CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

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| Applicant Name | Bayer Healthcare |
| Brand Name | Adempas [®] |
| Generic Name | Riociguat |
| Dosage Form | Immediate release tablet |
| Dosage Strengths | 0.5, 1.0, 1.5, 2.0, 2.5 mg |
| Proposed Indication | Pulmonary arterial hypertension (PAH) |
| r roposed maleation | Chronic thromboembolic pulmonary hypertension (CTEPH) |
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1 EXECUTIVE SUMMARY

Bayer Healthcare is seeking approval of riociguat (NDA 204819) for use in treatment of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), two sub-groups of pulmonary hypertension (PH). Riociguat is a first in class soluble guanylate cyclase stimulator (sGC). Currently, several prostacyclin analogues (PCA) and endothelin receptor antagonists (ERA) are approved for use in treatment of PAH. There are no approved treatments in CTEPH.

In support of the PAH and CTEPH indication, the applicant conducted 41 Phase 1 and Phase 2 studies in healthy individuals and the relevant populations, two placebo controlled efficacy and safety studies (PATENT-1 and CHEST-1) and long term safety studies. Both PATENT-1 and CHEST-1 were placebo controlled studies consisting of an eight week titration phase¹ followed by a maintenance phase of four and eight week duration, respectively. The primary 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.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 204819. The CPB information provided is adequate to perform an exposure-efficacy/safety analysis and evaluate the impact of various intrinsic and extrinsic factors to derive the necessary dosing instructions. The NDA can be approved from a clinical pharmacology perspective provided agreement is reached with the applicant on labeling. Proposed recommendations are listed below.

- The recommended starting dose is 0.5 mg *tid*, to be titrated in increments of 0.5 mg *tid* to a maximum dose of 1.5 mg *tid* in PAH and CTEPH patients.
- The recommended maximum dose in smokers is 3.0 mg *tid*.
- Based on the proposed dosing regimen and exposure-safety analysis, concomitant administration of multi-CYP inhibitors such as ketoconazole with riociguat is acceptable. This should also be considered if riociguat was to be administered with a specific CYP1A1 inhibitor. Monitoring for hypotension is recommended upon initiation of treatment with the inhibitor.

1.2 Phase 4 Commitments

None.

¹ Dose could be titrated every two weeks based on subject's systolic blood pressure according to a prespecified dosing algorithm. Treatment was initiated at 1 mg riociguat *tid*. The dose was increased, maintained or decreased if SBP was \geq 95 mm Hg, 90-94 mm Hg, < 90 mm hg, respectively.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The key findings are listed below.

Pharmacokinetics

- The pharmacokinetics of riociguat and its active metabolite M1 ($\sim 1/3^{rd} 1/10^{th}$ the potency of riociguat) following administration of single and repeat doses are dose proportional in the range studied in healthy subjects (0.25 to 5 mg) and in subjects with pulmonary hypertension (PH) (1 and 2.5 mg).
- The absolute bioavailability of riociguat following administration of an immediate release tablet is 96%. Peak plasma riociguat and M1 concentrations were observed within 2 and 5 hours, respectively, of oral administration of riociguat in both healthy subjects and subjects with PH.
- Riociguat is metabolized by several cytochrome P450 enzymes (CYP 1A1, 3A4, 2C8, 2J2). Formation of the M1 is mainly catalyzed by CYP1A1. At therapeutic concentrations riociguat or M1 does not inhibit any of the major CYPs.
- Riociguat appears to be mainly eliminated by metabolism followed by excretion in both urine and feces in the mass balance study (n=4). A small fraction of the administered drug is also eliminated unchanged in urine and feces. Unchanged riociguat was the major component in the one of the four subjects studied. The reason for this is not clear.
- Clearance of riociguat in subjects with PH is about half that in healthy subjects (1.8 vs 3.4 L/h). Consequently, systemic exposure to riociguat and M1 in the PH population is 2.6X and 1.6X, respectively that in healthy subjects. Exposure to the active metabolite M1 is about half that of riociguat in subjects with PH.

Pharmacodynamics

- Riociguat causes a dose dependant decrease in peripheral blood pressure in healthy subjects and subjects with PH.
- Riociguat decreases pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP) and other measures of pulmonary hemodynamics. In the proof of concept study the maximal decrease in pulmonary hemodynamics appeared to be the similar between the two doses (1 and 2.5 mg).

Dose/Exposure-Response relationship

• *Exposure-efficacy relationship*

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

quantiles of 2.5 mg stable dose (which matched the exposure in lowest quantile of 1.5 mg stable dose) showed similar efficacy as at higher exposures, confirming the flat E-R relationship (**Figure 4**).

In the phase 3 trial for CTEPH population, similar flat exposure-response relationship for efficacy (change in 6 minute walk distance, 6MWD) was also seen in CTEPH population (**Figure 5**).

• Dose-Safety relationship

There was a lack of substantial sample size of patients with extended exposures to 1.5 mg dose (due to a small 1.5 mg arm in PAH phase 3 trial and absence of 1.5 mg dose arm in CTEPH phase 3 trial) to evaluate the true extent of potential hypotension related safety risk going from 1.5 mg dose to 2.5 mg dose. In the PAH phase 3 trial, the preliminary evaluation of event-rates adjusted for the sample size (patients) and the time they were exposed to a particular dose, suggest a numerical trend towards increase in hypotension (SBP<90) event-rates with >1.5 mg dose as compared to the 1.5 mg dose (**Table 1**).

Approximately 45% of all on (riociguat) treatment hypotension events (defined by SBP<90) encountered in the PAH phase 3 trial are occurring on day 1 and day 2 itself when the patients are taking 1 mg *tid* dose. There was statistically significant correlation of increase in these events for patients with higher C_{trough} exposure on day 1 (**Figure 7**). Almost all of these events are occurring in patients with baseline SBP of <=110 mmHg (median SBP in the PAH trial). Based on this exposure-safety relationship, it would be appropriate to recommend the initial starting dose of 0.5 mg, which would lower patients' systemic exposure by 50% on day 1/day 2.

Effect of intrinsic factors

- A 100% increase in the total systemic exposure (AUC) to riociguat was observed in non-smokers with impaired renal function irrespective of the severity of impairment as compared to non-smokers with normal renal function. A graded increase in AUC across renal function categories with increasing severity of renal impairment was seen with M1. In subjects with severe impairment of renal function AUC of M1 increased by 100%. Peak plasma concentrations (C_{max}) of riociguat or M1 were not significantly affected. No dose adjustment is required for patients with impaired renal function as they were studied in the Phase 3 without significant safety concerns.
- A 70% increase in the total systemic exposure (AUC) to riociguat was observed in subjects with impaired hepatic function (C-P Class: A & B). The pharmacokinetics of M1 appears to be not affected. This change is not considered significant to warrant dose adjustment.
- Mean C_{max} was ~ 30% higher in females as compared to males. Mean AUC was ~ 46% higher in the elderly compared to the young. No dose adjustment is required.

Effect of extrinsic factors

Effect of smoking

• Smoking induces CYP1A1, the main enzyme responsible for the metabolism of riociguat. Consequently, systemic exposure to riociguat in smokers is half that observed in non-smokers. Increasing the maximal dose to twice that in non-smokers should be considered.

Drug interactions

• Nitric oxide donors

Nitric oxide donors potentiate the blood pressure reduction effect of riociguat and the use of NO donors in individuals prescribed riociguat is contraindicated.

• Phosphodiestrese-5 inhibitors

Concomitant administration of riociguat and sildenafil, a PDE-5 inhibitor, did not appear to show additional effect on pulmonary hemodynamics or 6MWD when compared to sildenafil alone. No difference in blood pressure reduction was seen in the controlled phase of the study. However, hypotension events were reported in the long term extension. Hence, co-administration of riociguat with PDE-5 inhibitors should be avoided.

• Ketoconazole and other multi-CYP/transporter inhibitors

Total systemic exposure (AUC) to riociguat was increased by 150% when administered concomitantly with ketoconazole 400 mg QD. The PK of ketoconazole was not affected by riociguat. Based on the exposure-safety analyses, no dose adjustments are required. This should also be considered if riociguat was to be administered with a specific CYP1A1 inhibitor. Monitoring for hypotension is recommended upon initiation of the inhibitor.

• Antacids

Systemic exposure (AUC and C_{max}) to riociguat and M1 was decreased by 35 to 55% when riociguat was administered with Maalox. Based on these results antacids, if needed, are recommended to be administered 1 h after the administration of riociguat by when majority of the drug would have been absorbed.

• Warfarin, Clarithromycin, omeprazole, midazolam, and aspirin

No clinically relevant interactions were observed.

2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

Riociguat is a soluble guanylate cyclase (sGC) stimulator. The applicant is seeking approval of this first in class molecule for use in treatment of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). The development program for riociguat was conducted under IND 75629.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

| Appearance | Yellowish to white crystalline solid |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Chemical name | Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4- b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate |
| Molecular formula | $C_{20}H_{19}FN_8O_2$ |
| Molecular weight | 422.42 |
| Structural formula | |
| Solubility | Practically insoluble in water (4 mg/L), very slightly soluble in 0.1M HCl (250 mg/L), freely soluble in DMSO (109280 mg/L) |
| рКа | 4.3 ± 0.02 |
| Partition coefficients | Log $P_{o/w}$ at pH 7 = 2.37 |

Drug substance (micronized)

Drug product

Riociguat was formulated as round biconvex film-coated tablets in strengths of 0.5, 1.0, 1.5, 2.0, 2.5 mg differentiated by color and debossing. The excipients were lactose, microcrystalline cellulose, crospovidone, magnesium stearate, hypromellose and sodium lauryl sulfate. The film-coat consisted of hydroxypropyl cellulose, hypromellose, propylene glycol, titanium dioxide and/or iron oxide (red and/or yellow).

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Riociguat and M1 increase the activity of sGC, the enzyme that catalyses the formation of cGMP. Elevation of cGMP in smooth muscle causes relaxation. In the pulmonary bed it is expected to result in vasodilation. In studies in sGC overexpressing CHO cells, the

 EC_{50} of riociguat was estimated to be 80 nM (32 ng/mL). Potency of M1 was estimated to be ~ $1/3^{rd} - 1/10^{th}$ that of riociguat.

On approval, riociguat will be indicated in the treatment of PAH and CTEPH.

2.1.3 What are the proposed dosage strengths and routes of administration?

Riociguat is formulated as immediate release tablets (0.5, 1.0, 1.5, 2.0, 2.5 mg) for oral administration, individually titrated to tolerability². The applicant is seeking approval of all five strengths.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

The clinical pharmacology program for riociguat and M1 consisted of 41 *in vivo* Phase 1/Phase 2 studies. These included studies characterizing pharmacokinetics and pharmacodynamics following single and multiple doses of riociguat and M1 (six studies were conducted with M1), a mass balance study, drug interactions studies, absolute and relative bioavailability studies, food effect studies, studies in specific populations, and proof-of-concept studies in PH population³. Twenty six *in vitro* studies were conducted to identify the relevant enzymes and transporters involved in the metabolism and transport of riociguat and M1, and to determine the protein binding and RBC distribution characteristics of riociguat and M1. Twenty nine of the *in vivo* and 26 of the *in vitro* studies of the submitted studies were reviewed and the individual study reviews are included in the appendix.

Two Phase 3 studies, one conducted in the PAH population (PATENT-1) and the other in the CTEPH population (CHEST-1), were submitted in support of efficacy and safety of riociguat. Both studies were similar in design and consisted of an individual titration phase followed by a maintenance phase. All five strengths of riociguat were used in these studies.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

Change from baseline⁴ in systolic and diastolic blood pressure, and heart rate were the pharmacodynamic response endpoints in all Phase 1 studies. Change from baseline in pulmonary hemodynamic measures⁵, and six minute walk distance (6MWD) were the response endpoints measured in Phase 2 studies. Change from baseline in 6MWD was the primary endpoint in both Phase 3 studies.

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

decreases below 95 mmHg and the patient shows signs or symptoms of hypotension, the current dose should be decreased by 0.5 mg. 3 \\cdssub1\evsprd\nda204819\0000\m5\52-tab-list\tabular-listing.pdf

⁴ Pre-dose

⁵ Mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), cardiac index (CI) measured by right heart catheterization

Riociguat is expected to exert its effect in PH by increasing the formation of cGMP, a mediator of vasodilation. Hence, systemic and pulmonary hemodynamic measures can be informative of riociguat's effect on systemic and pulmonary vasculature, respectively.

Reduced exercise capacity is one of the clinical manifestations of PH and 6MWD has been used traditionally to assess this. Hence, change from baseline in 6MWD is an appropriate measure of the effect of riociguat in PH. The 6MWD test was performed according to the American Thoracic Society guidelines.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Riociguat and M1 are the active moieties in plasma. These were appropriately identified and measured in plasma (and urine where applicable) to permit adequate assessment of pharmacokinetics.

2.3 Exposure-Response

2.3.1 What was the basis for dose selection for Phase 3?

Dose and dosing regimen for Phase 3 was selected based on PK/PD data from Phase 1 studies and the interim results of the Phase 2 study.

In healthy subjects, the 0.5 mg dose of riociguat was identified as the no-effect dose and a dose of 5 mg was not well tolerated (**11258**). A single dose of 1 mg resulted in clinically relevant lowering of peripheral and pulmonary hemodynamic measures in subjects with PH and was well tolerated (**11874**). In the same study a total dose of 5 mg (1+2+2 mg administered an hour apart) resulted in severe hypotension in one of the two subjects with PH. These data formed the basis for selecting the dose range and dosing regimen to be evaluated in Phase 2.

The feasibility of a dosing strategy similar to that employed in PATENT-1 and CHEST-1 was tested in an uncontrolled Phase 2 study conducted in subjects with PH (PAH or CTEPH with mPAP ≥ 25 mm Hg, PVR > 300 dynes/cm⁻⁵*s) (**12166**). The study consisted of an eight week titration phase followed by a 4 week maintenance phase. The doses tested in this study spanned and slightly exceeded the Phase 1 experience in healthy subjects (after accounting for the 2.5X increased exposure to riociguat in subjects with PH).

Subjects were started at a dose of 1 mg *tid* and their dose was uptitrated based on the dosing algorithm (Figure 1).



Dosing algorithm

If trough SBP > 100 mm Hg, \uparrow dose (+0.5 mg *tid*), if 90 mm Hg \geq trough SBP < 100 mm Hg, \leftrightarrow dose, if trough SBP < 90 mm Hg without symptomatic hypotension, \downarrow dose (-0.5 mg *tid*), if trough SBP < 90 mm Hg with symptomatic hypotension, stop treatment and restart after 24 at \downarrow dose (-0.5 mg *tid*)

Figure 1 Schematic of titration scheme employed in 12166 (Adapted from CSR 12166).

A statistically significant change from baseline in pulmonary hemodynamic measures (mPAP, PVR and SVR) and 6MWD was observed (**Figure 2**) at end of study, suggesting that peripheral hemodynamics may be used as an indicator of the drug's effect on the pulmonary vasculature.



Figure 2 Change from baseline in 6MWD.

Results from an interim analysis (after 25 subjects completed 12 weeks) of the study informed the design of PATENT-1.

2.3.2 What are the characteristics of the exposure-response relationships for efficacy?

In the Phase 3 trial for PAH population, the dose-response relationship showed similar efficacy between 1.5 mg fixed dose arm and 2.5 mg individual dose titration (IDT) arm and both arms had clinically significant benefit in efficacy over placebo (Figure 3).



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

The exposure-response (E-R) relationship for efficacy (change in 6 minute walk distance, 6MWD) was also flat for the exposures (AUC) corresponding to the 1.5 mg and 2.5 mg dose. The lowest quartile of 1.5 mg dose arm showed lower efficacy, but the investigation of efficacy in the lowest quantiles of 2.5 mg stable dose (which matched the exposure in lowest quantile of 1.5 mg stable dose) showed similar efficacy as at higher exposures, confirming the flat E-R relationship (Figure 4).

Change in 6MWD vs. Treatment



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

Figure 4 Change from baseline in 6MWD: by quantiles of combined exposure for highest stable doses (1.5 and 2.5 mg) allowed in each of the two riociguat arms (Upper panel); and by quantiles of exposure for 1.5 and 2.5 mg maximum dose arms separately (lower left panel) for patients maintained on highest possible dose of Riociguat in each arm at the end of the study (12 weeks) in PAH phase 3 trial. The lower right panel shows smaller exposure quantiles for 2.5 mg dose, where the median exposure in lowest quantile for 2.5 mg dose group is similar to median exposure in lowest quantile of 1.5 mg dose group, but the efficacy is higher and similar to other exposure quantiles.

In the phase 3 trial for CTEPH population, similar flat exposure-response relationship for efficacy (change in 6 minute walk distance, 6MWD) was also seen in CTEPH population (**Figure 5**).



Figure 5 Change from baseline in 6MWD (efficacy) separated by quantiles of exposure in patients on all stable doses (upper panels) or maintained on highest stable dose of 2.5 mg (lower panels) Riociguat at the end of the study (16 weeks) in CTEPH phase 3 trial. The median (left panels) as well as mean (right panels) of efficacy data are shown.

2.3.3 What are the characteristics of the exposure-response relationships for safety?

There was a lack of sample size of patients with extended exposures to 1.5 mg dose (due to a small 1.5 mg fixed dose arm in PAH phase 3 trial and absence of 1.5 mg fixed dose arm in CTEPH phase 3 trial) to evaluate the true extent of potential hypotension related safety risk going from 1.5 mg dose to 2.5 mg dose. In the PAH phase 3 trial, the preliminary evaluation of event-rates adjusted for the sample size (patients) and the time they were exposed to a particular dose (schematic of time-course shown in (**Figure 6**), suggest a numerical trend towards increase in hypotension (SBP<90) event-rates with >1.5 mg dose as compared to the 1.5 mg dose, but the data does not lend itself to any statistical comparisons of safety risk for the significance (**Table 1**).



Figure 6 Schematic of time-course of first hypotension event (time-to-event, SBP <90 mmHg) and the dose associated with the event are depicted for PAH phase 3 trial (PATENT-1). The counts for events occurring within 2 days and those occurring beyond 2 days in the course of trial are also shown in the figure. The bold lines depict the approximate average length of time the patients were exposed to a particular dose within an arm.

| Table 1 | Hypotension | event-rates v | with c | different | doses | in | PA | ΓENT | -1 | tria | 1 |
|---------|-------------|---------------|--------|-----------|-------|----|----|------|----|------|---|
|---------|-------------|---------------|--------|-----------|-------|----|----|------|----|------|---|

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

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

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

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

Approximately 45% of all on (riociguat) treatment hypotension events (defined by SBP<90) encountered in the PAH phase 3 trial are occurring on day 1-2 itself when the patients are taking 1 mg *tid* dose and these events are very high as compared to events on placebo within the same time period (Figure 6). The exposure-response (logistic regression) analysis showed that there was statistically significant correlation of increase in these hypotension events for patients with higher C_{trough} exposure on day 1 (Figure 7). Almost all of these events were occurring in patients with baseline SBP of <=110 mmHg (median SBP in the PAH trial). Thus, it would be appropriate to recommend the initial starting dose of 0.5 mg in this subpopulation, which would lower their systemic exposure by 50% on day 1/day 2. The titration of 2 weeks at reduced dose of 0.5 mg in the entire group (rather than SBP based subgroup) would not alter the efficacy benefit gained from this drug which is going to be taken for extended periods of time. Also there is known high inter-individual/inter-occasion variability in baseline measurements of SBP, which would have potential impact on the prescription of starting dose. Thus for the sake of simplicity in labeling, and to avoid potential early hypotensive events, we recommend a starting titration dose of 0.5 mg for the entire population.







Figure 7 Exposure-response analysis for hypotension events defined by SBP<90 mmHg (Panels A-C) and hypotension AEs as reported by CSR protocol (Panels D-E) occurring within 2 days of start of study treatment in PAH phase 3 trial (PATENT-1). Panel A shows E-R for all the patients/events while panels B-C and panels D-E show E-R for patients categorized into 2 different baseline SBP categories. Most of the hypotension events are occurring in patients with lower baseline SBP (Panels B and D) as against higher baseline SBP (Panels C and E) and in this subgroup there is significant increase in probability of event with higher C_{trough} associated with 1st dose on day 1.

2.3.4 Does this drug prolong QT/QTc Interval?

No, riociguat does not appear to prolong QTc interval. Please refer to the QT-IRT review (DARRTS date 05/08/2013).

2.3.5 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

As per the sponsor's proposal, riociguat will be individually titrated based on tolerability as assessed by change in SBP. Sponsor has proposed a starting titration dose of 1 mg and

a maximum titration dose of 2.5 mg. The exposure-response relationship for efficacy (change in 6 minute walking distance) is flat within the exposure range studied in the PAH phase 3 trial corresponding to 1.5 mg and 2.5 mg doses and both doses had clinically significant benefit over placebo (**Figure 3**). In the dose-safety relationship for riociguat going from 1.5 mg to higher doses within the studied population, there are trends toward higher safety signal of hypotension events (defined by SBP<90) with such dose increase. Taking into account the facts that: 1) the BP measurements in the trial were all supine measurements and there is likelihood of further drop in SBP in standing position, 2) the population excluded in the phase 3 trial could have higher propensity of drop in blood pressure due to co-morbidities, and 3) the exposure-efficacy relationship is flat within the exposure range of 1.5 and 2.5 mg doses, we recommend the highest titration dose of 1.5 mg that has better safety-efficacy profile..

Regarding the starting dose of 1 mg, ~45% of all on (riociguat) treatment hypotension events (defined by SBP<90) encountered in the PAH phase 3 trial are occurring on day 1 and day 2 itself when the patients are taking 1 mg *tid* dose. There was statistically significant correlation of increase in these events for patients with higher C_{trough} exposure on day 1. Since almost all of these events were occurring in patients with baseline SBP of <=110 mmHg (median SBP in the PAH trial), it would be appropriate to recommend the initial starting dose of 0.5 mg in this subpopulation, which would lower their systemic exposure by 50% on day 1/day 2 through week 2. The titration of 2 weeks at reduced dose of 0.5 mg in the entire group (rather than lower SBP subgroup) would not alter the efficacy benefit gained from this drug which is going to be taken for extended periods of time. Also there is known high inter-individual/inter-occasion variability in baseline measurements of SBP, which would have potential impact on the prescription of starting dose in case of SBP threshold-based starting dose recommendation. Thus for the sake of simplicity in labeling, and to avoid potential early hypotensive events, we recommend a starting titration dose of 0.5 mg for the entire population.

2.4 What are the PK characteristics of the drug?

2.4.1 What are the single and multiple dose PK parameters?

Single and multiple dose pharmacokinetics of riociguat and M1 were evaluated in the dose range of 0.25 to 5 mg (**11258**) and 0.5 to 2.5 mg *tid* (**11260**), respectively. Riociguat and M1 pharmacokinetics was evaluated in subjects with PH at 1 and 2.5 mg dose (**11897**). Riociguat and M1 exhibited dose proportional PK in both healthy subjects and subjects with PH in the dose range tested.

Peak riociguat plasma concentrations were observed within 0.5 to 2 h of administration of the tablet. Mean CL of riociguat was ~ 3.1 L/h (%CV = 60) in healthy non-smokers and ~ 6 L/h (%CV = 93) in healthy smokers. Similarly, the mean terminal elimination half-life $(t_{1/2 \ \lambda})$ of riociguat was ~ 9 h (%CV = 66) and ~ 4.5 h (%CV = 94) in healthy non-smokers and smokers, respectively (**11910**). On repeat *tid* administration, riociguat accumulated by ~ 50% at steady state indicating that the effective $t_{1/2}$ (~ 4h in healthy non-smokers) was lesser than the terminal elimination $t_{1/2 \ \lambda}$.

Peak M1 plasma concentrations were observed on average within 4 to 6 hours of administration of riociguat. The mean terminal elimination half-life $(t_{1/2 \lambda})$ of M1 was ~

14 h. On repeat *tid* dosing, the accumulation ratio of M1 is \sim 5. As seen in **Figure 8**, systemic exposure to M1 on repeat *tid* dosing in healthy subjects is similar to that of riociguat.



Figure 8 Mean plasma concentration time course for riociguat (\bullet) and M1 (\blacktriangle) following repeat *tid* administration for 10 days.

2.4.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

The PK of riociguat and M1 in subjects with PH differ from that in healthy subjects most likely because of impaired elimination in the PH population. Exposure to riociguat and M1 in subjects with PH (non-smokers) was assessed in the proof-of-concept study using a rich PK sampling scheme (**11847**). Additionally, PK was also assessed in Phase 2 and Phase 3 studies using a sparse sampling scheme.

Peak plasma riociguat and M1 concentrations were observed within 1.5 and 5 h, respectively, of administration of riociguat oral solution (**Figure 9**). This is similar to that observed in healthy subjects. Mean CL/F of riociguat in subjects with PH was ~ 1.8 L/h (%CV = 40) in study 11847 (approximately halved when compared to ~ 3.4 L/h (%CV = 70) in healthy subjects). The terminal elimination half-life of riociguat was about 12 h (%CV = 40). Systemic exposure (AUC and C_{max}) to M1 was about half that of riociguat, unlike that seen in healthy subjects.



Figure 9 Mean plasma riociguat (•) and M1 (\blacktriangle) concentration time course following oral administration of a single dose of riociguat 1 or 2.5 mg in PH patients.

In an empirical analysis (**16501**, using data from Phase 1 and Phase 2 studies) comparing exposures in PH patients and healthy subjects, the total systemic exposure (dose normalized AUC) to riociguat in the PH population was estimated to be 2.6X (90% CI = 2.1, 3.3) that in healthy subjects. Peak exposure (dose normalized Cmax) to riociguat in the PH population was estimated to be 1.7X (90% CI = 1.4, 2.0) that in healthy subjects. Total systemic exposure (dose normalized AUC) to M1 in the PH population was estimated to be 1.6X (90% CI = 1.4, 1.9) that in healthy subjects. Peak exposure (dose normalized C_{max}) to M1 in the PH population was estimated to be 1.6X (90% CI = 1.4, 1.9) that in healthy subjects. Peak exposure (dose normalized C_{max}) to M1 in the PH population was estimated to be 1.2X (90% CI = 1.0, 1.4) that in healthy subjects.

2.4.3 What are the characteristics of drug absorption?

Riociguat and M1 were detected in plasma 15 minutes (earliest sampling time) following oral administration of riociguat as a solution or a tablet. The absolute bioavailability of riociguat following administration as a tablet was assessed to be ~ 0.96 (**11910**). Further, there is region dependent absorption of riociguat, with less absorption at distal sites of the gastrointestinal tract (**11525**).

2.4.4 What are the characteristics of drug distribution?

Riociguat and M1 do not appear to distribute extensively. The volume of distribution (Vss) for riociguat was estimated to be $\sim 30L$ in healthy subjects and subjects with PH (**11910**, **11847**).

Riociguat is ~ 95% bound plasma proteins. Binding is concentration independent (47.6 to 2370 ng/mL). The protein binding of M1 is ~97% (**15000**) and is concentration independent. The main binding proteins in human plasma were serum albumin and α 1-acidic glycoprotein. Mean plasma/blood concentration ratio was 1.5 (**PH-33817**).

2.4.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Riociguat appears to be eliminated mainly by metabolism followed by excretion in urine and feces. A small fraction of the drug was also eliminated unchanged in urine and feces.

Following oral administration of $[^{14}C]$ - riociguat as a solution (**11911**), about 40% and 53% of the administered dose was recovered in urine and feces, respectively. About 6 and 15% of the administered dose was recovered as unchanged riociguat in urine and feces, respectively in three out of four subjects in the mass balance study. M4, the inactive glucuronidated conjugate of M1, was also detected in all subjects (**Figure 10**) in plasma and urine. Trace amounts of M3 was detected in urine.

M1 was the major component in plasma/urine/feces in 3 out of the four subjects in the study while unchanged riociguat was the major component in the fourth subject. The reason for this is not clear.



Figure 10 Total radioactivity (•, ng eq/mL), riociguat (\blacktriangle), active metabolite M1 (×) and inactive metabolite M4 (Δ) concentration time course in plasma following administration of 1 mg ¹⁴C-riociguat solution in four healthy individuals.

2.4.6 What are the characteristics of drug metabolism?

Riociguat is metabolized by several CYPs (CYP1A1, CYP3A4/5, CYP2C8, CYP 2J2). It mainly undergoes de-methylation at the carbamate N to form its active metabolite M1. Formation of M1 is mainly catalyzed by CYP1A1. M1 is further metabolized to form the inactive glucuronide conjugate M4. Metabolites M3 (N-debenzylated metabolite of riociguat) and M8 (glucuronidated riociguat) were detected in *vitro* studies, but only M3 was detected *in vivo* in trace amounts in urine (A51309, 11911). A schematic of the metabolic pathway is presented in Figure 11.

Kinetic parameters estimated using recombinant CYPs indicate that the order of affinity of riociguat to be the following. CYP1A1 (K_m =1.1 μ M) > CYP2J2 (K_m =11 μ M) > CYP2C8 (K_m = 22 μ M) > CYP3A4/5 (K_m > 100 μ M) (A51309).



Figure 11 A schematic of the metabolic pathway of riociguat (BAY 63-2521) in humans (Ref: Biotransformation report, CSR 11911).

2.4.7 What are the characteristics of drug elimination?

Riociguat appears to be eliminated mainly by metabolism followed by excretion in urine and feces. A small fraction of the drug was also eliminated unchanged in urine and feces. Please see section 2.4.5.

2.4.8 Based on PK parameters, what is the degree of linearity in the doseconcentration relationship?

Riociguat follows dose-proportional PK following oral administration in the dose range tested. Increasing the administered dose resulted in a close to proportional increase in plasma concentrations in both healthy subjects (exponent of power model = 1.09 (1.04, 1.14), **13009**) and subjects with PH (**Table 2**).

| | Riociguat / Geon | netric Mean (%CV) | M1 / Geometric Mean (%CV) | | |
|--------------------------|------------------|-------------------|---------------------------|------------|--|
| Dose (mg) | 1.0 | 2.5 | 1.0 | 2.5 | |
| AUC (ng/mL*h) | 602.3 (15) | 1411 (39) | 189.6 (22) | 517.6 (38) | |
| C _{max} (ng/mL) | 59.4 (6) | 119.4 (16) | 7.8 (15) | 19.7 (53) | |
| CL/F (L/h) | 1.7 (15) | 1.8 (39) | - | - | |

 Table 2 PK measure for riociguat and M1 in subjects with PH (Ref: CSR 11847)

2.4.9 How do the PK parameters change with time following chronic dosing?

Riociguat or M1 do not exhibit time dependent PK.

2.4.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients?

The between subject variability (BSV) for riociguat PK is high. The mean estimate for BSV in CL/F in healthy subjects (non-smokers) was estimated to be ~ 60 % while that in subjects with PH (non-smokers) was estimated to be ~ 40% (11910, PH-35222, 13187). The within-subject variability for riociguat was estimated to be ~ 30% in both healthy subjects and subjects with PH (PH-35222, 13187).

2.5 What are the PD characteristics of the drug?

The time course of riociguat's effect on peripheral and pulmonary hemodynamics in individuals with PH was measured in 11874 following administration of a single dose of 1 or 2.5 mg of riociguat. As seen in **Figure 12** riociguat exerts its effect on both peripheral and pulmonary vasculature. It exhibits a discernible dose dependent effect on peripheral blood pressure (Figure 10 left) and heart rate.



Figure 12 Riociguat decreases peripheral and pulmonary pressure. dSBP = Change from baseline in systolic blood pressure, dPVR = Change from baseline in pulmonary vascular resistance

The maximal change in pulmonary hemodynamics observed was comparable at both doses. A trend towards increased effect with increasing dose was observed in PATENT-1. The mean (SD) change from baseline in PVR was -223.3 (260.1), (-8.9 (316.6), -167.8 (320.2) for the individual dose titration arm, placebo and capped titration arm, respectively.

2.6 Intrinsic Factors

2.6.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Riociguat is eliminated mainly by metabolism followed by excretion in both urine (53%) and feces (40%). Given this, impairement in renal or hepatic function is expected to impact the pharmacokinetics. The active metabolite M1 is excreted mainly unchanged in urine and feces. Consequently, increased total systemic exposure to M1 is expected in subjects with impaired renal function.

Renal impairment

The effect of renal impairment was assessed following administration of a single dose of 1 mg of riociguat (15000) conducted in subjects with mild, moderate, and severe renal impairment. This study was conducted in non-smokers. A 200% increase in the total systemic exposure (AUC) to riociguat was observed in subjects with impaired renal function. A graded increase in AUC, reaching 200% in subjects with severe renal impairment was seen with M1. Peak plasma concentrations (C_{max}) of riociguat or M1 were not significantly affected (Figure 13).



Figure 13 Total systemic exposure to riociguat and M1 (total) is increased in individuals with impaired renal function. The closed circles represent the geometric mean ratio (test/reference) for AUC_{inf} and C_{max} and the horizontal line represents the 90%CI associated with the mean.

Increased systemic exposure to riociguat and M1 may result in an increased drop in blood pressure eventually affecting tolerability and the ability to uptitrate dose. About 60% of the subjects in PATENT-1 had mild to moderate renal impairment at baseline. Of the subjects randomized to the 1.0 to 2.5 mg individual titration arm, about 70-77% who had mild or moderate renal impairment at baseline had their dose uptitrated to 2.5 mg by end of study. In comparison about 80% of the subjects with normal renal function at baseline had their dose uptitrated to 2.5 mg by end of study. These data suggest that there does not

appear to be a lack of tolerability to dose uptitration in individuals with impaired renal function. Therefore, dose adjustments are not required in this population.

Hepatic impairment

The effect of hepatic impairment was assessed following administration of a single dose of 1 mg of riociguat (15001) conducted in subjects with mild (C-P A) or moderate (C-P B) hepatic impairment. This study was conducted in non-smokers. A 70% increase in the total systemic exposure (AUC) to riociguat was observed in subjects with impaired hepatic function (Figure 14). The PK of M1 appears to be not affected by impaired hepatic function.



Figure 14 Total systemic exposure to riociguat is higher in individuals with impaired hepatic function. The closed circles represent the mean fold change relative to reference for AUC_{inf} and C_{max} and the horizontal line represents the 90%CI associated with the mean.

Based on the inclusion/exclusion criteria specified for PATENT-1, subjects with mild hepatic impairment were enrolled in the study. There does not appear to be a lack of tolerability to dose uptitration in individuals with impaired hepatic function. Therefore, dose adjustments are not required.

<u>Age, sex</u>

The effect of age and sex on the pharmacokinetics of riociguat and M1 was assessed following administration of a single dose of 2.5 mg riociguat (**11914**) in healthy individuals matched for demographics and smoking habits. The mean fold change in systemic exposure (AUC and Cmax) in non-smokers is presented in Figure 15.

Mean Cmax was $\sim 30\%$ higher in females as compared to males. While an increase in Cmax may result in an increased drop in blood pressure, a gender related increase in hypotension was not observed in Phase 3 trials (80% in PATENT were females).



Figure 15 Systemic exposure to riociguat and M1 is higher in the elderly - E (> 65 y) as compared to the young - Y (< 45 y) and peak plasma concentrations are higher in women as compared to men.

Mean AUC was ~ 46 % higher in the elderly compared to the young. This increased exposure may be related to a decline in renal function in the elderly. About 22% of the subjects in PATENT-1 were > 65 years of age. Excessive hypotension was not reported in this group. Therefore, a dose adjustment is not required.

Ethnicity

Chinese

The pharmacokinetic properties of riociguat was assessed following administration of single and repeat administration of 1 and 2 mg *tid* (**14361**) in healthy Chinese stratified by smoking status. Riociguat appears to follow dose proportional pharmacokinetics with CL/F (\sim 4 L/h (%CV \sim 90) in non-smokers) comparable to that observed in Caucasians.

Japanese

The pharmacokinetic properties of riociguat was assessed following administration of single administration of 0.5, 1 and 2.5 mg and repeat administration of 1 and 1.5 mg *tid* (**12639, 12640**) in healthy Japanese. Riociguat appears to follow dose proportional pharmacokinetics with average CL/F ~ 3 L/h in non-smokers. The variability in pharmacokinetics (%CV ~ 30%) was lower than that observed in Caucasian non-smokers. The reason for this decreased between subject variability is not clear.

Genetics

To investigate the contribution of genetic variation on the variable pharmacokinetics of riociguat, the sponsor genotyped healthy men (147 Caucasian, 12 Japanese) from their phase 1 pharmacokinetic studies for 1069 polymorphisms in 172 drug metabolizing enzyme and transporter genes. Genotype- and allele-based association testing for riociguat half-life, clearance, dose normalized AUC and dose normalized AUC(0-8) of the primary metabolite M1 yielded no statistically significant (defined as p < 0.0001) effects of the tested variants on pharmacokinetics. Haplotype estimation and analyses in

Caucasians identified significant genetic associations with half-life and clearance at the following loci: XDH, CYP1B1, CHST10, SULT1C1, CULT1C2, CYP11B1, ALDH1A1, and SLC28A3. The largest R² value from this analysis was 15%, indicating that genetic factors accounted for a small proportion of the overall variability. It is also notable that variants in CYP1A1 and other genes involved in the metabolism were not significantly associated with riociguat disposition. Preemptive genotyping to guide dosing is not indicated on the basis of the above findings, particularly considering that riociguat doses are titrated.

2.6.2 What pregnancy and lactation use information is there in the label?

Riociguat is contraindicated in pregnancy because of the risk of embryo-fetal toxicity.

2.7 Extrinsic Factors

2.7.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

In addition to the extrinsic factors listed/discussed under section 2.4.2, systemic exposure to riociguat is reduced by about half in smokers. As presented in section 2.2.5.1, CL/F of riociguat in smokers is twice that in non-smokers.

Smoking induces CYP1A1, the enzyme mainly responsible for riociguat metabolism. CYP1A1 is induced by compounds in tobacco smoke via activation of the aryl hydrocarbon receptors. In *in vitro* studies, M1 turnover % in lung microsomes from smokers (0.9-1.5%) was much higher than that in non-smokers ($\sim 0.1\%$) (A51309) further supporting this hypothesis.

About 6.5% of the subjects in PATENT-1 were current smokers. Despite the reduced exposure to riociguat, smokers in PATENT-1 had a change from baseline in 6MWD similar to that in non-smokers at end of study (**Figure 16**).



Figure 16 Change from baseline in 6MWD is similar between smokers (n=9) and nonsmokers (n=115) despite reduced plasma riociguat concentrations on day 84. All subjects were receiving 2.5 mg *tid*.

Based on the exposure-response analyses, the maximum dose proposed is 1.5 mg *tid*. Given that exposures in smokers is about half that in non-smokers, a maximum dose of 1.5 mg *tid* will result in exposures similar to that achieved with 0.75 mg *tid*. Because there is not enough information at this lower dose level, increasing the maximal dose to 3 mg *tid* should be considered in smokers.

2.7.2 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Results of *in vitro* studies suggest that pharmacokinetic drug interactions between riociguat and multi-CYP/P-gp/BCRP inhibitors, CYP1A1 substrates/inhibitors/inducers, or antacids are likely.

Riociguat is metabolized by several CYPs. The active metabolite M1 is mainly formed via CYP1A1. Other isoforms (CYP3A4/5, CYP 2C8, CYP 2J2) contribute to a minor extent to the formation of M1 (**51309**). Riociguat is an inhibitor of CYP1A1 (IC₅₀ 0.8 μ M, 320 ng/mL) and CYP 2C19 (IC₅₀ 44 μ M) (**PH33080**). Riociguat does not inhibit other major CYPs (IC₅₀ > 50 μ M). Its active metabolite M1 is also an inhibitor of CYP1A1 (IC₅₀ 0.7 μ M) but does not inhibit other major CYPs (IC₅₀ > 50 μ M) (A49419). At therapeutic concentrations both riociguat and M1 are not expected to induce CYP3A, CYP 1A2, CYP 2B6 or CYP 2C19 (**PH35817**, **PH35806**).

Riociguat is a substrate of the efflux transporters P-gp and BCRP, but not an inhibitor (36092, 36091, 3602). Further, the solubility of riociguat decreases with increasing gastric pH and therefore a change in gastric pH may affect absorption also supported by results of the absorption site study (11525).

Additionally, pharmacodynamic drug interactions mainly via potentiation of its vasodilatory effect are expected with other drugs that affect the NO pathway.

2.7.3 What are the drug-drug interactions?

The potential/extent for drug interaction with CYP substrates/inhibitors, and other concomitant medication was evaluated in several dedicated studies conducted in healthy subjects. Most studies were repeat dosing studies and measured systemic exposure to riociguat, M1 and the interacting drug.

Ketoconazole (multi-CYP/transporter inhibitor)

The effect of concomitant administration of repeat administration of ketoconazole on a single dose of riociguat was assessed in dedicated PK study conducted in healthy subjects. Total systemic exposure (AUC) to riociguat was increased to 2.5X when administered concomitantly with ketoconazole 400 mg QD (Figure 17). The pharmacokinetics of ketoconazole was not affected by riociguat.



Change relative to riociguat alone

Figure 17 Concomitant administration of ketoconazole and riociguat increases systemic exposure to riociguat. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

Based on the exposure-safety analyses, increased exposure does not affect tolerability to the drug, no adjustments are required. This should also be considered if riociguat was to be administered with a specific CYP1A1 inhibitor. However, since such inhibitors are most likely to be added to a stable regimen of riociguat, we recommend frequent monitoring for hypotension upon initiation of therapy with the inhibitor.

Antacids

The effect of concomitant administration of Maalox (10 mL) on a single dose of riociguat 2.5 mg was evaluated in a sequential design study in healthy subjects (**11890**). Systemic exposure (AUC and Cmax) to riociguat and M1 was decreased when riociguat was administered with Maalox (**Figure 18**).



Figure 18 Concomitant administration of Maalox and riociguat decreases bioavailability of riociguat and M1. The closed circles represent the geometric mean and the horizontal line represents the 90%CI associated with the mean.

Based on these results, antacids, if needed, are recommended to be administered 1 h after the administration of riociguat by when majority of the drug would have been absorbed.

Clarithromycin (time dependant moderate CYP 3A4 inhibitor)

The effect of repeat administration of 500 mg clarithromycin bid on a single dose of 1 mg riociguat was evaluated in healthy subjects (**13284**). Total systemic exposure (AUC) of riociguat was increased by ~ 40% when administered with clarithromycin. Peak systemic exposure (C_{max}) was not affected by clarithromycin.

<u>Omeprazole</u>

The effect of repeat administration of 40 mg omeprazole QD on a single dose of 2.5 mg riociguat was evaluated in healthy subjects (**11262**). Total and peak systemic exposure (AUC and C_{max}) of riociguat was reduced by ~ 26% and 35%, respectively when administered with omeprazole. No dose adjustments are recommended.

Bosentan

From population pharmacokinetic analysis, patients receiving bosentan as a comedication had 35.6% higher clearance of riociguat compared to patients without bosentan as a co-medication. This translated to lowered exposures by ~27% in patients receiving bosentan as compared to patients not receiving bosentan.

Nitric oxide donors

The effect of a single dose of 0.4 mg nitroglycerin (NTG, Nitrolingual[®] mite) on the pharmacodynamics of a single dose of 2.5 mg riociguat immediate release tablet was evaluated following staggered dosing times (24, 8, 4 and 1 h post riociguat administration on days 1, 3, 6 and 9) in a placebo controlled study in healthy subjects (**14360**). Maximal decrease in seated SBP within 4 h post administration of riociguat/placebo was the pharmacodynamic endpoint.

Peak blood pressure reduction effect of both riociguat and nitroglycerin was observed at about 30 minutes post administration. As presented in **Table 3**, shortening the interval

between NTG and riociguat dosing resulted in a larger peak blood pressure reduction effect.

| Table 3 Model predicted | LS means) average maximal | change form pre-dose (NTG) |
|-----------------------------|---------------------------|----------------------------|
| levels in vital signs (Ref: | CSR 14360, table 14.2/3) | |

| | Day 1 (24h interval) | | | Day 3 (8 h interval) | | | |
|-----|----------------------|-------|------|----------------------|------|-------|--|
| | Rio | Plc | Diff | Rio | Plc | Diff | |
| SBP | -14.3 | -10.4 | -3.9 | -16.9 | -5.7 | -11.2 | |
| DBP | -14.7 | -8.3 | -6.3 | -15.3 | -7.1 | -8.2 | |
| HR | 11.8 | 8.7 | 3.1 | 17.9 | 8.2 | 9.6 | |

Model - TRT + TRTGP + SUB • (TRTGP) + PERIOD + BASELINE

The study was terminated because the blood pressure reductions were not considered to be safe and because of occurrence of syncope in the 4h interval dosing group.

Based on the above results, currently, the use of NO donors in individuals prescribed riociguat is contraindicated in the label.

Phosphodiesterase - 5 inhibitors

The effect of concomitant administration of sildenafil and riociguat on pharmacodynamics was evaluated in placebo-controlled Phase IIb study conducted in subjects with PAH receiving stable doses of sildenafil (20 mg *tid*) (**15096**, PATENT PLUS). Specifically, riociguat (1 to 2.5 mg *tid*) was individually titrated, on a background of stable sildenafil (20 mg *tid*) on SBP at the end of 12 weeks was evaluated.

The results of the study are presented in Table 4.

Table 4 Summary of SBP at visit 6 (end of 12 week controlled phase of study).

| Treatment (n) | VS Position | Mean SBP |
|------------------|-------------|----------|
| | | at EoS |
| Riociguat (n=10) | Standing | -18.0 |
| | Supine | -20.7 |
| Placebo (n=6) | Standing | -15.5 |
| | Supine | -17.8 |

As seen in **Table 4**, treatment with riociguat did not result in additional reduction in blood pressure. Additionally, change from baseline in 6MWD was numerically greater in the group randomized to receive placebo+sildenafil (30.2 m, n=5) as compared to riociguat+sildenafil (8.5 m, n=10) and there was no difference in pulmonary hemodynamic measures between the two treatment groups.

There was no pharmacokinetic interaction observed between sildenafil and riociguat in a separate study conducted in healthy subjects (**11917**).

Warfarin

The effect of repeat administration of riociguat 2.5 mg *tid* on the pharmacokinetics and pharmacodynamics of a single dose of 25 mg of warfarin was evaluated in a placebo-

controlled double-blind study in healthy subjects. As seen in **Figure 19**, mean prothrombin time was not affected by riociguat.



Figure 19 Mean prothrombin time course following a single dose of Coumadin.

The pharmacokinetics of riociguat was not affected by warfarin and similarly that of Sand R- warfarin was not affected by riociguat.

<u>Aspirin</u>

The effect of concomitant administration of aspirin and riociguat on the pharmacodynamics of aspirin was evaluated following administration of a single dose of ASA 500 mg and riociguat 2.5 mg. No significant effects on bleeding time, platelet aggregation or serum thromboxane was observed. However, at this dose, the effect of ASA is already on the upper plateau of the dose-platelet aggregation inhibition relationship making it hard to detect interactions, if any exist.

2.7.4 What other co-medications are likely to be administered to the target population?

Individuals with PH may receive vasodilators of endothelin receptor antagonists or prostacyclin analogs, other vasodilators such as diuretics and Ca²⁺ channel blockers, oral anticoagulants, and oxygen supplementation.

In Phase 3 studies a significant fraction of subjects received and ERA or a PCA, antihypertensives, and oxygen supplementation (**12934**, Table 8-12).

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutics classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Riociguat is a BCS class II (low solubility, high permeability) drug.

It is practically insoluble in water (4 mg/L), very slightly soluble in 0.1M HCl (250 mg/L), freely soluble in DMSO (109280 mg/L). In Phase 1 studies, both riociguat and M1 were detected in plasma 15 minutes post administration of an immediate release tablet, suggesting that the drug is highly permeable.

2.8.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the immediate release formulation?

The final to-be marketed formulation was used in the pivotal clinical trial. Hence, bioequivalence studies were not conducted for riociguat.

2.8.3 What is the effect of food on the bioavailability of the drug from the dosage form?

Food does not significantly affect systemic exposure to riociguat and M1 following administration of riociguat tablets (5 mg) with a standard high fat meal (**13010**). The 90% CI for AUC was contained within the pre-determined 80 to 125% BE limits (**Figure 20**) while C_{max} was ~ 35% lower.



Figure 20 Food does not affect the extent of absorption of riociguat. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BE metrics and the horizontal line represents the associated 90%CI. The reference is riociguat administered in fasted state.

2.9 Analytical Section

Details of the bioanalytical method used to support PK studies are presented in **Table 5**. The method satisfied all criteria for 'method validation' and 'application to routine analysis' set by the '*Guidance for Industry: Bioanalytical Method Development*', and was therefore acceptable.

| Report # | Method | Range | | Matrix | Validation |
|----------|------------|---------|-----------|--------|------------|
| | | Rio | M1 | | |
| M1213 | HPLC/MS/MS | 0.1-100 | 0.2-100 | plasma | Acceptable |
| M1286 | HPLC/MS/MS | 0.1-100 | 2-500 | plasma | Acceptable |
| M1370 | HPLC/MS/MS | 2-500 | 2-500 | plasma | Acceptable |
| M1250 | HPLC/MS/MS | 0.5-100 | 0.5-100 | plasma | Acceptable |
| M1425 | HPLC/MS/MS | 0.5-100 | 0.5-100 | plasma | Acceptable |
| M1425 | HPLC/MS/MS | 10-1000 | 10-1000 | urine | Acceptable |

Table 5Summary of the bio-analytical methods used.

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/s/

DIVYA MENON ANDERSEN 06/28/2013

DHANANJAY D MARATHE 06/28/2013

YANING WANG 06/28/2013

PING ZHAO 06/28/2013

HOBART ROGERS 07/01/2013

RAJANIKANTH MADABUSHI 07/01/2013

| BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment | | | | | |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|--|--|--|
| Application No.: | NDA 204-819 | | | | |
| Submission Date: | 2/8/2013; 3/22/2013; 5/28/2013 | Reviewer: Kareen Riviere, Ph.D. | | | |
| Division: | DCRP | Acting Team Leader: Sandra Suarez Sharp, Ph.D. | | | |
| Applicant: | Bayer Healthcare Pharmaceuticals, Inc. | nc. Acting Supervisor: Richard Lostritto, Ph.D. | | | |
| Trade Name: | Adempas | Date 2/13/2013 | | | |
| Generic Name: | Riociguat | Date of Review: 6/11/2013 | | | |
| Indication: | Treatment of patients with chronic thromboembolic pulmonary hypertension (WHO Group 4) and pulmonary arterial hypertension (WHO Group 1) | Type of Submission: 505(b)(1) Original NE | | | |
| Formulation/strengths: | IR Tablet/ 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg | | | | |
| Route of Administration: | Oral | | | | |

SUMMARY:

This submission is a 505(b)(1) New Drug Application for 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg Adempas (Riociguat) immediate release tablets. The proposed indications are for the treatment of patients with chronic thromboembolic pulmonary hypertension (WHO Group 4) and pulmonary arterial hypertension (WHO Group 1).

This submission includes a drug product development section with the proposed dissolution method and acceptance criterion. The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion.

A. Dissolution Method

The proposed dissolution method is shown below.

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|------------------|-------------------|-----------------|------|-----------------------------|
| 2 | 75 rpm | 900 mL | 37°C | pH 6.8 buffer w/0.1% SLS |

The proposed dissolution method has adequate discriminating power, and therefore is deemed acceptable.

B. Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion is shown below.

| Acceptance Criterion | | | |
|----------------------|---------|--|--|
| Q = | (b) (4) | | |

The proposed dissolution acceptance criterion is considered permissive. In an IR letter to the Applicant dated May 3,

2013, the ONDQA Biopharmaceutics Team recommended a dissolution acceptance criterion of $\mathbf{Q} = \begin{pmatrix} \mathbf{b} & \mathbf{q} \end{pmatrix}$ at 15 minutes based on the mean in-vitro dissolution profiles of the pivotal clinical batches at release. In a submission dated May 28, 2013, the Applicant accepted the team's recommendation.

Bases of Approval for the Lower Strengths

To support approval of the lower strengths (0.5 mg, 1.0 mg, 1.5 mg, and 2.0 mg), the Applicant conducted a relative BA study with lowest and highest strengths. Also, the Applicant conducted a dose proportionality study using all the proposed strengths. These data is under review by the Clinical Pharmacology reviewer.

<u>RECOMMENDATION</u>:

- 1. Adempas (riociguat) immediate release tablets, 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg are recommended for approval from a Biopharmaceutics standpoint.
 - The following dissolution method and acceptance criterion are recommended and have been agreed upon with the Applicant (submission dated May 28, 2013):
 - i. <u>Dissolution method</u>: Apparatus II, 75 rpm agitation rate, 900 mL media volume, 37 °C, pH 6.8 buffer with 0.1% SLS.
 - ii. Acceptance criteria: $Q = {}^{(b)(4)}$ at 15 minutes.

Comment to the CMC Review Team:

It is noted that the proposed particle size particle size for the clinical batches was criterion be revised (^{(b) (4)} ^{(b) (4)} for the API is permisive considering that the API (^{(b) (4)}). Therefore, we recommed that the particle size acceptance

<u>Kareen Riviere, Ph.D.</u> Biopharmaceutics Reviewer Office of New Drug Quality Assessment

Sandra Suarez Sharp, Ph.D. Acting Biopharmaceutics Team Leader Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

The Applicant considers riociguat as a BCS Class 2 compound. The structure of riociguat is shown in Figure 1.



Figure 1. Chemical structure of riociguat

Table 1 summarizes the solubility of riociguat in different organic solvents and in aqueous buffers at different pH values.

Table 1. Solubility in Organic Solvents and Aqueous Buffers at 25 °C

Table 2 presents the solubility of riociguat in different buffer solutions and in water at 37 °C.

(b) (4)

Reviewer's Assessment:

Drug Product

The Applicant stated that proposed commercial product is of the same core composition as the clinical phase III formulation (b) (4) The composition of the proposed commercial tablet formulation for all the proposed strengths is displayed in Table 3.

| Composition | Dose | | | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|--------|--------|--------|--------|---------|
| | Function | 0.5 mg | 1.0 mg | 1.5 mg | 2.0 mg | 2.5 mg |
| (Development no.) | | (501) | (502) | (503) | (504) | (505) |
| Drug substance | | | | | | |
| Riociguat micronized | drug substance | 0.50 | 1.00 | 1.50 | 2.00 | 2.50 |
| Excipients Cellulose microcrystalline Crospovidone Hypromellose 5 cP Lactose monohydrate Magnesium stearate Sodium laurilsulfate (b) (4) | | | | | | (b) (|
| (b) (4) | | | | | | |
| Film-coating Hydroxypropylcellulose Hypromellose 3 cP Propylene glycol Titanium dioxide Ferric oxide yellow Ferric oxide red | | | | | | |
| Weight (coated tablet) | | 87.5 | 87.5 | 87.5 | 87.5 | 87.5 |
| | | | | | | (b) (4) |

(b) (4)

(b) (4)

Reviewer's Assessment:

The strengths are considered proportionally similar in composition according to the BA/BE guidance. To support approval of the lower strengths, the Applicant conducted a relative BA study with lowest and highest strengths. Also, the Applicant conducted a dose proportionality study using all the proposed strengths. These data is under review by the Clinical Pharmacology reviewer.

2. Dissolution Method

The proposed dissolution method is shown below.

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|------------------|-------------------|-----------------|------|-----------------------------|
| 2 | 75 rpm | 900 mL | 37°C | pH 6.8 buffer w/0.1% SLS |

Dissolution Method Development

Selection of the Dissolution Apparatus

The drug product has been developed as an immediate release tablet formulation. The Applicant selected the USPapparatus 2 for the dissolution test of Riociguat Coated Tablets since it is widely used for tablet formulations.

Reviewer's Assessment:

The Application's justification for the selection of Apparatus 2 is acceptable.

Selection Dissolution Medium, Surfactant, and Surfactant Concentration

The solubility of Riociguat in different media is shown in Table 4.

Table 4. Solubility of Riociguat in Different Media

(b) (4)

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Reviewer's Table 1. API Particle Size Distribution of Batches Used in the Phase 3 Clinical Trials (b) (4)

(b) (4)

3. Dissolution Acceptance Criterion

The proposed acceptance criterion is shown below.



Figures 9 and 10 show the dissolution profiles for the lowest and highest strength of the proposed product using the proposed dissolution method.

Figure 9. Dissolution Profiles of Riociguat 0.5 mg IR Tablets Used in Different Stages of Clinical Development

Figure 10. Dissolution Profiles of Riociguat 2.5 mg IR Tablets Used in Different Stages of Clinical Development

Reviewer's Assessment:

Figures 9 and 10 demonstrate that greater than ^{(b) (4)} of the proposed product (used in Phase 3 studies) dissolves by 15 minutes. Hence, the dissolution acceptance criterion can be

The following IR comment was conveyed to the Applicant on

May 3, 2013.

FDA Comment

Based on the mean *in-vitro* dissolution profiles from the clinical batches at release, the following dissolution acceptance criterion is recommended: $Q = {}^{(b)(4)}$ at 15 minutes. We recommend that you revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product.

Bayer's Response

The dissolution acceptance criterion was revised to $Q = {}^{(b)(4)}$ after 15 minutes. The drug product specifications were amended. Sections 3.2.P.5.1, 3.2.P.5.2 and 3.2.P.5.6 are updated accordingly.

In a submission dated May 28, 2013, the Applicant accepted the team's recommendation. Thus, the dissolution acceptance criterion is acceptable.

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

/s/

KAREEN RIVIERE 06/11/2013

SANDRA SUAREZ 06/11/2013