CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204819Orig1s000

OFFICE DIRECTOR MEMO

Office of Drug Evaluation-I: Decisional Memo

Date	October 8, 2013
From	Ellis F. Unger, M.D., Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
NDA #	204819
Applicant Name	Bayer Healthcare Pharmaceuticals Inc.
Date of Submission	February 8, 2013
PDUFA Goal Date	October 8, 2013
Proprietary Name/ Established (USAN) Name	Adempas (riociguat)
Dosage Forms/ Strengths	0.5, 1, 1.5, 2, and 2.5 mg Tablets
Indication	1) Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (WHO Group 4) after surgical treatment or when inoperable, to improve exercise capacity and WHO functional class. 2) Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.
Action:	*Approval*

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Edward J. Fromm, Daniel Brum
Medical Officer Clinical Review	Preston Dunnmon
Clinical Pharmacology Review	Divya Menon-Andersen, Dhananjay D. Marathe, Hobart Rogers, Ping Zhao
Statistical Review	John P. Lawrence
Pharmacology Toxicology	Paul Brown, Elizabeth Hausner, Thomas Papoian
Executive Cancer Assessment Committee	Abby Jacobs, Paul Brown, Kara Davis Bruno
Chemistry Manufacturing and Controls	Pei-I Chu, Ramesh K. Sood, Monica D. Cooper.
ONDQA Biopharmaceutics Review	Kareen Riviere
Method Validation	Michael L. Trehy, John F. Kauffman
Statistical Review- Carcinogenicity Study	Mohammad Atiar Rahman
Office of Scientific Investigation	Sharon K. Gershon
Division of Medication Error Prevention and Analysis	Kimberly A. DeFronzo
Pediatric Review Staff	Amy M. Taylor, Lynne P. Yao
Division of Medical Policy Programs	Sharon Mills
Risk Evaluation and Mitigation Strategy (REMS) Review	Somya Dunn
Office of Prescription Drug Promotion	Emily Baker
QT/IRT	Qianyu Dang, Joanne Zhang, Satjit S. Brar, Monica Fiszman, Kevin M. Krudys.
SEALD Labeling Team	Sharon R. Mills, Emily Baker
Maternal Health	Tammie Brent-Howard
Bone Safety	Eric Andreasen, Stephen Voss, Teresa Kehoe, Hylton Joffe
Epidemiology Reviewer	Jie J. Li
Cross-Discipline Team Leader	Norman Stockbridge
Director, Division of Cardiovascular and Renal Products	Norman Stockbridge

Introduction:

Riociguat is a new molecular entity, a vasodilator with a novel mechanism of action. An agonist of soluble guanylate cyclase (sGC), riociguat purportedly exerts its effects through a dual mode of action: 1) sensitizing sGC to endogenous nitric oxide (NO) by stabilizing NO-sGC binding; and 2) directly stimulating sGC via a binding site independent of NO.

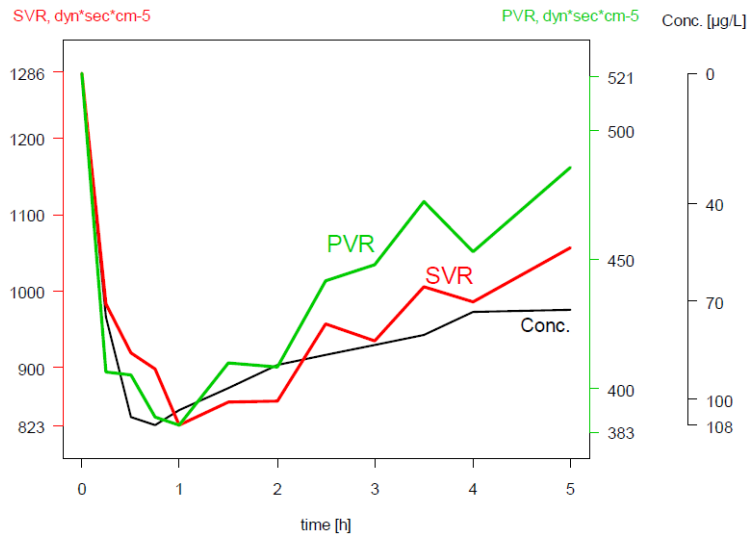
When NO binds to sGC, the enzyme catalyzes synthesis of the signaling molecule cyclic guanosine monophosphate (cGMP). Intracellular cGMP plays an important role in regulating vascular tone, cellular proliferation, fibrosis, and inflammation.

PAH is associated with endothelial dysfunction, impaired NO synthesis, and insufficient stimulation of the NO-sGC-cGMP pathway.

Riociguat is not selective for the pulmonary vasculature, and causes dose-dependent decreases in both pulmonary and systemic vascular resistance. The drug also causes an increase in heart rate in dose-dependent fashion; presumably this is at least partially compensatory in nature.

Figure 1 shows the mean pulmonary and systemic vascular resistances along with plasma concentration, over time (N=10). The similarity in relative changes in systemic (red) and pulmonary vascular resistance (green) as a function of riociguat concentration is striking.

Figure 1: Effects of Riociguat on Systemic and Pulmonary Vascular Resistance



The applicant is seeking 2 indications: 1) Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class, and to delay clinical worsening; and 2) persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment or when inoperable, to improve exercise capacity and WHO functional class.

There are a number of therapies available for PAH, but this will be the first approval of a drug for the treatment of CTEPH.

Approval will be based on one randomized, double-blind, placebo-controlled study in each of the 2 indications (CTEPH and PAH).

Regulatory Action:

The review team agrees that approval for both indications is the appropriate regulatory action, and this is consistent with the recommendations of the Cardiovascular and Renal Drugs Advisory Committee (convened August 6, 2013).

Other Therapies for PAH

Currently, several prostacyclin analogues (PCA), phosphodiesterase type 5 inhibitors, and endothelin receptor antagonists (ERA) are approved for the treatment of PAH. There are no approved treatments for CTEPH.

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	1.25 – 100 ng/kg/min (little experience > 40 ng/kg/min
Treprostinol – SQ	
Treprostinol – inhaled	3 - 9 breaths (18 mcg – 54 mcg) QID

Regulatory History:

The regulatory history has been well summarized by Dr. Dunnmon; this largely represents his summation:

Date	Regulatory Activity
February 22, 2007	pre-IND meeting
May 29, 2008	End of Phase 2 meeting
October 9, 2009	Type C meeting: PAH associated with left ventricular systolic disease
December 14, 2011	advice/information request letter
July 26, 2012	advice/information request letter
November 1, 2012	pre-NDA meeting preliminary comments
December 19, 2012	teleconference to follow up with ONDQA and DMEPA on items from the Division's pre-NDA preliminary comments

The principal efficacy trials for CTEPH and PAH were CHEST-1 and PATENT-1, respectively. The following advice was rendered by the agency during the May 29, 2008, end-of-phase-2 meeting regarding the sponsor's proposed design of their 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.

In the discussion that ensued, the Division explained that the sponsor's proposal to perform a forced titration study would not sufficiently characterize the drug's dose-response. The Division suggested that if titration is necessary for patient safety, the trial should include multiple treatment arms to avoid confounding the effects of dose and time. The sponsor proposed to study a dose range, 1.0 to 2.5 mg, based on changes in hemodynamic effects in earlier studies. The Division noted that the difference between doses was small, and recommended study of a broader range of doses.

The Division also emphasized the critical importance of blinding to the interpretation of the study results. (A patient in an open-label study achieved a documented 100-meter improvement in 6MWD, a result the Division deemed as questionable.)

The Division also suggested inclusion of an active control arm.

The Division's advice on these design elements was only partially incorporated into the clinical development program. Active therapy was confined to a single trial arm in CHEST-1, wherein the 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 in size and underpowered for some of the secondary endpoints. The applicant did not elect to extend the dose range beyond 1.0 to 2.5 mg tid.

Indications Sought:

Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adult patients with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) WHO group 4, after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class.

Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adult patients with pulmonary hypertension (PAH) WHO group 1, to improve exercise capacity, WHO functional class and to delay clinical worsening.

Chemistry Manufacturing and Controls (CMC):

There were no Chemistry, Manufacturing and Control issues that would preclude approval (refer to the review by Dr. Cooper, July 5, 2013). There are no issues with regard to drug substance or drug product, and approval with a 36-month expiry is recommended. Establishment inspections are complete and satisfactory.

Pharmacology/Toxicology:

Riociguat was demonstrated to be negative in the standard battery of genotoxicity assays, the rodent 2-year carcinogenicity studies, and in special studies of phototoxicity and immunotoxicity.

In rats, the femur showed disorganization of the epiphyseal bone and marrow cavity with thickening of the trabecular bone and resultant decreases in the marrow cavity and marrow cells. Activated (undefined) osteoblasts and multinucleated osteoclasts were observed.

Hyperostosis and remodeling were noted in the metaphyseal and diaphyseal bone in both sexes. The no observed adverse effect level (NOAEL) was not identified in the study.

Findings were less well described in several other studies. The applicant and reviewer believe these findings are related to the cGMP mechanism of action. Whether they have relevance to humans (particularly adults) is unknown. Nothing of concern was observed in the clinical studies, although these were adult patients. Consultants in the Division of Bone, Reproductive and Urologic Products concluded that the signal is of no concern in adults, and that the concerns there may be in very young children should not preclude pediatric studies if otherwise indicated. I agree with the concept that the pediatric development program should gather data in adolescents, and then work progressively into younger populations, if possible.

Riociguat caused some fetal loss (two species) that Dr. Hausner believes is likely related to vasodilatory effects. There was also an increase in ventricular septal defects at the highest dose tested in one species.

Because of the risk of embryo-fetal toxicity, the label will carry a box warning, and there will be a REMS for all female patients with Elements to Assure Safe Use and restricted distribution.

Clinical Pharmacology/ Biopharmaceutics:

Both the parent and M1, the principal metabolite, were appropriately identified and measured in plasma (and urine, where applicable) to permit adequate assessment of riociguat's pharmacokinetics. Most of the activity resides with the parent molecule. Absolute bioavailability is high (0.96) and peak levels are obtained ~5 hours after administration in the PAH population. Riociguat follows dose-proportional pharmacokinetics.

Elimination is largely by CYP metabolism, mainly CYP1A1, which is up-regulated in smokers. Exposure was markedly reduced in the 6% of subjects who smoked; however, the treatment effect (change in 6MWD) in smokers appeared similar to that of non-smokers (despite reduced exposure).

Renal impairment doubles exposure, and labeling will say to use care when titrating the dose in patients with creatinine clearance 15 – 80 mL/min; use in patients with creatinine clearance <15 mL/min is not recommended.

A 70% increase in the total systemic exposure (AUC) was observed in subjects with impaired hepatic function (C-P Class: A & B). M1 pharmacokinetics were not affected. These effects were not deemed important enough to warrant dose adjustment.

The solubility of riociguat decreases with increasing gastric pH, and concomitant administration of antacids (Maalox) roughly halves exposure. The label will direct patients to separate administration of riociguat and antacids by at least 1 hour. Total and peak systemic exposure (AUC and Cmax) of riociguat were reduced by ~25% and 35%, respectively, when administered with omeprazole. No dose adjustments are recommended.

There are important pharmacodynamic interactions with nitric oxide, delivered in various forms, and this will be handled through a contraindication in labeling.

The exposure-response relationship for efficacy (area under the time-concentration curve, AUC, versus 6MWD) was described as "flat" for exposures corresponding to the 1.5 mg and 2.5 mg

doses. The lowest quartile of 1.5 mg dose arm showed lower efficacy than the other quantiles, but efficacy in the lowest quantiles of the 2.5 mg stable dose (which matched the exposure in lowest quantile of 1.5 mg stable dose) was similar to that of the higher exposure quantiles. Together, these data were deemed to confirm a "flat" exposure-response relationship. I would note, however, that the variability around 6MWD in each quantile was fairly large, such that no firm conclusions can be drawn regarding exposure-response. And although I agree that most of the treatment effect on 6MWD is observed at a dose of 1.5 mg, the data seem inadequate to decide whether or not 2.5 mg is more effective. Presumably, the higher dose could be more effective in at least some patients, and assessment of blood pressure provides a means upon which to base dose titration.

Site Inspections:

DSI inspected 4 clinical sites of the phase 3 program and the applicant. The data from these sites were deemed to be reliable.

Evidence of Effectiveness:

The phase 3 development program included two studies: one in PAH WHO Group I (PATENT-1) and another in CTEPH (CHEST-1). PATENT-1 and CHEST-1 were placebo-controlled studies consisting of an 8-week titration phase followed by maintenance phases of 4 and 8 weeks, respectively. The 1° endpoint in both trials was change from baseline in six minute walk distance (6MWD) at end-of-study. Riociguat showed a statistically significant increase in change from baseline 6MWD compared to placebo in both studies. The to-be marketed formulation was used in both Phase 3 trials.

PAH – PATENT-1:

PATENT-1 was a double-blind, parallel design study wherein 405 subjects with PAH were randomized 4:1:2 to riociguat titrated between 1 and 2.5 mg TID (based on trough systolic blood pressure), riociguat titrated between 1 and 1.5 mg TID (exploratory arm), and placebo. The etiology of PAH was idiopathic in ~60%, associated with connective tissue disease (~25%) and congenital heart disease (~7%), and the remainder were attributed to miscellaneous causes. Nearly all patients were functional class 2-3 at baseline. About 43% were on an endothelin receptor antagonist; about 9% were on a prostacyclin. Approximately 50% of patients were taking diuretics, and 25% were on calcium antagonists. About 20% of patients were using supplemental oxygen.

Approximately 6% of patients were from the US. Approximately 50% were from the EU, ~35% were from Asia/Pacific/China, and ~10% were from South America.

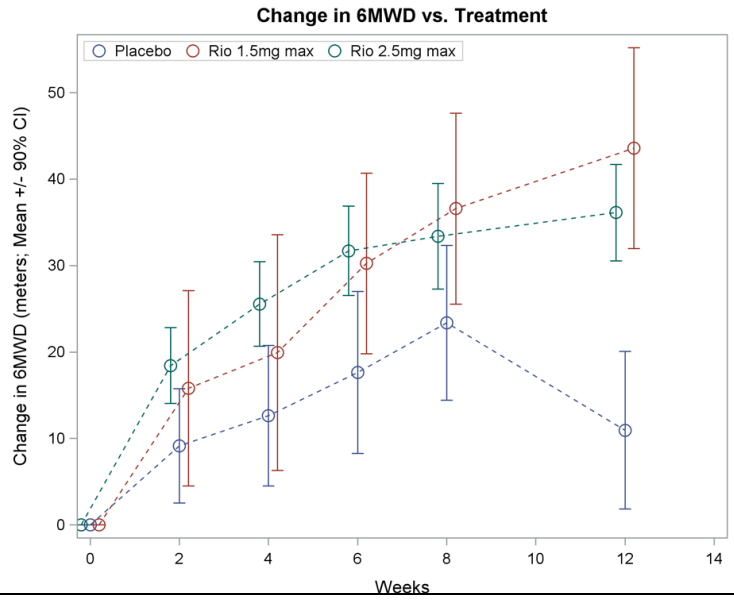
As noted above, the primary endpoint was distance walked in 6 minutes (6MWD) at Week 12, computed as change from baseline. The efficacy analyses were planned on a modified ITT population, which in this case was essentially the same as the "as-treated" population. Missing values were imputed as worst case for subjects who died or experienced clinical worsening, but last observation carried forward (LOCF) was used for withdrawals with no termination visit data. Approximately ~10% of subjects had imputed values.

The results for the 1- to 2.5-mg dose group were statistically significant ($p<0.0001$). The mean effect was ~30 m, and as noted by Dr. Stockbridge, the mean effect seems to be representative of the overall results, as indicated by the cumulative distribution curve for 6MWD. The

treatment effect is largely manifested by the first visit (Week 2). Relative to placebo, there is little change thereafter, until Week 12, when the 6MWD of the placebo group decreases.

The FDA statistician's un-adjusted reanalysis of the raw primary efficacy datasets from PATENT-1 is shown in Figure 2 (6MWD, mean ± 90% CI).

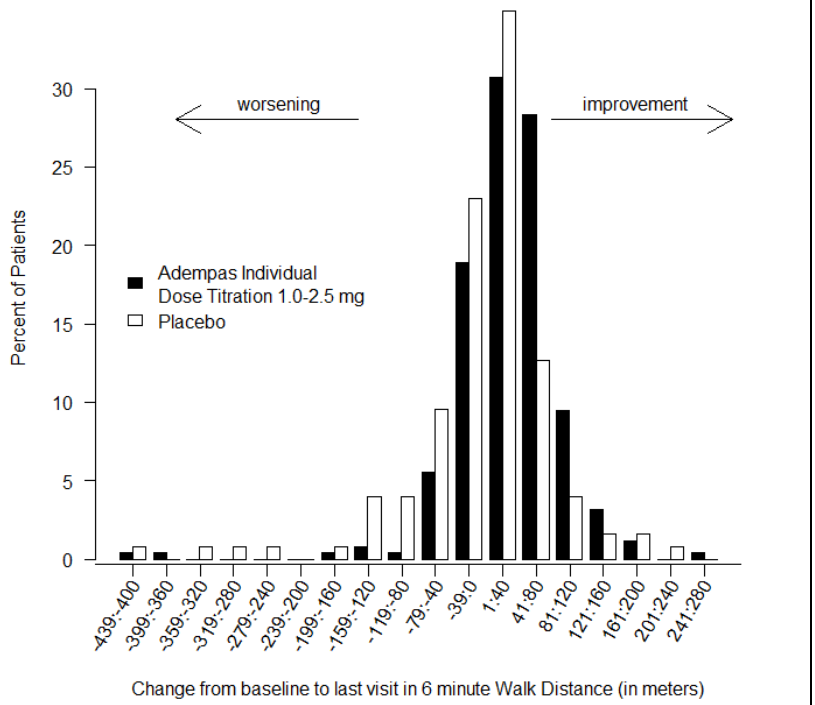
Figure 2: Change in 6MWD vs. Time – Primary Study Endpoint



Multiple sensitivity analyses were carried out and were consistent with the 1° analysis. There were no individual sites, countries, or regions that, if removed, would have annulled the statistical significance of the treatment effect.

The results were consistent across subgroups by pre-treatment drug category, PAH etiology, baseline 6MWD category, and demographics. Of note, however, for the 19% of patients from North and South America, the treatment effect on 6MWD was essentially zero. (Given that only 6% of patients were from the US, this is difficult to interpret.)

Figure 3: Change from Baseline in 6MWD – PATENT-1



Another way to represent the change in 6MWD is through the use of a histogram (Figure 3), where a shift to the right represents improvement.

There is no long-term withdrawal study, but during the 24-month open-label extension study, the 6MWD improves in the former placebo group, and the 6MWD in the group originally assigned to riociguat remains stable.

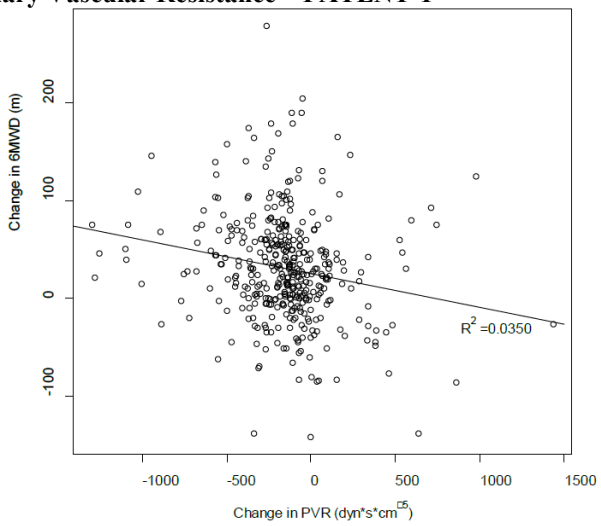
These findings are consistent with efficacy, but difficult to interpret in light of the open-label design.

Statistical significance was achieved on the hierarchy of 2° endpoints of pulmonary vascular resistance, NT-proBNP, WHO functional class, time to clinical worsening, and the Borg CR 10 dyspnea scale.

A number of hemodynamic parameters were assessed at the time of right heart catheterization (pre- and post-treatment), and show statistically significant improvement. These seem appropriate for section 12 of labeling.

Notably, however, there was no correlation whatsoever between changes in 6MWD and PVR (R^2 = 0.035; Figure 4).

Figure 4: No Correlation between Changes in 6MWD and Pulmonary Vascular Resistance – PATENT-1



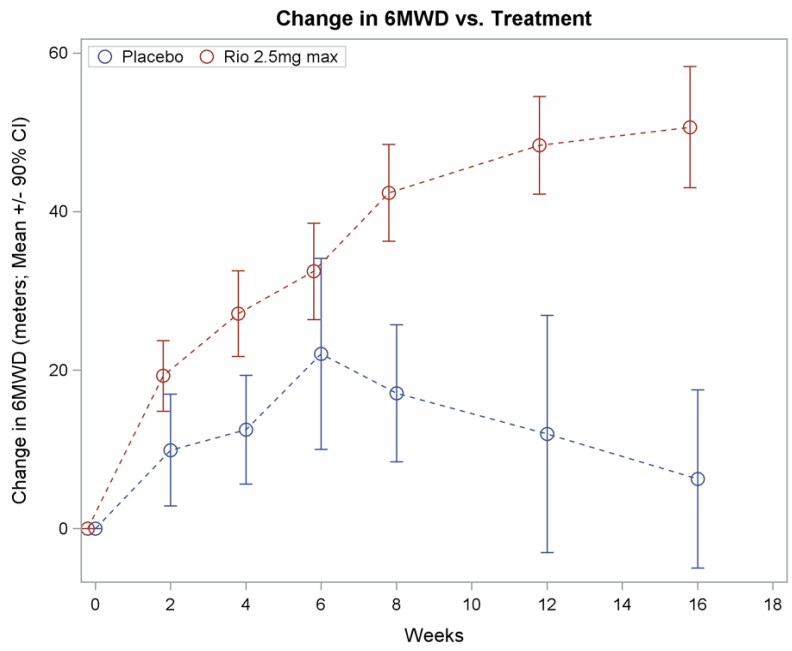
The clinical review and the clinical pharmacology review both questioned and addressed the small incremental benefit of increasing the riociguat dose above 1.5 mg TID. As Dr. Stockbridge points out, the arm where the dose was capped at 1.5 mg has only one-fourth the size of the 1- to 2.5-mg arm, which limits conclusions that can be drawn. He suggests that labeling should say that the incremental benefit of dose increases beyond 1.5 mg tid is not clear, but not openly discourage up-titration, because pharmacokinetic variability is high, even without considering factors such as concomitant medications and smoking that would decrease exposure. Some individuals (e.g., smokers) may need a dose of 2.5 mg or more to get the average response expected from 1.5 mg. Thus, labeling will point out that doses higher than 2.5 mg may be needed/acceptable, and that patients should discuss this with their doctors.

CTEPH – CHEST-1

CHEST-1 was a double-blind, parallel design study in which 262 subjects with CTEPH were randomized 2:1 to riociguat titrated 1 to 2.5 mg or to placebo and followed for 16 weeks. Most subjects were WHO functional class 2 (30%) or 3 (63%) at baseline. About 10% were using vasodilators, mostly prostacyclins, off-label. Some 20% were using supplemental oxygen. The primary end point was 6MWD. The primary analysis was ITT, and again, this population was virtually the same as the as-treated population. Imputation was necessary for ~7% of subjects who failed to complete 16 weeks.

The data were not normally distributed, so that a Wilcoxon rank-sum test was used as the test of hypothesis (per the statistical plan). The mean between-group treatment difference was ~40 m ($p<0.0001$), and again the distribution of responses was fairly uniformly shifted. The difference between riociguat and placebo was observed at the first visit (Week 2), sustained through Week 6, and increased thereafter. The FDA statistician's un-adjusted reanalysis of the raw primary efficacy datasets from CHEST-1 is shown in Figure 5 (6MWD, mean ± 90% CI) Multiple sensitivity analyses were consistent with the 1° analysis.

Figure 5: Change in 6MWD vs. Time – Primary Study Endpoint

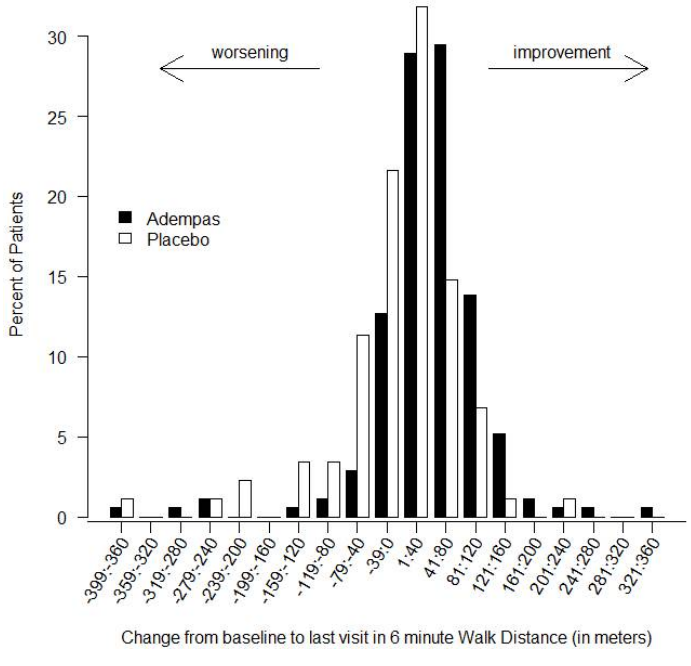


The results are consistent across subgroups by demographics, disease severity, and geographical region.

Statistically significant effects were found on ordered secondary end points: PVR, NTproBNP, and WHO functional class. Borg would have been statistically significant, but could not be tested because time to clinical worsening failed (and was higher than Borg in the hierarchy of 2° endpoints).

The study results are represented in a histogram in Figure 6. As in CHEST-I, improvements in PVR and a number of other hemodynamic parameters were evident, but there was no correlation between improvement in PVR and improvement in 6MWD (scatter plot not shown).

Figure 6: Change from Baseline in 6MWD – CHEST-1



Discussion:

The applicant submitted two independent adequate and well-controlled studies for two indications. Importantly, however, the indications are pathophysiologically related, and the studies are, therefore, mutually supportive for their respective indications. Both were multinational studies that demonstrated reasonable effect sizes (30 to 45 m is not atypical for drugs for PAH; there are no data for studies of drugs for CTEPH). Both were statistically persuasive, robust to sensitivity analyses, and consistent across important subgroups (to the extent they were represented). Salutary effects were demonstrable in both studies across multiple secondary endpoints, and such findings were supportive of the certainty of the primary endpoint. The 6MWD endpoint is susceptible to bias, i.e., a subject's performance is motivationally dependent, and performance be influenced by the attitude of the tester. The hemodynamic endpoints, on the other hand, can be influenced to only a small extent by the observer, and not at all by the patient.

It is disappointing and perhaps perplexing, however, that neither study showed even a trend in terms of a correlation between reduction in PVR and improvement in 6MWD. Such a correlation, had it been observed, would have gone far to support efficacy, or at least convinced us that we understand the relation between hemodynamics and exercise capacity.

Based on these two studies, it can be said that the assessment of PVR, assessed through invasive right heart monitoring in a cardiac catheterization laboratory, i.e., the "gold standard," was not "reasonably likely" to predict efficacy as assessed by the 6MWD. Fortunately, for these studies, the results are positive for both endpoints.

There were some on the review team (clinical pharmacology and clinical) who were keen to provide a modified dosing algorithm, to start at 0.5 mg TID, increasing the dose no sooner than every two weeks by 0.5 mg TID, to a maximum dose of 1.5 mg TID. The clinical pharmacology review team suggested a maximum dose of 3 mg tid to accommodate smokers (who would metabolize the drug more rapidly).

The rationale for a lower starting dose was that riociguat is not selective for the pulmonary vasculature, such that it will cause clinically important hypotension in some individuals. The patient population for CTEPH differs considerably from the PAH patient population, in that it is older with more cardiovascular co-morbidities. Patients with CTEPH are therefore more hemodynamically fragile, and more susceptible to the blood pressure lowering effects of riociguat. In discussions, Dr. Dunnmon was particularly concerned about the potential for riociguat to precipitate untoward cardiovascular events in patients with underlying coronary artery and cerebrovascular disease.

I would point out that a starting dose of 1 mg was used in both clinical trials, such that starting at 0.5 mg would be untested. Nevertheless, given that the dose is to be up-titrated, it would not be irrational to start at 0.5 mg tid; the question is whether or not it is necessary. I would note that alpha adrenergic blockers are used in thousands of men for symptoms of prostatism in a similar (older) patient population. They cause postural hypotension and carry warnings for such, but they are not known to precipitate important cardiovascular events.

Having considered the arguments, the review team has decided to encourage a starting dose of 0.5 mg tid for patients who seem susceptible to hypotension, presumably those who have a low blood pressure at baseline.

The other concern has been that the minimal incremental benefit in increasing the dose higher than 1.5 mg tid. But given the considerable pharmacokinetic variability, the heterogeneity of effect at a given serum concentration, and the fact that the drug is titrated, there may be some individuals who derive greater symptom benefit from doses in excess of 1.5 mg tid. Moreover, there are drug-drug interactions (and interactions in smokers through CYP1A1 induction) that could necessitate higher doses.

Safety:

Between the phase 3 studies and their long-term extensions, there is over 1200 patient-years of exposure to riociguat; mean exposure is ~600 days. In the PATENT-1 and CHEST-1 together, there were 490 subjects who received riociguat and 214 who received placebo, and these subjects constitute the safety base for labeling.

The majority of riociguat's side effects can be attributed to its mode of action as a smooth muscle relaxant, especially its gastrointestinal effects (nausea, vomiting, diarrhea, constipation, and dysphagia).

There were five deaths in these studies on riociguat, the overall rate being lower on study drug than on placebo. Common adverse reactions include headache, dizziness, and dyspepsia in both studies, all consistent with other vasodilators.

The applicant's QT study ruled out an effect as large as 20 ms.

Pregnancy:

The applicant and the review team concluded that the teratogenicity findings are a sufficient basis for a REMS for all females, regardless of age. All female patients who use riociguat must enroll in the program. The REMS includes a Medication Guide and Elements to Assure Safe Use—prescriber certification, pharmacy certification, and documentation of safe use conditions. Comments on this plan were conveyed to the applicant.

Hypotension:

Hypotension is dose-related. The shift in blood pressure is clear, developing as plasma levels rise. About 10% of subjects in the phase 3 blinded trials reported hypotension as an adverse event, and hypotension tended to be dose-related. Approximately 45% of all hypotension (i.e., systolic blood pressure <90 mmHg) encountered in the PAH phase 3 trial occurred on Days 1 and 2, when patients were taking 1 mg tid, and mostly in patients with baseline systolic blood pressure $\leq$110 mmHg. This provided a rationale for recommending an initial starting dose of 0.5 mg, at least in patients with lower baseline blood pressure. Counter to this, syncope was reported more commonly on placebo in both phase 3 studies, which was viewed by some as reassuring. In any case, riociguat's labeling will carry a warning for vasodilatory action.

Bleeding:

There were excess serious adverse events for hemorrhage in the riociguat groups in both CHEST-1 (6 [3.5%] in the riociguat group vs. 0 in the placebo group) and PATENT-1 (4 [1.6%] in the riociguat group, vs. 0 in the placebo group). Patients with CTEPH are generally anticoagulated, such that their baseline risk of hemorrhage is higher than a population with PAH.

In my inspection of the adverse event dataset (adae.xpt), I found 12 serious adverse events related to bleeding, and all were in the riociguat group: 5 hemoptysis, 2 vaginal hemorrhage, 2 catheter site hemorrhage, 1 subdural hematoma, 1 hematemesis, and 1 intra-abdominal hemorrhage. With 490 subjects exposed to riociguat, 2.4% of subjects had a bleeding serious adverse event, vs. 0% in placebo. This will be handled with a warning in labeling.

Considering all adverse events, I found adverse events related to bleeding in 55 subjects in the riociguat group (55/490 = 11.2%), vs. 20 in the placebo group (19/214 = 8.9%). Thus, the major imbalance in the serious adverse events for bleeding was not recapitulated when all adverse events were considered.

Increasing platelet cGMP through stimulation of sGC has been reported to have anti-aggregatory effects *in vitro*. The applicant studied the potential for riociguat to affect platelet aggregation following stimulation with arachidonic acid and collagen. In healthy subjects, riociguat had no effect on platelet aggregation or bleeding time. Moreover, there was no additive effect of administering 2.5 mg riociguat on top of 500 mg aspirin on either bleeding time or platelet aggregation. No clinically important interactions were observed between riociguat and warfarin that might explain excess bleeding with riociguat in patients on warfarin.

Bone Changes:

Potential bone toxicity events were carefully assessed, including a consult to the Division of Bone, Reproductive and Urologic Products. There is no excess of treatment-emergent pain events in either study. The database seems too small to detect imbalances in fractures.

Use with PDE-5 Inhibitors:

Interactions with nitric oxide donors and with PDE5 inhibitors can cause significant hypotension. Use of riociguat will be contraindicated with nitrates, NO donors, and phosphodiesterase inhibitors.

Advisory Committee:

A meeting of the Cardiovascular and Renal Drugs Advisory Committee was held on August 5, 2013 to discuss the approvability of riociguat, dosing, and risk of hypotension. The Committee voted unanimously in favor of approval for both CTEPH and PAH, opining that there was enough relevance of PAH to approve CTEPH on the basis of a single trial. There were no significant concerns about trial designs or execution. Hypotension did not appear to be markedly worse on riociguat than has been seen with other vasodilators. Risks of hypotension with use of nitric oxide donors and PDE5 inhibitors were felt to be adequately managed by labeling.

Phase 4 Commitments/ Requirements:

None.

Conclusion:

The applicant submitted two independent adequate and well-controlled studies for two indications: PAH and CTEPH. Although there is only one study for each indication, the

indications are pathophysiologically linked. Thus, the studies are mutually supportive for their respective indications. Results of both studies are highly persuasive, and the treatment effects are typical of other agents in PAH (there is no precedent for treatment effects in CTEPH). Although a number of other vasodilators are approved for PAH, this will be the first approval for a drug for CTEPH.

The review team supports approval for both indications, and the Cardiovascular and Renal Drugs Advisory Committee supported approval as well.

There was some disagreement among the review team with respect to the optimal starting dose. Although the starting dose in both phase 3 trials was 1 mg tid, there was some enthusiasm for starting patients, or at least a subset of patients, at 0.5 mg tid, because of hypotension. We have opted to recommend 1 mg tid in labeling, with the provision for using 0.5 mg tid for patients who might not tolerate the hypotensive effects of the drug.

There was no correlation between decreases in pulmonary vascular resistance (as determined through invasive hemodynamic monitoring) and improvements in 6MWD. Some sponsors have opted to use pulmonary hemodynamics in phase 2 studies to guide dose selection; however, these results suggest that hemodynamic changes bear little relationship to efficacy, as assessed by 6MWD.

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

/s/

ELLIS F UNGER
10/08/2013