and femoral neck respectively; decrease in urine NTX

(54%); increase in BSAP (35%); and by pQCT of radius and tibia, increases in volumetric trabecular BMD (9-12%), cortical thickness (14-25%), periosteal circumference (3-7%), polar section modulus (10-11%) and polar moment of inertia (7-15%) (nominal p-values for each of the above parameters were <0.001).[8] The authors of this study observed that the apparent uncoupling of indices of bone formation/resorption with NTG is unusual, and that the increases in cortical size and circumference of radius and tibia were also unusual and suggest that the drug stimulates periosteal apposition of bone. However, another randomized study involving 186 postmenopausal women (age 40-65 y/o, lumbar T-score 0 to -2.5) showed no effect of nitroglycerin 22.5 mg/d after 3 years, with BMD declines at all skeletal sites very similar to placebo.[9] The reason for the marked discrepancy in BMD findings between these two placebo-controlled trials is unclear. No trials of organic nitrates have been adequately powered to evaluate fractures; observational studies have suggested that these drugs may have a protective effect.

Riociguat/ bone - nonclinical evidence

Exposure comparisons between animals and humans below are based on the AUC levels in animals multiplied by a factor of 3 or 4 (AUCfu animals / AUCfu human) to account for differences in the percentage of free drug in plasma (fraction unbound, fu) in animals and humans.

Although riociguat caused thickening of the growth plate in adult mice and rats and slight to moderate hyperostosis in rats, this is not expected in adult humans at the maximum recommended dose (MRHD) of 2.5 mg TID. The bone findings in adult mice are not considered relevant to clinical use because they occurred at a lethal dose (~30x MRHD) and adverse bone finding were not reported after a lifetime of exposure at ~8-12 times the MRHD. Similarly, bone findings in adult rats are not predicted to occur in humans because findings in mature rats occurred at large multiples of the MRHD (generally ≥ ~20x MRDH, with a few animals with slight findings at exposures ~5-8 times the MRHD); findings were usually coincident with exaggerated pharmacology that is expected to preclude dosing people at this level. No bone effects were observed in mature rats after a lifetime of exposure at ~13-20 times the MRHD.

Bone findings were not reported in mature dogs dosed for up to one year at exposures ~7 times the MRHD.

Due to the mechanism of action, riociguat would be expected to affect fetal skeletal development. However, in animals placental transfer and lactational exposures were low, and clear adverse bone findings in fetal rats and rabbits and neonatal rats were not observed or were questionably related to treatment.

The most adverse bone findings observed with riociguat were seen in a preliminary study in infant-juvenile rats that were dosed orally for 2 weeks (6 to 20 days postnatal) at ≥ ~11 times the MRDH. Developmentally, this time period is equivalent to the third trimester, neonatal, and infant periods in humans. In these infant-juvenile rats, minimal to severe hyperostosis and bone remodeling were observed dose dependently at exposures ~11-24 times the MRHD in the diaphyseal and metaphyseal bone, along with minimal to massive

trabecular thickening in the epiphysis at ≥ ~11 times the MRHD. Additionally, reduction in marrow cells was observed dose dependently in the epiphysis at ≥ ~4 times the MRHD. These findings were not confirmed in the definitive follow-up study with dosing for 14 weeks, also beginning at 6 days post partum. However, the doses in the longer definitive study were below those which caused the severe adverse finding in the preliminary study. The exposure in the definitive study declined from 8 to ~1-2 times the MRHD from the first to last dose, likely due to continued development of the liver and improved capacity to metabolize and excrete the drug. It is unclear if the findings in the preliminary study would progress if dosing continued beyond 20 days after birth, how severe findings would be with continued dosing, and if adverse effects on bone are reversible following cessation of treatment.

Riociguat/ bone - clinical evidence
Phase 1 PD crossover study (13790):
This study was designed to explore the effects of riociguat 2.5 mg PO TID x 14 days, relative to placebo, on bone- and mineral-related parameters in 16 healthy young adult males (mean age 30 y/o). Subjects were on controlled diets and were given daily supplements of 1000 mg calcium and 1000 IU vitamin D during each of the two treatment phases (riociguat or placebo, referred to as Rio or Plac in this review).

The bone resorption markers CTX and NTX were measured in urine (24-hr collection), and CTX in serum, at multiple points. The 24-hr urinary excretion of CTX after 14 days of treatment with Rio exceeded that with Plac (estimates corrected for baseline) by a mean of 8.3% ($p<0.0001$). The investigators postulated that the increase in excretion of CTX, which is filtered at the glomerulus, was related to the vasodilator effect of Rio, which increases GFR significantly (by 7.5% in this study). Following normalization for CrCl, the increase in urinary CTX with Rio was 2.1% relative to Plac and no longer significant. Serum CTX increased by a mean of 1.8% relative to Plac, a non-significant difference. Urinary NTX increased with both treatments; the change with Rio was 2.3% greater than with Plac ($p=0.48$), but after normalization for CrCl, was 9.2% below Plac ($p=0.12$). The study report concludes that there was no evidence of an effect of Rio on bone resorption.

Bone formation markers P1NP, BSAP and osteocalcin all decreased significantly (-5.5%, -12%, -8.3% respectively) with Rio compared to Plac. The report notes that serum/plasma concentrations of many analytes are reduced because of an apparent increase in vascular volume with Rio, e.g. RBC, Hct, and Hgb declined by 3-4% and albumin by 1.1% within 2-3 days of treatment in this study. However, normalization of P1NP, BSAP and osteocalcin for albumin did not eliminate the statistical significance of declines in these parameters with Rio.

Serum PTH increased by a mean of 0.19 pmol/L (1.8 pg/mL) or 5.3% with Rio relative to Plac ($p=0.0167$). Because of a difference in the respective baselines (Rio 3.45 vs. Plac 3.80 pmol/L), the report concludes that a relationship of Rio treatment to PTH was unlikely.

With Rio, there was an increase in urinary excretion of calcium, by ~40 mg/day or 22% relative to Plac. After normalization for CrCl there remained a significant 13% increase in urine calcium relative to Plac. Concurrently, serum calcium declined by a mean 0.12 mg/dL with Rio relative to Plac (or 0.06 mg/dL after albumin-correction). Serum phosphorus also declined by 3.8%.

Vitamin D and magnesium levels were not in the protocol and were assayed post hoc. Levels of 1, 25-OH-vitamin D showed stable or increasing trends with Rio (possibly due to small increase in PTH), and stable or declining trends with Plac, with most individual values within normal range. Magnesium levels were all WNL, with slight increasing trends during either treatment.

Reviewer comment: *In summary, this phase 1 trial demonstrated that riociguat was associated with a moderate increase in calcium excretion, possibly related to changes in renal function; this may have contributed to a small decline in serum calcium and a small increase in serum PTH. The latter, in turn may have led to small increases in 1, 25 (OH) vitamin D. This study also showed increases in bone resorption markers with riociguat, however these were small and confounded by change in GFR therefore probably insignificant clinically. Decreases in bone formation markers were statistically significant, but also of small magnitude. These findings in young, healthy males may not necessarily apply to the PAH population.*

Phase 2/3 studies

All riociguat clinical studies were limited to adults (≥18 y/o). The following were the phase 2 studies:

- 2 PAH/CTEPH studies, 12 wk with long term extensions (12166 and 15096, total N=96)
- 2 studies, 16 wk with long term extension, in PH related to left ventricular dysfunction (14308 and 14549, total N=202)
- 1 study in PH related to COPD (12915, single doses, N=33)
- 1 study in PH related to interstitial lung disease (12916, 12 wk, N=22)

Most of the data relevant to bone was collected in the two pivotal phase 3 RCT efficacy/safety trials, each with open label extensions that are still ongoing (see table below). One study (11348 or CHEST-1) enrolled CTEPH patients who were not surgical candidates or had persistent/recurrent postop symptoms; the other (12934 or PATENT-1) enrolled PAH patients.

Riociguat phase 3 trials

Study	Population	Design	Riociguat regimen	Comparator	# riociguat subjects	# placebo subjects
11348 (CHEST-1)	CTEPH	Rand 2:1 Double blind, 16 weeks	Individual titration 0.5-2.5 mg tid	Placebo	173 rand/ treated, 160 completed	88 rand/ treated, 83 completed
11349 (CHEST-2)	CTEPH	Open label extension,	Individual titration	N/A	194 enrolled,	N/A

		up to 33 months	0.5-2.5 mg tid		182 ongoing	
12934 (PATENT-1)	PAH	Rand 4:2:1* Double blind, 12 weeks	Titration 0.5-2.5 mg tid*	Placebo	317 rand/ treated, 294 completed*	126 rand/ treated, 111 completed
12935 (PATENT-2)	PAH	Open label extension, up to 35 months	Individual titration 0.5-2.5 mg tid	N/A	363 enrolled, 308 ongoing	N/A
* In study 12934, 2 different riociguat dose titration methods were used: subjects were randomized 4:2:1 to 0.5-2.5 mg tid by individual dose titration: placebo: 0.5-1.5 mg tid by capped dose titration						

The design and endpoints of these phase 3 CTEPH and PAH studies were similar. Because symptomatic hypotension is a frequent adverse effect, Rio doses were titrated individually, every 2 weeks as tolerated, from 1 mg TID → 1.5 mg TID → 2.0 mg TID→ 2.5 mg TID; or if necessary the dose could be lowered to 0.5 mg TID. In the PAH study only, a subset (20%) of Rio subjects were titrated only up to 1.5 mg TID and dose was capped at that level. Plac subjects underwent sham titration.

Phase 3 study populations:
These studies enrolled PAH/CTEPH adult patients with a baseline 6-minute walking distance (6MWD) between 150-450 meters, and hemodynamic parameters of mean pulmonary artery pressure > 25 mmHg and elevated pulmonary vascular resistance.

In study 12934, most subjects had a diagnosis of idiopathic PAH (61%) or PAH due to connective tissue disease (26%). About half were therapy-naïve; the remainder were pre-treated with ERAs (43%) or PCAs (6%), and remained on this background treatment during the study. PDE inhibitors and nitrates, which can exacerbate hypotension, were not allowed. Subjects were predominantly female (80%), with a mean age of 50 y/o (range 18-80 y/o); 52-60% were white and 30-55% were Asian. About 40% were WHO/NYHA functional class II and 50% were class III.

In study 11348, subjects had either inoperable CTEPH (72%) or post-operative recurrent/ persisting CTEPH (28%). Subjects were mostly female (67%), with a mean age of 59 y/o (range 19-80 y/o); 70% were white and 20% were Asian. About 30% were WHO/NYHA functional class II and 65% were class III. None of the approved PAH drugs were allowed as concomitant therapy.

Phase 3 results:
The double blind treatment phases of studies 11348 and 12934 (16 and 12 weeks respectively) were completed by 93% and 91% of subjects. The primary efficacy endpoint, change in 6MWD, was achieved in both studies. Secondary endpoints also were favorable to Rio over Plac, including pulmonary vascular resistance measured by R heart catheterization; serum NT-pro-BNP, a marker for severity of heart failure; and WHO/NYHA functional class.

Bone/mineral related endpoints

Serum CTX and osteopontin were measured in some phase 2/3 studies; however PTH, NTX, P1NP, BSAP and osteocalcin were not. There were no evaluations of bone density, nor any other radiographic imaging of bones in any of the studies.

Serum CTX, the bone resorption marker, was measured in most subjects in the double blind phases of 3 studies:

- 11348 (CTEPH Phase 3): N=261
- 12934 (PAH Phase 3): N=443
- 15096 (PAH Phase 2b): N=18

For these 3 studies combined (Pool-3 database), mean baseline serum CTX was 0.383 µg/L in the Rio group and 0.392 µg/L in the Plac group (see Table 3.2.4.1/41 from ISS, next page). At week 2, there was a slight decline from baseline in both treatment groups. At week 12 the PAH patients showed small mean increases from baseline in both Rio and Plac groups of 0.032 and 0.042 µg/L; and at week 16, CTEPH patients showed similar small increases of 0.055 (Rio) and 0.016 µg/L (Plac) respectively.

The ISS reported these CTX data for various subgroups. For females (N=368), Rio and Plac showed similar moderate increases in CTX from baseline at weeks 12 and 16. Postmenopausal status is recorded in the medical history for only 40 women, out of 623 in the Pool-3 dataset, i.e. for most women this status was not recorded. For males (N=136) there was a small difference between treatment groups: with Rio there were mean CTX increases of 0.024 and 0.060 µg/L (weeks 12 and 16); with Plac, mean decreases of 0.024 and 0.053 µg/L. There was little apparent difference in Rio/Plac between subgroups of age (< 65 y/o, ≥ 65 y/o), BMI, smoking status and history of osteoporosis. (There was a trend in baseline CTX by body mass: mean of 0.421 vs. 0.359 µg/L for subjects with BMI < 25 vs. ≥ 25 respectively.)

Osteopontin: This secreted phosphoprotein is a major non-collagen component of bone matrix whose function includes the attachment of osteoclasts to bone. Osteopontin is also expressed in cardiovascular tissues; elevated plasma levels are found in PAH patients and correlate with worse prognosis. Serum osteopontin levels were measured in phase 2/3 studies, apparently both as an exploratory signal for increased bone turnover and as a prognostic marker for PAH.

For the CTEPH/PAH studies combined (Pool-2 database), baseline serum osteopontin was 443.8 ng/mL in the Rio group and 442.8 ng/mL in the Plac group (see Table 2.3.4/42 from ISS, below). As with CTX, there were slight declines at week 2 in both groups. At week 12 there were slight increases from baseline in both Rio and Plac groups of 17.5 and 46.1 ng/mL (PAH patients); and at week 16, increases of 123.5 and 49.4 ng/mL respectively (CTEPH patients). There were no trends indicating a Rio/Plac difference within subgroups of gender, age, BMI, smoking status or history of osteoporosis.

Serum CTX

Table 3.2.4.1 / 41: Summary statistics for body liquids values and changes from baseline by visit - Type I Collagen C-Telopeptides (ug/L) - all BAY 63-2521 studies (safety analysis set)

Analysis Value

Treatment group	Analysis Visit	Value at Visit						Change from Baseline					
		n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
BAY 63-2521 (main) (N=754)	BASELINE	354	0.383	0.223	0.03	0.340	1.32						
	WEEK 1	25	0.247	0.207	0.06	0.190	0.93	0	.	.	.	.	.
	WEEK 2-3	352	0.369	0.215	0.04	0.330	1.39	311	-0.011	0.170	-0.59	-0.012	1.30
	WEEK 4-5	3	0.500	0.070	0.42	0.530	0.55	3	0.117	0.228	-0.13	0.160	0.32
	WEEK 10-11	2	0.385	0.163	0.27	0.385	0.50	1	-0.210	.	-0.21	-0.210	-0.21
	WEEK 12-13	223	0.403	0.238	0.05	0.360	1.27	185	0.032	0.163	-0.39	0.020	0.66
	WEEK 14-15	10	0.511	0.383	0.20	0.390	1.43	9	0.090	0.355	-0.31	0.000	0.98
	WEEK 16-17	114	0.449	0.255	0.07	0.390	1.28	95	0.055	0.181	-0.31	0.030	0.66
	WEEK 18-19	7	0.681	0.581	0.18	0.430	1.85	6	0.388	0.704	-0.24	0.220	1.76
Placebo (main) (N=289)	BASELINE	150	0.392	0.246	0.03	0.350	1.95						
	WEEK 1	20	0.303	0.143	0.09	0.300	0.59	0	.	.	.	.	.
	WEEK 2-3	148	0.345	0.184	0.02	0.330	0.95	124	-0.020	0.133	-0.42	-0.030	0.49
	WEEK 4-5	1	0.070	.	0.07	0.070	0.07	1	0.010	.	0.01	0.010	0.01
	WEEK 10-11	1	0.130	.	0.13	0.130	0.13	1	0.050	.	0.05	0.050	0.05
	WEEK 12-13	88	0.400	0.213	0.04	0.370	1.10	76	0.042	0.193	-0.86	0.040	0.50
	WEEK 14-15	3	0.247	0.116	0.14	0.230	0.37	2	-0.090	0.042	-0.12	-0.090	-0.06
	WEEK 16-17	59	0.404	0.212	0.04	0.380	1.05	44	0.016	0.195	-0.45	0.015	0.69
	WEEK 18-19	2	0.265	0.219	0.11	0.265	0.42	2	0.090	0.057	0.05	0.090	0.13
BAY 63-2521 (LTE, main) (N=475)	BASELINE	290	0.376	0.220	0.03	0.340	1.32						
BAY 63-2521 (LTE, placebo in main) (N=167)	BASELINE	115	0.366	0.213	0.03	0.310	1.09						
	WEEK 12-13	1	0.220	.	0.22	0.220	0.22	0	.	.	.	.	.

Source: ISS PH-37089, p. 17900/18744

Osteopontin

Table 2.3.4 / 42: Summary statistics for body liquids values and changes from baseline by visit - Osteopontin (ng/mL) - all multi-dose studies in PAH or CTEPH (safety analysis set)

Analysis Value

Treatment group	Analysis Visit	Value at Visit						Change from Baseline					
		n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
BAY 63-2521 (main) (N=577)	BASELINE	353	443.848	292.233	14.00	391.300	2127.00						
	WEEK 1	30	621.997	508.228	99.00	450.500	2478.00	0	.	.	.	.	.
	WEEK 2-3	202	453.812	324.182	17.00	397.500	1861.00	160	-40.996	191.823	-688.00	-14.850	609.60
	WEEK 10-11	2	746.500	218.496	592.00	746.500	901.00	1	10.000	.	10.00	10.000	10.00
	WEEK 12-13	218	434.266	308.821	9.00	361.000	1772.00	175	17.502	197.186	-839.00	12.000	703.00
	WEEK 14-15	10	522.350	279.850	233.00	481.400	1261.00	9	4.144	159.166	-201.00	-10.000	344.80
	WEEK 16-17	125	569.254	492.593	32.85	431.100	4075.00	101	123.473	369.379	-1006.00	59.200	1406.80
	WEEK 18-19	7	561.329	367.687	136.80	552.500	1135.00	6	8.403	137.070	-215.40	40.750	173.50
Placebo (main) (N=220)	BASELINE	150	442.837	290.739	9.00	381.700	1841.00						
	WEEK 1	23	475.248	296.875	179.00	379.600	1555.00	0	.	.	.	.	.
	WEEK 2-3	71	418.435	233.866	22.00	375.000	1264.00	56	-26.761	255.675	-1463.40	4.500	560.00
	WEEK 10-11	1	371.000	.	371.00	371.000	371.00	0	.	.	.	.	.
	WEEK 12-13	87	438.138	303.293	22.00	380.000	1497.00	74	46.089	204.160	-471.00	22.000	607.00
	WEEK 14-15	3	226.533	136.842	81.00	246.000	352.60	2	108.650	87.186	47.00	108.650	170.30
	WEEK 16-17	60	547.333	316.550	39.55	441.550	1360.00	42	49.429	392.907	-1029.70	53.450	1105.51
	WEEK 18-19	1	1348.000	.	1348.00	1348.000	1348.00	1	967.000	.	967.00	967.000	967.00
BAY 63-2521 (LTE, main) (N=475)	BASELINE	285	434.128	293.028	14.00	379.200	2127.00						
BAY 63-2521 (LTE, placebo in main) (N=167)	BASELINE	118	397.791	241.404	9.00	347.100	1248.00						

Source: ISS PH-37089, p. 11898/18744

Serum calcium
The table on the following page shows changes in mean serum calcium for the initial (usually double blind) part of all phase 2/3 studies combined (Pool-3; note that this was added by protocol amendments, and most subjects did not have calcium measured). As shown there was minimal deviation (less than ~0.1 mg/dL) from baseline in the Rio-treated patient group mean, and a small increase averaging ~0.1 mg/dL in the Plac-treated group mean. In the long term extensions up to 5 years (not shown), there were slight declines from baseline in mean calcium at most timepoints, with mean changes ranging from +0.160 to -0.363 mg/dL.

Reviewer comment: *Serum calcium was not corrected for serum albumin, which (unlike in the phase 1 study discussed above) increased in Rio subjects by a mean of 0.13 g/dL at week 12-13 and by 0.09 g/dL at week 16-17 (and similar extent at most LTE timepoints), while in Plac subjects there were minimal changes in albumin of +0.04 and -0.01 g/dL respectively. Many more subjects had albumin measured than calcium, therefore these albumin changes cannot be used directly to correct the calcium changes in the table below; however it is likely that corrected serum calcium declined with Rio by ~0.1 mg/dL relative to baseline, and perhaps more relative to placebo.*

There was an imbalance in the number of subjects with at least one serum calcium below LLN: 14/89 (15.7%) with Rio vs. 0/30 (0%) with Plac for the pooled phase 3 studies. The lowest serum calcium was 6.73 mg/dL at day 28 of Rio therapy in a 50 y/o female (#12934-10002-4008) who was apparently asymptomatic and had all other values ≥ 8.5 mg/dL including days 15 and 43. Except for this one value, no serum calcium levels were below 7.62 mg/dL in any phase 2/3 subject, including long term extension studies.

Urine calcium was not evaluated in any of the phase 2/3 studies.

Serum phosphorus
In the DB period of pooled phase 3 studies, mean serum phosphorus was 3.57 and 3.54 mg/dL in Rio and Plac groups at baseline. There were very minimal changes from baseline in either group. Levels below LLN occurred in 7/90 (8.9%) of Rio subjects and 2/38 (5.3%) of Plac subjects. The lowest levels in Rio subjects were 1.77 mg/dL in the DB period and 1.89 mg/dL in the long term extension (normal range ~2.7-4.5 mg/dL).

Serum 1,25-OH-vitamin D
Mean levels at baseline in the pooled phase 2/3 studies were 0.135 and 0.158 nmol/L respectively in Rio and Plac groups. In the Rio group, there were slight inconsistent changes from baseline. In the Plac group, there were declines up to 28% in mean level, however this was in only 10 subjects.

Serum 25-OH-vitamin D was not evaluated in any of the phase 2/3 studies.

Serum calcium

Table 3.2.4.1 / 4: Summary statistics for chemistry values and changes from baseline by visit - Calcium (mg/dL) in Serum - all BAY 63-2521 studies (safety analysis set)

Analysis Value

Treatment group	Analysis Visit	Value at Visit						Change from Baseline					
		n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
BAY 63-2521 (main) (N=754)	PRE-TREATMENT	73	9.322	0.989	4.85	9.460	10.46						
	BASELINE	189	9.180	0.735	4.89	9.218	10.74						
	WEEK 1	38	9.021	1.278	4.82	9.320	10.58	26	0.163	0.506	-0.60	0.030	1.47
	WEEK 2-3	182	9.248	0.490	7.82	9.218	11.22	153	-0.002	0.455	-1.60	-0.040	2.00
	WEEK 4-5	182	9.231	0.505	6.73	9.200	10.74	150	0.044	0.462	-1.12	0.040	1.44
	WEEK 6-7	191	9.225	0.445	7.82	9.218	10.54	148	0.005	0.410	-0.80	-0.040	1.20
	WEEK 8-9	187	9.226	0.447	8.10	9.218	10.50	145	-0.005	0.442	-1.16	0.000	1.12
	WEEK 10-11	55	9.224	0.474	7.86	9.218	10.10	51	0.001	0.571	-1.60	0.000	1.16
	WEEK 12-13	174	9.228	0.459	7.62	9.220	10.42	140	-0.049	0.468	-1.60	-0.080	1.36
	WEEK 14-15	15	9.306	0.483	8.46	9.459	10.02	13	-0.125	0.559	-1.04	-0.160	0.80
	WEEK 16-17	46	9.379	0.440	8.62	9.320	10.54	33	-0.012	0.419	-0.80	-0.040	1.12
	WEEK 18-19	3	8.807	0.345	8.50	8.740	9.18	3	0.160	0.040	0.12	0.160	0.20
Placebo (main) (N=289)	BASELINE	40	9.119	0.542	7.94	9.300	9.94						
	WEEK 1	3	9.287	0.409	8.82	9.460	9.58	0	.	.	.	.	.
	WEEK 2-3	50	9.252	0.398	8.34	9.210	9.98	39	0.132	0.437	-0.68	0.120	1.20
	WEEK 4-5	47	9.259	0.448	7.90	9.300	9.98	33	0.176	0.377	-0.64	0.200	0.92
	WEEK 6-7	42	9.350	0.506	8.30	9.340	10.62	31	0.137	0.514	-1.20	0.080	1.12
	WEEK 8-9	49	9.274	0.494	7.94	9.300	10.30	36	0.153	0.399	-0.68	0.090	0.80
	WEEK 10-11	1	8.820	.	8.82	8.820	8.82	1	0.520	.	0.52	0.520	0.52
	WEEK 12-13	45	9.232	0.430	8.14	9.300	10.18	34	0.116	0.421	-0.60	0.060	1.44
	WEEK 14-15	2	8.480	0.198	8.34	8.480	8.62	2	0.120	0.283	-0.08	0.120	0.32
	WEEK 16-17	24	9.228	0.455	8.18	9.300	10.22	20	0.127	0.331	-0.40	0.110	0.90
	WEEK 18-19	1	9.220	.	9.22	9.220	9.22	1	-0.400	.	-0.40	-0.400	-0.40

Source: ISS PH-37089, p. 17737/18744

Clinical fractures were reported for the POOL-3 safety database, which incorporates all phase 2 and 3 studies. Most fractures occurred in the 4 ongoing open label, long-term extension (LTE) PAH/CTEPH studies (see table below). As of the cutoff dates for NDA submission, mean LTE phase exposure durations in the phase 3 extension studies 11349 and 12935 were just over 1 year, and in the phase 2 extension study 12166 was just over 3 years (up to 4.5 years).

Long-term extensions of phase 2/3 studies

Study	Population	Length of main phase (wk)	# subjects in LTE phase	Mean LTE phase exposure at time of interim report (mos)
11349	CTEPH	16	194	12.9
12935	PAH	12	363	14.6
12166	CTEPH, PAH	12	68	36.5
15096	PAH	12	17	5.8
Total			642	14.7 (median)
Sources: ISS Table 3-4 p. 120; Table 7-2 p. 362; and Table 7-12 p. 376 (of 429)				

The demographics of this long-term group are as follows: mean age 53.5 y/o (range 18-80); 72% female; 70% white, 25% Asian; BMI 26.3 kg/m^2; 6.5% current smokers; 57% Europe, 28% Asia/Pacific, 16% N/S America (5% U.S.).

The table below includes all fractures in the double blind and OL extension phases of the phase 2/3 studies. As noted, there were few fractures during the double blind phases, which were ≤ 16 weeks in duration. According to the dataset, the median duration of Rio therapy prior to the fracture was 211 days. Excluding the patients with hand, foot or facial bone fractures, 82% of patients with fractures were female and median age was 66 y/o (range 28-77 y/o).

Pooled Phase 2/3 studies: Subject incidence of fractures (all rand/tx)

	Riociguat Double blind N=754	Placebo Double blind N=289	Rio/Rio Extension N=475	Plac/Rio Extension N=167
Any fracture AE	5 (0.7%)	1 (0.3%)	15 (3.2%)	6 (3.6%)
Upper limb	0	0	2	0
Humerus	0	0	0	2
Radius	0	0	2	0
Ulna	0	0	1	0
Femur	0	0	1	1
Tibia	0	0	1	0
Ankle	2	0	0	0
Vertebra	1	0	3	1
Rib	1	1	1	0
Foot	0	0	3	1
Hand	0	0	1	1
Facial bones	0	0	1	0

Osteoporotic fx*	0	0	1	0
Pathological fx**	1	0	0	0
* "vertebral fracture secondary to osteoporosis" ** "spontaneous fracture of L rib" Adapted from Table 3/2, ISS, p. 92/397, report #PH-37087 (Pool 3) M5.3.5.3				

The incidence rates of all fracture AEs per 100 person-years were calculated by the Applicant to be 3.59 and 1.36 for Rio and Plac double blind phases respectively, and 3.10 for the pooled long term extension phases (ISS PH-37087, Table 3/2, p. 92/397). The rate for fractures of spine, upper and lower limbs (excluding hand/foot) combined in the extension studies was 2.03 per 100 person-years.

Reviewer comment: *For comparison, reference data in a healthy population[10] indicated that for the 50-54 y/o age group (about the mean for the above studies), the incidence of all fractures was 2.2 (women) and 1.8 (men) per 100 person years. For fractures of spine, upper and lower limbs (excl. hand/foot) combined, the expected rates for 50-54 y/o were 1.2 (women) and 0.7 (men) per 100 person years. The riociguat studies had many older subjects and the relationship of age to fracture incidence is not linear, also the number of fractures was small, therefore it cannot be concluded that the fracture rate was higher than expected. Even if there were a higher fracture risk with riociguat in the PAH/CTEPH population, this would not be unexpected given the debilitating effects of the disease.*

Riociguat/bone – summary of clinical evidence

There is limited evidence from clinical studies pertaining to the effects of riociguat on bone. In a phase 1 study of healthy subjects and pooled phase 2/3 data from CTEPH/PAH adult patients, there were trends of lower serum calcium with riociguat relative to placebo, but change from baseline was small, generally ≤ ~0.1 mg/dL. This may be due to an increase in urine calcium, which was documented in the phase 1 healthy-volunteer study but was not measured in the CTEPH/PAH studies. PTH increased slightly in the Phase 1 study, perhaps related to slightly lower serum calcium, and was also not evaluated in phase 2/3. It is unlikely that these small changes reflect any clinically significant change in bone metabolism. There was no evidence of clinically relevant trends in serum phosphorus, magnesium or 1,25-OH-vitamin D.

A small, 14-day study of riociguat in healthy young volunteers showed possible increase in a marker of bone resorption (CTX) and decreases in markers of bone formation (P1NP, BSAP and osteocalcin). These changes however were small in magnitude, possibly confounded by changes in renal function, and inconsistent with the nonclinical findings, which suggest that riociguat increases rather than decreases bone mass. Phase 2/3 studies in PAH/CTEPH patients also showed small increases in CTX from baseline, but these were similar between riociguat and placebo. Collectively these bone marker data reduce the probability that the drug has a major effect (increase or decrease) on bone mass, but other measures e.g. DXA would be more informative.

The riociguat clinical fracture data are not adequate to reach any conclusions about possible effects of the drug on fracture risk, particularly with a lack of placebo control for

any exposure beyond 16 weeks, and the uncertain effects of the underlying disease (or other treatments) on fracture risk.

Discussion

Literature suggests that sGC agonists, including nitric oxide and organic nitrates, can promote anabolic effects on bone. This would be expected to be manifested most obviously in rapidly growing bone as seen during development or fracture healing. Findings in rodents treated with riociguat suggest that hyperostosis and increased thickness of the growth plate are unlikely to occur in adults at the maximum recommended dose (MRHD = 2.5 mg TID). Assessment of the potential for adverse skeletal development effects from fetal and lactational exposure in animals were limited by low placental and lactational transfer. Although adverse effects in infants and adolescents are not anticipated at the MRHD, minimal to severe hyperostosis is predicted in infants at exposures between 8 to 11 times the adult MRHD. Effects of riociguat treatment on fracture healing have not been assessed in animals or humans but adverse effects are not anticipated at the MRHD in adults.

There are limited clinical data relevant to the potential effects of riociguat on bone metabolism. In the riociguat studies, markers of bone turnover and mineral metabolism showed minor changes of probably minimal significance clinically; no evaluations of bone density or bone imaging were done; fracture data were limited and showed no apparent safety signal. There are no clinical data to date involving children and adolescents. The most potentially vulnerable groups based on the nonclinical evidence are neonates and very young children. The nonclinical data equivalent to adolescents did not show evidence of significant bone findings but the dose equivalent was much lower. Therefore, the risk to the adolescent population treated with riociguat is unclear.

If riociguat-treated children or adolescents were to experience the potential hyperostotic changes in bones and growth plates, it is difficult to anticipate how this might manifest clinically. Heritable disorders resulting in increased bone mass may provide some insight of worst-case scenarios, as in the following examples.

Osteopetrosis (“marble bone disease”) is caused by one of a large number of possible defects in osteoclast function. Most cases are related to genetically mediated defects in the capacity of osteoclasts to generate an acid environment for bone resorption. The impairment of resorption results in generalized increase in trabecular and cortical bone density and thickness throughout the skeleton which is usually readily apparent radiographically. In children, modeling defects may produce an “Erlenmeyer flask” deformity with broadening of metaphyses. Alternating sclerotic and lucent bands may be seen in pelvic bones or near the ends of long bones. In the most severe form with onset in infancy, massive bony overgrowth may lead to obliteration of the marrow cavity with extramedullary hematopoiesis, hepatosplenomegaly and cytopenias. Thickening of the base of the skull may result in cranial nerve entrapment with hearing or visual disturbance, oculomotor or facial palsy. Other clinical manifestations may include short stature, a large head, delayed eruption of teeth, osteomyelitis of the jaw, a propensity to

fracture due to poor bone quality, hypocalcemia and elevated serum levels of PTH, acid phosphatase and/or BB-CK.

Pyknodysostosis, due to deficiency of an osteoclast lysosomal enzyme, also causes generalized osteosclerosis and manifests with characteristic deformities including very short stature and limbs, dysmorphic face, large cranium with persistent patency of the anterior fontanel, and lack of pneumatization of the paranasal sinuses.

Sclerosteosis and Van Buchem disease result from loss-of-function mutations involving sclerostin, an inhibitor of osteoblasts. This results in endosteal thickening of diaphyseal cortex with narrowing of the medullary canal, generalized bony overgrowth and sclerosis involving especially the skull and facial bones. Clinical manifestations, usually with childhood onset, may include jaw enlargement and facial disfigurement; cranial nerve entrapment with facial palsy, deafness or optic atrophy; raised intracranial pressure due to diminished cranial capacity with headaches and risk of brainstem herniation; and sometimes tall stature or syndactyly.

Progressive diaphyseal dysplasia, due to *TGF-β1* mutations, typically presents with hyperostosis of the diaphysis of long bones, especially tibia and femur, as well as muscle wasting and weakness and bone pain. Skull involvement with large head, prominent forehead, hydrocephalus or cranial nerve palsies may occur.

Most of these disorders of increased bone mass are genetically based, but some cases are acquired. For example, a published report documented a case of a 12 y/o boy who developed osteopetrosis, including pathognomonic X-ray and biopsy features, following 2.75 years of treatment with high doses of pamidronate, a potent IV bisphosphonate.[11] Excessive vitamin A supplementation, and synthetic retinoids used to treat skin disorders, are associated with a spectrum of skeletal toxicity with long term use. The most common manifestations of retinoid toxicity are DISH-like hyperostoses in the spine and calcification of tendons and ligaments, especially in older adults. Children are probably at lower risk for the hyperostotic changes, but may manifest slender long bones with thin diaphysis, reduced bone density, or premature closure of the epiphysis. Periodic radiographic skeletal surveys are recommended to screen for hyperostosis in patients on long-term retinoid therapy.

DCRP Questions/ DBRUP responses

1. Is there evidence of a bone effect in the animal or pivotal trial data that is concerning for human bone health or fractures in adolescents? In postmenopausal women? In men?

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.

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.

We do not have major concerns about skeletal effects of riociguat in adults, as the studies in rodents provide an adequate safety margin. Adults with PAH/CTEPH tend to have low bone mass, but there is no compelling nonclinical or clinical evidence suggesting that riociguat would increase their fracture risk. The mature skeleton of adults probably makes them less susceptible, compared to children/adolescents, to developing severe hypertrophy of bone. If hyperostosis were to occur in adults, based on the experience with retinoid bone toxicity, it may present in a manner similar to the syndrome of diffuse idiopathic skeletal hyperostosis (DISH), with ossification of ligament and tendon insertions, especially the anterior spinal ligament.

2. If a pediatric waiver would otherwise not be granted for PAH, would the animal bone findings described in the above noted pre-clinical studies justify a waiver/ contraindication for this drug in adolescent humans with PAH?

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.

3. If this drug is approved, is there justification for a PMC/R for a BMD study in post-menopausal women? In adolescents? Other bone assessments in adolescents?

A DXA study in adults could be considered, but DXA is only useful in evaluating bone loss (and not gain), and evidence does not suggest that riociguat will cause a decline in BMD.. However, it may be appropriate to investigate the possible development of hyperostosis with long term use. In particular, lateral spine X-rays (perhaps even PA/lateral chest X-rays) could readily detect calcification of the anterior spinal ligament in patients in the ongoing extension studies, at least in those with any complaints of back pain or stiffness. However, such calcifications are common in the general population of older adults so such findings may be difficult to interpret without a control group or baseline imaging.

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.

If the answer to question 2 above is yes, would the answer to the question 2 above be different based on the outcomes of such a PMC/R trial in women/adolescents, or some other sequential imaging study in adolescents?

Please see answer to Q2.

References

1. Berger RMF et al, Clinical features of paediatric pulmonary hypertension: a registry study, *Lancet* (2012), 379: pp. 537-546

2. Moledina S et al, Childhood idiopathic pulmonary arterial hypertension: a national cohort study, *Heart* (2010), 96: pp. 1401-1406

3. Malik N et al, Prevalence and significance of decreased bone density in pulmonary arterial hypertension, *South. Med. J.* (2012), 105: pp. 344-349

4. Saura M, Tarin C, Zaragoza C. Recent insights into the implication of nitric oxide in osteoblast differentiation and proliferation during bone development. *Scientific World J.* (2010); 10: pp. 624-632.

5. Wimalawansa SJ. Nitric oxide and bone. *Ann N Y Acad Sci* (2010); 1192: pp. 391-403.

6. Jamal SA, Reid LS, Hamilton CJ. The effects of organic nitrates on osteoporosis: a systematic review. Osteoporos Int (2013); 24(3):763-770.

7. Jamal S et al, Isosorbide mononitrate increases bone formation and decreases bone resorption in postmenopausal women: a randomized trial, *J. Bone Miner. Res.* (2004), 19: pp. 1512-1517

8. Jamal S et al, Effect of nitroglycerin ointment on bone density and strength in postmenopausal women, a randomized trial, *JAMA* (2011), 305: pp. 800-807

9. Wimalawansa SJ et al, Transdermal nitroglycerin therapy may not prevent early postmenopausal bone loss, *J.Clin. Endocrinol Metab.* (2009), 94: pp. 3356-3364

10. Melton LJ et al, Fracture incidence in Olmsted County, Minnesota: Comparison of urban with rural rates and changes in urban rates over time, *Osteoporos. Int.* (1999), 9: pp. 29-37

11. Whyte MP et al, Bisphosphonate-induced osteopetrosis, *N. Engl. J. Med.* (2003), 349: pp. 457-463

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

/s/

STEPHEN R VOSS
04/26/2013

THERESA E KEHOE
04/26/2013

HYLTON V JOFFE
04/26/2013