Bayer HealthCare
Science For A Better Life

Briefing Document for
Cardiovascular and Renal Drugs Advisory Committee

Riociguat (BAY 63-2521)

Reviewer's Guide

This document provides 3 levels of review with increasing levels of detail:

1. Overview (page 12): Provides an extended review of key program characteristics, results, and conclusions. References are provided to supporting sections, tables, and figures in the Core Document.

2. Core Document (Sections 1 through 10 beginning on page 51): Includes detailed summaries and discussions in support of the Overview.

3. Appendices (beginning on page 196): Provide descriptions of scales/questionnaires, narratives for selected patients, and selected summary tables for individual, controlled, phase 3 studies. These appendices are referenced in the Core Document when relevant.

This review structure allows review at varying levels of detail; however, reviewers who read at multiple levels will necessarily encounter repetition of key materials across the levels.

For those reviewing this document in electronic format, references to table and figure are electronically linked to the corresponding table or figure. For those reviewing this document in paper format, the page number is provided when the table or figure is in a different section. Note that variability among printers may cause page numbers of printed documents to differ slightly from those provided.

06 August 2013 Advisory Committee Meeting

ADVISORY COMMITTEE BRIEFING MATERIALS
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List of Abbreviations Used in Text

6MWD	6-minute walking distance
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AUC	area under the curve
BCRP	breast cancer resistance protein
cGMP	cyclic guanosine monophosphate
CI	confidence interval
C_{max}	maximum observed concentration
CT	capped titration
CTEPH	chronic thromboembolic pulmonary hypertension
CTX	carboxy-terminal collagen crosslinks
CYP	cytochrome P_{450}
ECG	electrocardiogram
ERA	endothelin receptor antagonist
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
GFR	glomerular filtration rate
hERG	human ether-a-go-go related gene
IC_{50}	inhibitory concentation$_{50}$
IDT	individual dose titration
INR	international normalized ratio
LPH	Living with Pulmonary Hypertension
ITT	intent-to-treat
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	mean pulmonary artery pressure
NDA	New Drug Application
NO	nitric oxide
NT-proBNP	N-terminal prohormone brain-type natriuretic peptide
PAH	pulmonary arterial hypertension
PDE5	phosphodiesterase 5
pGC	natriuretic peptide- particulate (membrane-bound) guanylate cyclase
P-gp	P-glycoprotein
PVR	pulmonary vascular resistance
QTc	QT interval from ECG, corrected for heart rate
QTcB	QT interval from ECG, corrected for heart rate (Bazett formula)
QTcF	QT interval from ECG, corrected for heart rate (Fridericia formula)
REMS	Risk Evaluation and Mitigation Strategy
sGC	soluble guanylate cyclase
SAE	serious adverse event
SMQ	standardized MedDRA query
SULT	sulfotransferase
TID	three times daily
UGT	glucuronosyl transferase
ULN	upper limit of laboratory reference range
WHO	World Health Organization

Abbreviations used only in a table or figure are defined with the table or figure.

Overview

Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure (mPAP) >25 mmHg at rest as assessed by right heart catheterization. This clinical definition includes a group of diseases that share symptoms of dyspnea, fatigue, and reduced exercise capacity. Pulmonary hypertension has been classified into 5 groups (1):

- Group 1: PAH, which includes subtypes of idiopathic, heritable, and association with other diseases (e.g., connective tissue disease, infection with human immunodeficiency virus, portal hypertension, congenital heart disease);
- Group 2: Pulmonary hypertension associated with left heart disease, which includes atrial, ventricular, and valvular diseases;
- Group 3: Pulmonary hypertension associated with lung diseases and/or hypoxemia, which includes chronic obstructive pulmonary disease, interstitial lung disease, and sleep-disordered breathing;
- Group 4: Pulmonary hypertension due to chronic thrombotic and/or embolic disease, which includes CTEPH;
- Group 5: Miscellaneous

The main focus of the clinical development program for riociguat in the setting of pulmonary hypertension has been in Group 1 (patients with PAH) and Group 4 (patients with CTEPH).

Both CTEPH and PAH are rare. The number of patients with CTEPH from 1999 to 2007 was estimated as 63 patients per million among patients <65 years of age and 1007 patients per million among patients ≥65 year of age (2). The number of patients with PAH was estimated for these years as 109 patients per million among patients <65 years of age, and 451 for patients ≥65 years of age (2).

Although CTEPH and PAH are classified into different clinical groups, the similarities in symptoms, signs, and histopathology are summarized in Table 1. The most common symptoms of patients with CTEPH and PAH are dyspnea, fatigue, and reduced exercise capacity. The progressive nature of these symptoms is a consequence of structural and functional changes in the cardiopulmonary circulation. The signs and symptoms of these diseases depend on the severity of the disease. With the development of a significant degree of right ventricular dysfunction, exertional presyncope and syncope may become evident.

Both CTEPH and PAH are characterized by increased mPAP associated with pulmonary vascular resistance (PVR), which can lead to progressive right ventricular dysfunction/failure, and ultimately, premature death. Based on the pathophysiology, the pharmacologic activity of riociguat was expected to result in beneficial clinical effects in both CTEPH and PAH. Taken

together, the aforementioned was the rationale for designing 2 complementary and supporting phase III trials with riociguat in 2 related patient populations with pulmonary hypertension.

Although there are some common pathophysiological and histopathological similarities between CTEPH and PAH, important clinical differences in contributory mechanisms, diagnosis, and treatment are summarized in Table 1. For CTEPH, surgical pulmonary endarterectomy is the treatment of choice for patients with symptomatic, operable CTEPH. In many patients this is curative. There are no approved pharmacotherapies for patients with inoperable CTEPH or for patients with residual pulmonary hypertension following pulmonary endarterectomy.

There is no surgical cure for patients with PAH. Several vasodilator agents have been approved and these provide important symptomatic benefits to patients, and in some patients, may also improve long-term outcomes.

Pulmonary hypertension in CTEPH is due to chronic thrombotic and/or embolic disease. The etiology in PAH is more heterogeneous, including subtypes of idiopathic, familial, and association with other diseases (e.g., collagen vascular disease).

Table 1: Similarities and Differences in Chronic Thromboembolic Pulmonary Hypertension and Pulmonary Arterial Hypertension

	CTEPH	PAH
Similarities		
Symptoms	Shortness of breath (i.e., dyspnea), fatigue, weakness, syncope	
Signs	Pulmonary hypertension and right heart failure	
Histopathology	Plexogenic arteriopathy	
Differences		
Contributory mechanisms	Venous thromboembolic disease Potential role of endothelial dysfunction	Abnormal proliferation of endothelium and smooth muscle in vessel walls Potential other mechanisms
Diagnosis	Segmental perfusion defects on ventilation/perfusion lung scan Confirmation with right heart catheterization and pulmonary arteriography	No segmental perfusion defects on ventilation/perfusion lung scan Confirmation with right heart catheterization
Treatment	Pulmonary endarterectomy for patients considered operable	Medical treatments

Definition of abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension.

CTEPH is characterized by non-resolving thromboemboli that are located proximal or more distal in the pulmonary arterial tree. Pulmonary endarterectomy surgery is the treatment of choice for patients with symptomatic, operable CTEPH. Currently, there are no approved pharmacotherapies for CTEPH. A substantial proportion of patients with CTEPH are deemed inoperable, mainly due to criteria such as non-accessibility of thrombi, non-beneficial relation of PVR and anticipated thrombus mass, existing co-morbidities, or lack of decrease of pulmonary artery pressure after administration of inhaled NO at the diagnostic right heart catheterization (3). In addition, approximately 30% of patients who underwent surgery were found to have persistent or recurrent pulmonary hypertension (4). Postoperative persistent or recurrent pulmonary hypertension has been identified as the most important predictor of death. Of particular importance is the finding by Saouti et al (5) that baseline 6-minute walking distance (6MWD) was the only independent predictor of survival in inoperable CTEPH patients.

PAH is a uniformly fatal disease that affects adults and children, for which there is no cure. Despite the availability of several approved medicines to treat PAH, high morbidity and early

mortality remain a threat for the majority of patients (6). In 1984, the National Institute of Health compiled the first large registry of PAH patients confirming poor survival as the estimated median survival of these patients was 2.8 years (7, 8). While there have been improvements in PAH therapies, PAH remains a progressive and fatal disease. Advances in the understanding of the pathophysiology of PAH have led to introduction of specific treatments, including PDE5 inhibitors, endothelin receptor antagonists (ERAs), and prostanoids. These vasodilator agents provide important symptomatic benefits to patients, and may in some patients also improve long term outcomes.

The histopathological hallmark of all forms of pulmonary hypertension, regardless of the specific etiology, is the presence of structural changes to the pulmonary arterial vasculature, principally due to medial and adventitial thickening of the arteries and arterioles, a process termed vascular remodeling (9). This remodeling process is frequently observed in tandem with intimal proliferation, *in situ* thrombi, deposition of extracellular matrix (fibrosis) and inflammation. Despite having different clinical classifications (1), CTEPH and PAH share a common microvasculopathy, considered to be a main component of disease progression (Table 6, page 58).

Riociguat

Riociguat is the first-in-class of a new group of compounds, soluble guanylate cyclase (sGC) stimulators. Soluble guanylate cyclase is a key enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). Both CTEPH and PAH are associated with endothelial dysfunction, leading to an imbalance in circulating levels of endogenous vasodilators and vasoconstrictors. Impaired synthesis of NO, and insufficient stimulation of the NO-sGC-cyclic guanosine monophosphate (cGMP) pathway has been well-described in PAH. Riociguat directly stimulates sGC, thereby increasing levels of the signaling molecule cGMP. The cGMP molecule plays a pivotal role in regulating cellular processes, such as vascular tone, proliferation, fibrosis, and inflammation. Two key features of riociguat are (i) it directly stimulates sGC independently of NO, and (ii) it sensitizes sGC to low levels of NO (10). Collectively, these dual effects restore the NO-sGC-cGMP pathway.

Accumulating data suggest that some patients with CTEPH and PAH may have NO deficiency that limits the efficacy of phosphodiesterase 5 (PDE5) inhibitors. The PDE5 inhibitors act on the NO pathway by preventing cGMP degradation; however, these compounds are dependent on cGMP synthesis and the presence of NO. Riociguat's ability to directly stimulate sGC independently of NO enables it to be efficacious even in a NO-deficient state, and thus makes it unique in the setting of pulmonary hypertension. Riociguat has a different mechanism of action from all other drugs currently approved for PAH and is the first sGC stimulator to be evaluated in patients with CTEPH or PAH.

Currently, there are no approved pharmacotherapies for CTEPH. A series of small, non-controlled studies with drugs indicated for PAH have suggested some benefit in this patient

population, but the first randomized controlled study of bosentan in this indication failed to achieve its coprimary endpoints (11). However, CHEST-1 is the largest randomized, placebo-controlled study conducted to-date in CTEPH and is the first study to demonstrate a statistically significant difference from placebo for the primary efficacy endpoint, thereby establishing clinical benefit in this disease.

In the expert pulmonary hypertension community, there is widespread agreement on the need for new pharmacotherapies. Additionally, the treatment of PAH has undergone an evolution in the past few years. The average survival of patients with PAH is estimated to be 4 to 5 years after diagnosis. The seriousness of the disease, the inability of single drugs to prevent deterioration, and the fact that the approved drugs target different vasodilator pathways have made combination therapy a necessity for most patients. In the largest PAH registry conducted to-date, which includes 2,525 adults in the United States meeting traditional haemodynamic criteria, nearly half of the patients are treated with 2 or more PAH-specific medications (12). Nevertheless, many patients still deteriorate on combination therapy, creating a major unmet medical need in these patients.

While combination therapy has mechanistic and biological plausibility, there remains a paucity of data to support this emerging practice (13, 14, 15). In the PATENT 1 study, however, both treatment-naïve patients and patients on stable pre-treatment therapy with an ERA or a non-intravenous prostacyclin analogue were enrolled. Pre specified subpopulation analyses of patients who were therapy-naïve, pre-treated with ERAs, or pre-treated with prostacyclin analogues demonstrated the efficacy of riociguat in each of the subpopulations. These results provide robust, new information for clinicians regarding the efficacy and safety of add-on combination therapy for patients with PAH.

Proposed Indication

Bayer HealthCare has submitted a New Drug Application (NDA) for the use of riociguat to treat adult patients with chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). The proposed indications for riociguat are the treatment of adult patients with:

PAH (Group 1) to improve exercise capacity, WHO functional class, and to delay clinical worsening.

CTEPH (Group 4) with inoperable CTEPH or with persistent or recurrent CTEPH after surgical treatment to improve exercise capacity and World Health Organization (WHO) functional class, and

Clinical Program for Riociguat

The phase III clinical development program for riociguat in patients with CTEPH and PAH was designed based on input from the United States Food and Drug Administration (FDA). The objective was to have 2 complementary and supportive studies in 2 rare populations of patients with pulmonary hypertension, defined by different etiologies, who are in need of new therapeutic options. The 2 randomized, double-blind, placebo-controlled phase III studies had a similar design and used the same efficacy endpoints, which are widely accepted and used to assess efficacy in patients with pulmonary hypertension (16, 17). The 2 complementary phase III studies consist of a study conducted in patients with CTEPH (CHEST-1) and a second study in patients with PAH (PATENT-1). The shared pathology, signs and symptoms, and the mechanism of mortality (right ventricle failure due to increased pulmonary arterial pressure) provided the rationale for investigating the potential therapeutic benefit of riociguat in both CTEPH and PAH (Section 1.4, page 53).

Dose Recommendations for Riociguat (Section 2.4 [page 60] and Section 7 [page 176])

The Sponsor proposes dose titration of riociguat to establish an individualized dose per patient. The use of titration to safely increase dose to efficacious levels is an accepted and common practice in many therapeutic areas and is analogous to the treatment of PAH with parenteral prostanoids and of systemic hypertension (e.g., captopril which is initiated at 25 mg twice daily or 3 times daily [TID] and increased to 50 mg twice daily or TID). We make this proposal for riociguat based on the following:

- Pathophysiology of patients with pulmonary hypertension
- High between-patient variability in pharmacokinetics
- Certain intrinsic and extrinsic factors that affect riociguat exposure

It is well established that patients with CTEPH and PAH are characterized by chronic exposure to high pulmonary resistance, high pulmonary pressure, low cardiac output, and tendency to right heart failure resulting in low systolic blood pressure. The long-term persistence of these characteristics may make patients more sensitive to treatment, resulting in rapid and strong hemodynamic responses.

Early in development, pharmacokinetic/pharmacodynamic analyses demonstrated a close relationship between riociguat plasma concentrations and hemodynamic effects such as decreases in systemic and pulmonary vascular resistance, decrease in systolic blood pressure, and increase in cardiac output. Importantly, high between-patient variability in pharmacokinetics (coefficient of variation of approximately 60% across all doses) was observed, suggesting that a fixed dose of riociguat for all patients was not possible. The close relationship of riociguat exposure to its intended effect, coupled with between-patient variability, was anticipated to result in high between-patient variability in the efficacy response at a given dose.

Intrinsic factors such as severe renal and hepatic dysfunction, advanced age, and disease state, as well as extrinsic factors like co medication with strong multi-pathway inhibitors, and metabolic induction from smoking affect riociguat exposure.

Based on these biologic characteristics we developed an individual dose titration (IDT) scheme to be evaluated in our clinical program. Early in the program we conducted a single dose hemodynamic study that showed that 1.0 mg elicited clinically relevant changes in hemodynamic variables as measured by right heart catheter in patients with pulmonary hypertension and was the minimal effect dose in healthy subjects.

This information provided the rationale to start with a low dose of riociguat, then titrate slowly (2-week intervals), with the possibility to titrate to a dose of 2.5 mg TID. Indeed, this gradual IDT from 1 mg TID up to 2.5 mg TID, guided by monitoring of systolic blood pressure and signs/symptoms of hypotension, was developed in phase II, and provided the rationale for its use in phase III. Low within-patient variability (coefficient of variation of approximately 35%) was anticipated to provide consistent efficacy across time for an individual patient once an appropriate dose was established during titration. This was demonstrated successfully for CTEPH and PAH patients in Study 12166 (including long-term follow-up), and has been validated in phase III, with the majority of patients in the long-term extension studies being maintained on 2.5mg TID. A single dose of 5 mg riociguat caused a pronounced reduction in systolic blood pressure in patients with pulmonary hypertension and relevant symptomatic orthostatic hypotension in healthy subjects. A single dose of 2.5 mg was tolerated. This was confirmed in the multiple dose studies such as phase II Study 12166. Therefore, the 2.5 mg TID dose was chosen as the highest dose for phase III studies.

Individual dose titration ensures adequate therapeutic exposure in patients, and prevents underdosing of patients. The goal of IDT in phase III was to safely maximize the clinical benefits (exercise capacity and hemodynamics) for each patient with CTEPH or PAH by titrating each individual patient to the highest tolerated dose.

Choice of Dosing Interval

A TID regimen was chosen instead of a twice daily regimen to increase tolerability and reduce the incidence of symptomatic hypotension. Riociguat has a close and direct relationship between plasma concentrations and blood pressure. Riociguat has a mean half-life of about 13 hours with high inter-patient variability, and a range of 4 to 29 hours. Therefore, in order to bring all patients to effective riociguat plasma concentrations while preventing symptomatic blood pressure drops associated with peak concentrations, the TID regimen was considered preferable.

The TID dosing interval was successfully implemented in phase II Study 12166.

Choice of Titration Interval

Dose increases of 0.5 mg TID every 14 days at the discretion of the treating physician was considered appropriate based on phase II results. Dose decreases based on tolerability could be

made at any time. Pharmacokinetic steady-state was demonstrated after 3 days and pharmacodynamic steady-state (blood pressure) after 10 to 14 days. This slow and stepwise titration allows for adaptation to the altered hemodynamic state with decreasing PVR and increasing cardiac output compensating for the simultaneous decrease in systemic vascular resistance.

The 14-day titration interval was successfully implemented in phase II Study 12166.

Tablet Strengths

Five tablet strengths of riociguat (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg) were used in the phase III clinical program so that patients took 1 tablet TID, regardless of dosage. The Sponsor is requesting that all 5 tablet strengths of riociguat be approved in order to facilitate titration with minimal confusion for the patient

Phase III Results Supporting Individual Dosing

Each individual phase III study (CHEST-1 and PATENT-1) demonstrated clinically meaningful and statistically significantly superior efficacy of riociguat IDT compared with placebo for the primary endpoint. Thus, the choice of the IDT regimen was validated in phase III. An additional capped titration (CT) regimen of riociguat was included in PATENT-1; for this group, the maximum daily dose was 1.5 mg TID.

Although the number of patients included in the exploratory arm of the CT group is small and the results must be treated with caution, it is noteworthy that the mean change from baseline in 6MWD patients randomized to the riociguat CT group of PATENT-1 was similar to the mean change in baseline of riociguat IDT group (mean change to final visit of 31.1 meters and 29.6 meters in the riociguat CT and IDT groups, respectively). There were, however, further improvements shown in the IDT group titrated to 2.5 mg. The mean change from baseline to last visit showed hemodynamic improvement in the riociguat IDT group compared to the riociguat CT group for 2 clinically important measures:

- PVR: Mean change from baseline to last visit was -8.9 in the placebo group, -223.3 in the riociguat IDT group, and -167.8 dyne*second*cm^{-5} in the riociguat CT group.
- Cardiac output: Mean change from baseline to last visit was -0.01 in the placebo group, 0.93 in the riociguat IDT group, and 0.42 L/min in the riociguat CT group.

The hemodynamic measurements of PVR and cardiac output are objective markers of disease severity and are used by clinicians in addition to 6MWD to monitor the clinical progress and response to therapy of patients with pulmonary hypertension.

The safety database in PATENT-1 comparing IDT to CT is relatively small, making it difficult to discern a clear dose-related difference in the adverse event (AE) profile between the 2 randomized groups. However, a larger proportion of patients in the riociguat CT group than the

riociguat IDT group reported at least 1 AE and at least 1 serious adverse event (SAE). Thus, it appears that titration to a maximum dose of 2.5 mg TID is not associated with an increase in AE or SAE reporting.

The data clearly support that the riociguat CT with a maximum dose of 1.5 mg TID can be an effective and safe dose in patients with PAH. However, patients who can tolerate higher doses of riociguat may have additional clinical benefit.

The worsening of cardiopulmonary parameters in the progression of pulmonary hypertension requires flexible management to improve these parameters. The data of both PATENT-1 and CHEST-1 confirmed the usefulness of the 2.5 mg TID maximum dose when individualizing dose in the management of pulmonary hypertension. Many patients may benefit from a dose of 1.5 mg, but some will require further dose escalation in order to achieve maximum benefit. Further, the gradual dose escalation from 1.5 mg to 2.5 mg is well tolerated and does not appear to be associated with incremental safety concerns.

In summary, the PATENT-1 and CHEST-1 studies established that IDT dosing of riociguat (beginning at 1 mg TID and titrating to 2.5 mg TID, based on symptoms and systemic blood pressure) is safe and effective in both CTEPH and PAH, and should be the recommended dosing approach. The exploratory CT treatment group from the PATENT-1 study provides additional important information for prescribers. Although these data suggest that many patients with PAH may derive benefit from riociguat at a dose of 1.5 mg TID, dose escalation may be needed for these patients following disease progression and worsening hemodynamic status. Due to a variety of factors (e.g., variability in pharmacokinetics or in pharmacodynamic sensitivity to the vasodilating effects of riociguat), there are patients who will derive additional benefit from doses up to 2.5 mg TID. In both PATENT-1 and CHEST-1, the preponderance of patients were safely and successfully titrated to 2.5 mg TID and have continued on this dose for an extended period in the long-term extension studies.

Given that the goal of clinical therapy with riociguat should be to establish the safest effective dose for each patient, the availability of 5 tablet strengths will facilitate titration with minimal confusion for the patient.

Phase II Studies of Riociguat in CTEPH and PAH

Study 11874 was a single-dose, proof-of-concept study that evaluated invasive hemodynamics in 19 patients with PAH, CTEPH, and interstitial lung disease-associated pulmonary hypertension. Riociguat proved to be safe and well tolerated and showed efficacy based on invasive hemodynamic measurements. Individual titration seemed necessary due to the pronounced between-patient variability for the maximum plasma concentration of riociguat and overall drug exposure. Mean change from baseline for the 2.5 mg dose group was -5.1 mmHg for mPAP, -168 dyne*second*cm^{-5} for PVR, -546 dyne*second*cm^{-5} for systemic vascular resistance, and +0.95 L/min/m^2 for cardiac index.

Study 12166 was multicenter, non-randomized, non-blinded, and non-controlled. It was intended to show the feasibility and safety of IDT regimen of riociguat based on systolic blood pressure (Section 5.3 , page 127). Inclusion and exclusion criteria as well as study endpoints were similar to study CHEST-1 but included patients diagnosed with CTEPH as well as PAH. Patients were analyzed after a 12-week non-blinded and non-controlled treatment phase. Thereafter the patients could continue treatment with riociguat and enter a long-term extension phase. The treatment period for individual patients was up to 4.5 years at the time of the interim analysis.

Patients received riociguat starting with 1.0 mg TID, and depending on the patient's systolic blood pressure measured every 2 weeks, the riociguat dose was up- or down-titrated for the first 8 weeks by 0.5 mg TID or maintained. The lower and upper limits of daily dosing were 0.5 mg TID and 2.5 mg TID, respectively. During long-term extension, down- or titration of the study treatment dose was in the range of 0.5 mg TID to 2.5 mg TID.

For the 6MWD, clinically relevant improvements were observed after 14 days of treatment with riociguat. The increase was 61 meters until the end of titration on Day 56 and 68 meters until Day 84. Sixty-eight patients entered the extended treatment phase, including patients with CTEPH or PAH. Improvements in 6MWD were sustained during the period up to the 4.5 year observation period. Consistent improvements throughout both phases of the study were seen for other efficacy variables such as Borg CR 10 score, WHO functional class, and N-terminal prohormone brain-type natriuretic peptide (NT-proBNP).

Phase III Studies of Riociguat

The efficacy of riociguat for the treatment of CTEPH and PAH is primarily based on CHEST-1 in patients with CTEPH and PATENT-1 in patients with PAH. The 2 multicenter studies were randomized, parallel group, double blind, and global. CHEST-1 and PATENT-1 were designed and conducted in consultation with the FDA and in accordance with the international guidelines for the diagnosis and treatment of patients with pulmonary hypertension. The studies were conducted in accordance with Good Clinical Practices and with the ethical principles set forth in the Declaration of Helsinki.

Both studies included an 8-week titration phase, during which the dose of study medication was titrated from a starting dose of 1.0 mg TID by the investigators in steps of 0.5 mg every 2 weeks using the patient's systolic blood pressure as a safety measure. The dose of study medication was titrated to a maximum dose of 2.5 mg TID, using dose strengths of 1.5 mg, 2.0 mg and 2.5 mg. Every dose was given as a single film-coated tablet with or without food.

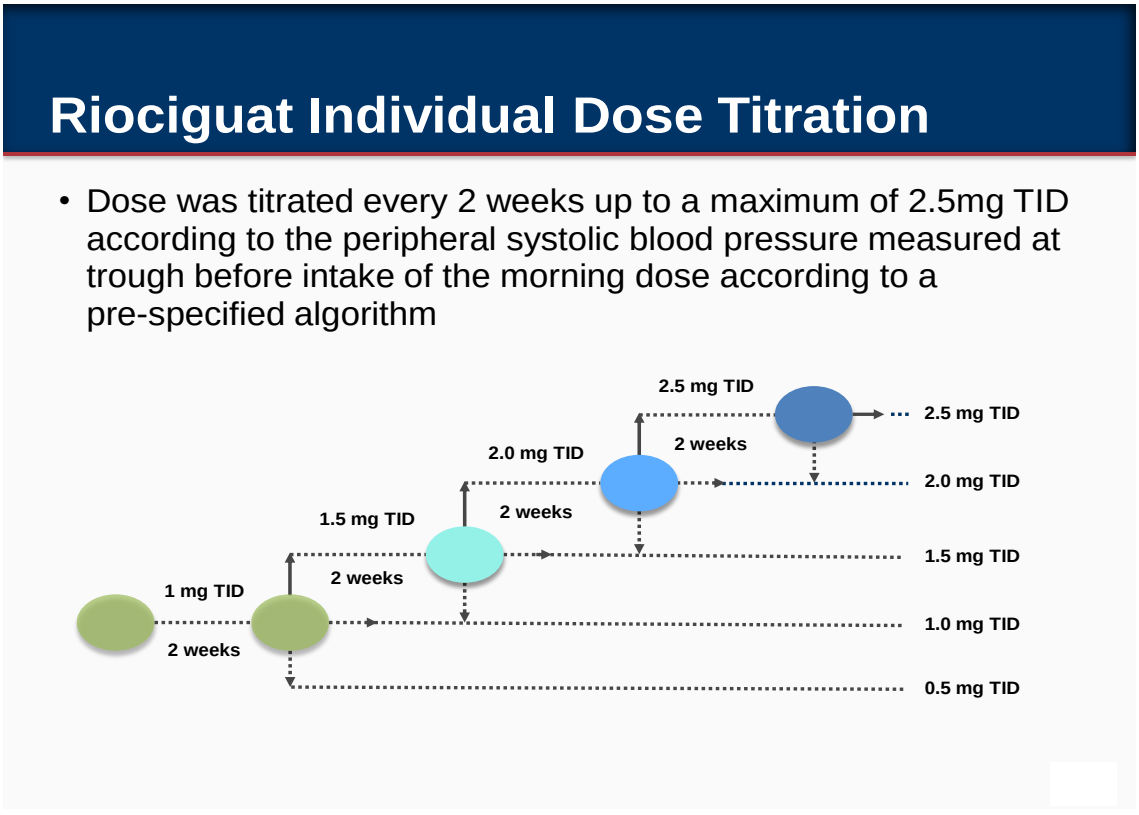
Blood pressure and heart rate were measured after the patient had been at rest for 10 minutes in a supine position. The same arm was to be used for these measurements. The non-invasive measurement was preferably with a mercury sphygmomanometer or a validated electronic device in accordance with published guidelines. The systolic blood pressure was measured at trough

before intake of the morning dose. The dose of study medication was adjusted in CHEST-1 and PATENT-1 based upon the following IDT scheme:

- If trough systolic blood pressure ≥95 mmHg, increase dose by 0.5 mg TID.
- If trough systolic blood pressure 90 to 94 mmHg, maintain dose.
- If trough systolic blood pressure <90 mmHg without symptoms of hypotension, reduce dose by 0.5 mg TID.
- If any systolic blood pressure <90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, stop study treatment; restart after 24 hours with dose reduced by 0.5 mg TID.

Modifications were permitted in the case of side effects (e.g., symptomatic hypotension), including down-titration to 0.5 mg TID. The IDT scheme for CHEST-1 is illustrated in Figure 1. The IDT was the same in PATENT-1; however, the total study duration was 12 weeks.

Figure 1: Individual Titration Dosing Scheme for Study Medication in CHEST-1



PATENT-1 included an additional exploratory riociguat CT group (titration from 1.0 mg to 1.5 mg TID). After reaching the 1.5 mg dose level, patients in the riociguat CT group underwent a sham titration in order to maintain blinding.

The primary endpoint in both studies was the change in 6MWD from baseline until end of study (after 16 weeks in CHEST-1 and after 12 weeks in PATENT-1). The 6MWD is widely acknowledged in the expert community to be clinically meaningful, as it reflects the ability of patients with pulmonary hypertension to perform usual activities of living. The 6MWD is routinely used in clinical practice to assess response to therapy and the overall clinical status of the patient. Moreover, the 6MWD correlates with disease severity and is a prognostic indicator of survival in patients with PAH (18). Data from the REVEAL Registry (12) and the French Registry demonstrate that the baseline 6MWD is predictive of outcome in PAH (19). Additionally, work by Saouti and co-workers (5) as well as Reesink et al. (20) suggests a positive correlation between the 6MWD and survival in patients with CTEPH.

Both studies included multiple, clinically relevant secondary endpoints to provide a more comprehensive picture of the efficacy of the drug. The secondary efficacy endpoints in both studies were:

- Change in PVR from baseline until end of study.
- Change in NT-proBNP from baseline until end of study.
- Change in WHO functional class (Appendix 11.1, page 196) from baseline until end of study.
- Time to clinical worsening, defined as time to the first occurrence of death (all-cause mortality), heart/lung transplantation, atrial septostomy, non-transient hospitalization due to persistent worsening of pulmonary hypertension, start of new pulmonary hypertension specific therapy or change of pre-existing ERA or prostacyclin analogue treatment due to worsening pulmonary hypertension, decrease in 6MWD at 2 consecutive visits due to worsening pulmonary hypertension or persistent (2 consecutive visits) worsening of WHO functional class due to deterioration of pulmonary hypertension
- Change in Borg CR 10 score (Appendix 11.2, page 197) measured at the end of the 6MWD test from baseline until end of study.
- Change in EQ-5D questionnaire (Appendix 11.3, page 199) from baseline until end of study. The EQ-5D is a standardized health outcome instrument. For the analysis, the answers to the 5 questions (each with 3 categories) were combined to a score which has a range of possible values from -0.594 (worst outcome, all 5 questions answered with 3) to 1.00 (best outcome, all 5 questions answered with 1).

- Change in Living with Pulmonary Hypertension (LPH) questionnaire (Appendix 11.4, page 200) from baseline until end of study. The LPH questionnaire is a quality of life instrument with a total score of 0 (no effect of pulmonary hypertension) to 105 (maximal effect of pulmonary hypertension).

The primary analysis set for efficacy analyses in both studies was the Safety/intent-to-treat (ITT) population, which was defined as all randomized patients who received at least 1 dose of study medication. Superiority of the riociguat IDT group over the placebo group was to be declared if the 2-sided significance level was less than or equal to 0.05 for the comparison of treatment groups for the primary efficacy variable. The secondary efficacy variables were to be formally tested for statistical significance of a difference between the riociguat IDT group and the placebo group only if the primary comparison was statistically significant at the 2-sided 5% level. A sequential testing procedure was to be performed for the 7 secondary efficacy variables, in the following order: PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg CR 10 score, EQ-5D, and LPH. Further details on statistical methods are provided in Section 5 (page 87).

Missing values were imputed with last observation carried forward, except imputation with worst value (e.g., 0 meters for 6MWD) for patients who died or withdrew due to clinical worsening without a 6MWD being measured at a termination visit.

CTEPH Efficacy Findings in CHEST-1

The CHEST-1 study is the largest study to-date in this patient population and the first randomized, placebo-controlled study in patients with CTEPH to meet its primary endpoint. CHEST-1 was a phase III, double-blind, randomized, multicenter, multinational, placebo-controlled study of the efficacy and safety of oral riociguat in patients with CTEPH (Section 5.1.1, page 92).

To be eligible for inclusion, patients had to have a diagnosis of inoperable or postoperative CTEPH and a baseline 6MWD test between 150 meters and 450 meters, inclusive. Patients with inoperable CTEPH had to have a PVR >300 dyne*second*cm^{-5} measured at least 90 days after start of full anticoagulation and mPAP >25 mmHg; inoperability was adjudicated by an experienced surgeon or a central adjudication committee. Patients with postoperative CTEPH (persisting or recurrent pulmonary hypertension after pulmonary endarterectomy) had to have a PVR >300 dyne*second*cm^{-5} measured at least 180 days after surgery. Patients were to be therapy-naïve with respect to PAH-specific medications. Patients pre-treated with NO donors in the 90 days prior to Visit 1 (randomization) or with ERAs, prostanoids, or specific (e.g., sildenafil or tadalafil) or unspecific phosphodiesterase inhibitors were not eligible for the study. Concomitant intake of such medications was not permitted during the treatment phase of the study.

Eligible patients were randomized in a 2:1 ratio (262 randomized patients) to receive riociguat or placebo TID as an IDT (Figure 1, page 22). The starting dose was 1.0 mg riociguat or placebo TID. The 3 daily doses were to be taken 6 to 8 hours apart during waking hours. A riociguat CT group was not included in the study.

The titration phase was followed by an 8-week main study phase (from Visit 5 to Visit 7). During the main study phase, all patients were to remain on their optimal dose of riociguat or placebo, as decided by the investigator based on the patient's systolic blood pressure at Visit 5 at the end of the titration phase. Dose reductions for safety reasons were allowed, but a subsequent re-increase during the main study phase was not possible.

At the end of the treatment period of 16 weeks, eligible patients had the option to enter an open-label extension trial (CHEST-2) where all patients were to be treated with an individual optimal dose of riociguat. The 19 patients who stopped study medication prematurely during the study and 6 additional patients who chose not to enter the open-label extension trial entered a 30-day safety follow-up phase.

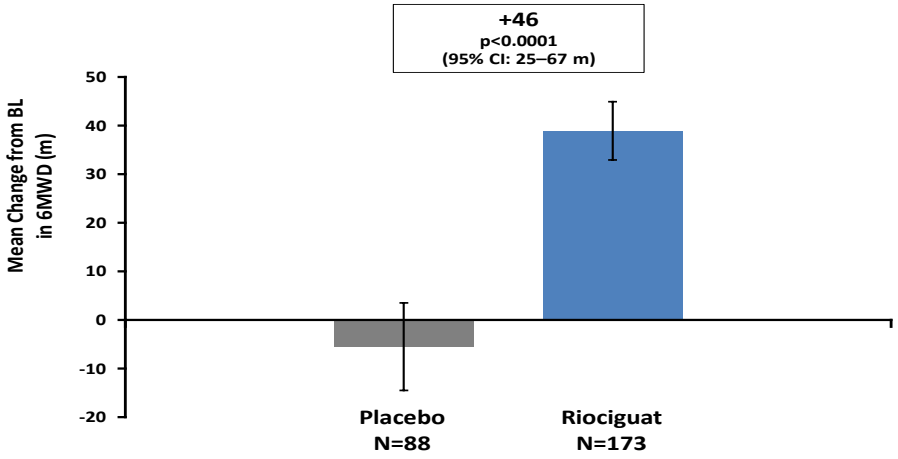
There were 446 patients enrolled in CHEST-1 at 89 study centers in 26 countries worldwide. Of these 446 enrolled patients, 184 failed screening criteria (most frequently due to confirmation of operability) and 261 of the 262 randomized patients received study medication (173 riociguat and 88 placebo). All 261 randomized, treated patients were included in the Safety/ITT population. The completion rate for the study was high (92.7% of randomized patients) and similar for the 2 treatment groups (Table 8, page 94).

The treatment groups were comparable with respect to demographic characteristics (Table 9, page 95). More than 60% of patients were female and approximately 70% of patients were white. Few patients were classified as black (<5%). Mean age was approximately 59 years in each treatment group and approximately 40% of patients in each treatment group were ≥65 years of age. The majority of patients in each treatment group had never smoked and approximately half of patients in each treatment group reported no alcohol consumption.

In both treatment groups, the majority of the patients had a diagnosis of inoperable CTEPH (69.9% riociguat IDT, 77.3% placebo group). More than 60% of patients in each treatment group were in WHO functional class III at baseline (61.8% riociguat IDT, 68.2% placebo). Most of the other patients in each group were in WHO functional class II (31.8% riociguat IDT, 28.4% placebo). The proportion of patients with a baseline 6MWD of less than 320 meters was slightly higher in the riociguat IDT group (34.7% riociguat IDT, 28.4% placebo).

In the primary efficacy analysis, treatment with riociguat IDT resulted in a statistically significant and clinically relevant improvement in 6MWD from baseline to last visit as compared to placebo in the Safety/ITT population (Figure 2). Sensitivity analyses indicated that there was clear evidence of a treatment effect regardless of the method used to take account for missing data.

Figure 2: Primary Endpoint: Mean (with Standard Error Bar) Change in 6MWD From Baseline to Last Visit in CHEST-1 (Safety/ITT Population)



Definition of abbreviations: 6MWD = 6-minute walking distance; BL = baseline; CI = confidence interval; ITT = intent-to-treat; m = meters.
Baseline means: 342.3 meters riociguat; 356.0 meters placebo.
Least squares mean treatment difference for change from baseline = 45.69 with 95% confidence interval of 24.74 to 66.63 ($p<0.0001$ for stratified Wilcoxon test).

The point estimate of the treatment difference for change the 6MWD from baseline to last visit suggested benefit in the pre-defined subgroups (Figure 3). The 95% confidence interval (CI) excluded zero in most subgroups with larger sample sizes. Consistent results with respect to the treatment difference for 6MWD were also seen for subgroups defined by weight, renal function, and cardiac function (not shown).

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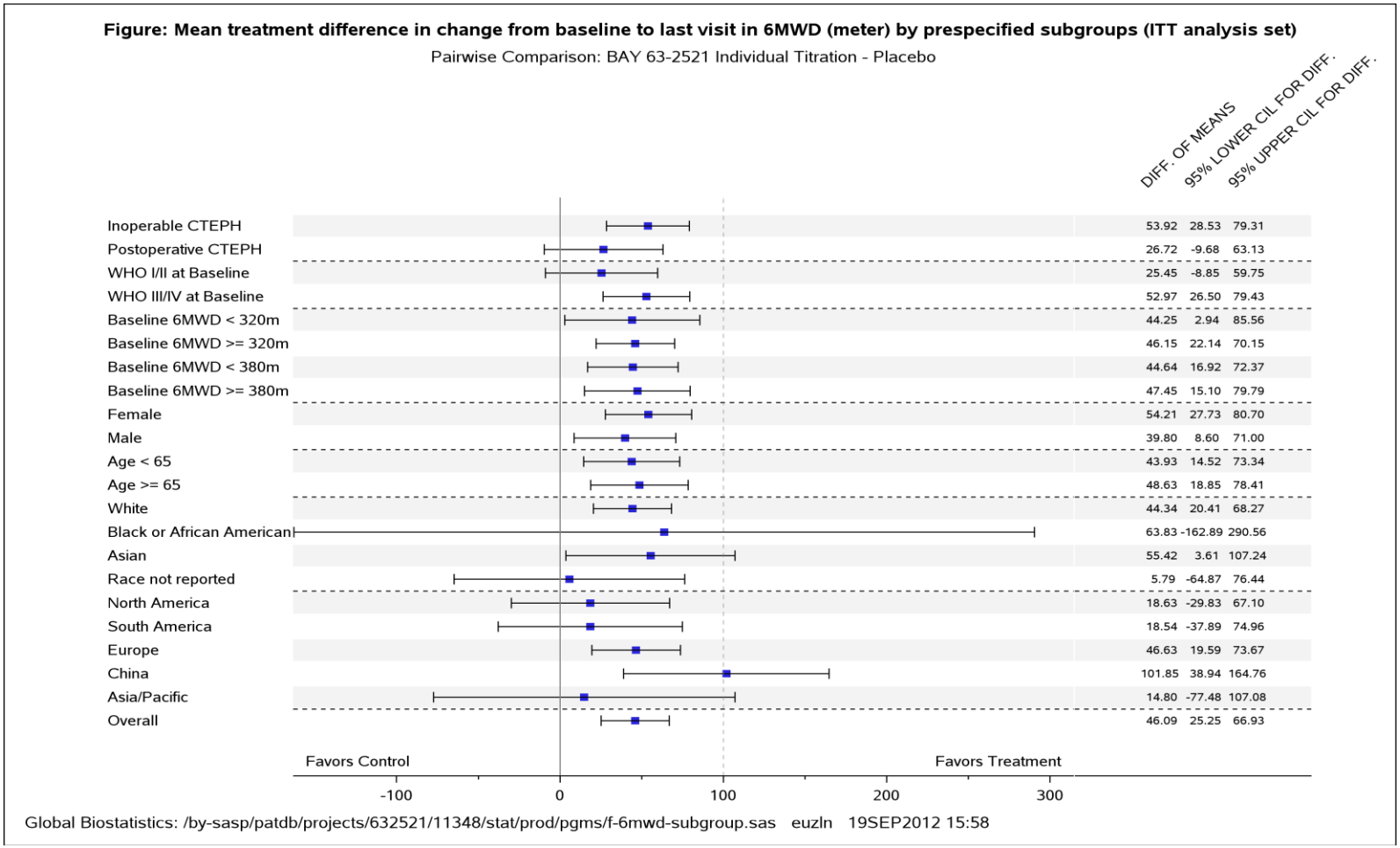
Figure 3: Subgroup Analyses: Mean Treatment Difference in Change in 6MWD From Baseline to Last Visit by Pre-specified Subgroups in Study CHEST-1 (Safety/ITT population)



Definition of abbreviations: 6MWD = 6-minute walking distance; CIL = confidence interval limit; CTEPH = chronic thromboembolic pulmonary hypertension; ITT = intent-to-treat; WHO = World Health Organization.

Number of patients (riociguat/placebo) in each subgroup:

Type of CTEPH: inoperable CTEPH (n = 121/68) and postoperative CTEPH (n = 52/20)
WHO functional class at baseline: I/II (n = 58/25) and III/IV (n = 115/62)
Baseline 6MWD: <380 meters (n = 109/50) and ≥380 meters (n = 64/38)
Sex: female (n = 118/54) and male (n = 55/34)
Age: <65 years (n = 99/52) and ≥65 years (n = 74/36)
Race: White (n = 120/65), Asian (n = 37/20), Black (n = 7/1), and not reported (n = 8/2)
Region: North America (n = 15/9), Europe (n = 104/53), Asia/Pacific (n = 18/9), South America (n = 15/6) and China (n = 21/11)

Treatment with riociguat IDT also resulted in a consistent improvement across the secondary efficacy variables of PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg CR 10 score, EQ-5D questionnaire, and LPH questionnaire. Based on the hierarchical testing procedure, secondary endpoints with a statistically significant improvement for the riociguat IDT group compared to placebo were PVR, NT-proBNP, and WHO functional class. Mean change in secondary endpoints from baseline to last week of treatment is summarized in Table 2. Results for the percentage of patients with changes in WHO functional class and for time to clinical worsening are presented following the table of mean changes.

Table 2: Mean Change in Secondary Endpoints From Baseline to Last Visit in Study CHEST-1 (Safety/ITT population)

	Mean (Standard Deviation) Change		
Endpoint	**Placebo (N=88)**	**Riociguat IDT (N=173)**	**Stratified Wilcoxon p-value**
PVR (dyne*second*cm^{-5})	23.1 (273.5)	–225.7 (247.5)	<0.0001
NT-proBNP	76.4 (1446.6)	–290.7 (1716.9)	<0.0001
Borg CR 10 score	0.17 (2.42)	–0.83 (2.39)	0.0035
EQ-5D questionnaire	–0.082 (0.345)	0.062 (0.277)	<0.0001
LPH questionnaire	–2.09 (19.31)	–6.72 (18.62)	0.1220

Definition of abbreviations: IDT = individual dose titration; ITT = intent-to-treat; LPH = Living with Pulmonary Hypertension; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PVR = pulmonary vascular resistance.
Shaded p-values are not considered statistically significant per hierarchical testing procedure.

A larger proportion of patients in the riociguat IDT group than in the placebo group had an improvement of at least 1 class in WHO functional class (32.9% versus 14.9%; Table 13, page 102). Additionally, a smaller proportion of patients in the riociguat IDT group than in the placebo group had a deterioration of at least 1 class in WHO functional class (5.2% versus 6.8%). The treatment group difference in the distribution of changes was statistically significant (p=0.0026).

The difference in time to clinical worsening between the riociguat IDT group and the placebo group in the Safety/ITT population was not statistically significant (p=0.1724, stratified log-rank test). This was to be expected because the study sample size was not powered to show statistical significance for this clinical endpoint, the treatment duration of the study was relatively short, and the overall number of events was low as expected. However, with 4/173 (2.3%) patients with events in the riociguat IDT group and 5/88 (5.7%) patients with events in the placebo group, there is a trend (not statistically significant) towards an improvement in clinical worsening for the active treatment.

CTEPH Efficacy Findings in CHEST-2

Study CHEST-2 is an ongoing phase III, open-label, multicenter, multinational, extension study of the long-term safety and efficacy of oral riociguat in patients with CTEPH (Section 5.1.2, page 103). The study included patients who had completed 16 weeks of treatment in the double-blind CHEST-1. Of the 243 patients who completed CHEST-1, 237 entered CHEST-2. All patients received riociguat TID, with respective single daily doses to be taken 6 to 8 hours apart.

In order to maintain the blind of CHEST-1 while beginning treatment in CHEST-2, there was an 8-week titration phase for each patient in CHEST-2, in which riociguat study medication was blinded with respect to dose. During the titration phase, riociguat study medication was titrated for formerly placebo-treated patients from a starting dose of 1.0 mg TID by the investigators in steps of 0.5 mg TID every 2 weeks in accordance with the same individual dose titration scheme as used in CHEST-1. Formerly riociguat-treated patients from CHEST-1 underwent sham titration and remained on the dose they were receiving at the end of CHEST-1. The titration phase ended at day 56 (Visit 5). At this visit, the actual dose of the patients was unblinded by the interactive voice response system while preserving the blind of the assigned treatment in CHEST-1.

During the subsequent main study phase, investigators openly modified the riociguat dose in a range between 0.5 mg TID and 2.5 mg TID according to the patient's need. In this context, investigators considered systolic blood pressure, potential side effects, and progression of the underlying CTEPH. For all patients stopping study treatment at any time, a safety follow-up visit was to be performed 30 days after the last dose of riociguat.

If medically indicated, ERAs and prostanoids could be administered starting after day 56 (Visit 5) of CHEST-2.

The interim analysis (data cut-off date 03 May 2012) included 194 patients: 129 patients from the former riociguat IDT group and 65 from the former placebo group. Twelve patients had prematurely discontinued study medication at the time of the visit cut-off (Table 15, page 106).

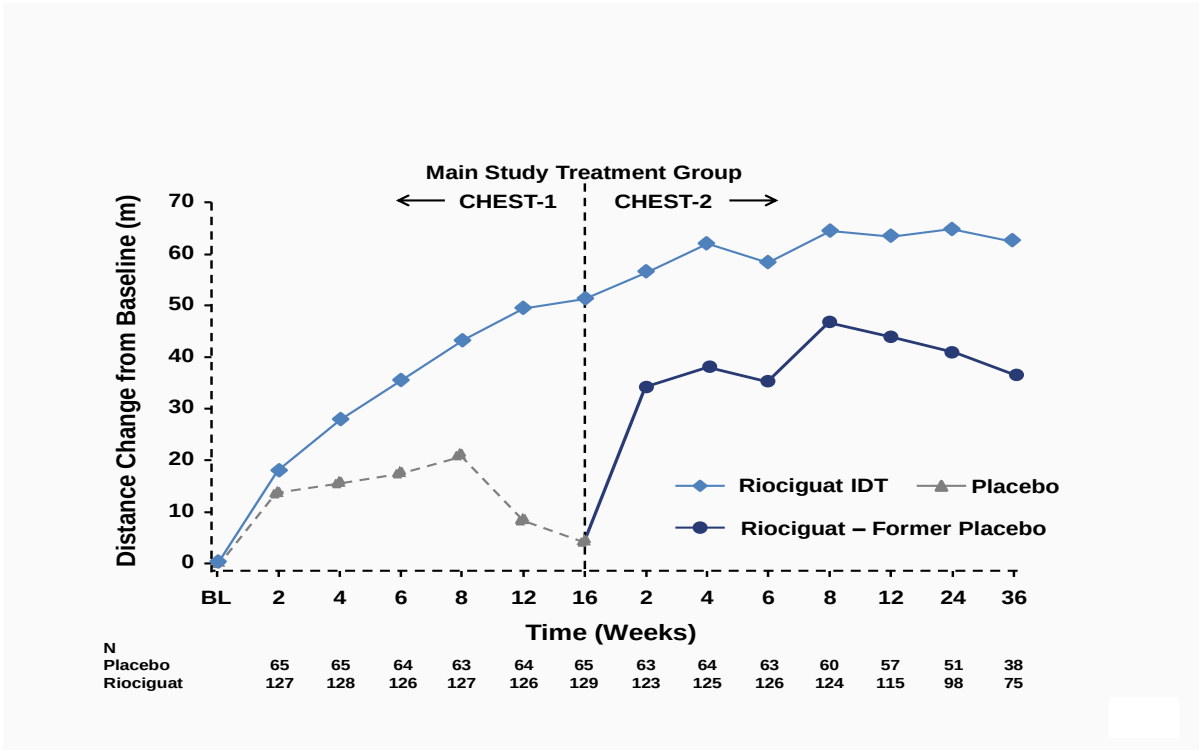
The majority of the 194 patients were female (63.9%). The majority of patients were white (69.1%) and 23.7% and were classified as Asian. Mean age was approximately 59 years and 40.7% of patients were ≥65 years of age. The majority of patients (60.3%) had never smoked and half of all patients reported no alcohol consumption (Table 16, page 107).

Mean changes in 6MWD from baseline for patients in CHEST-2 are displayed over time in Figure 4. The data available from CHEST-2 to-date suggest that the beneficial effects of riociguat observed in CHEST-1 are durable. During CHEST-2, the mean 6MWD for the cohort of patients who had been treated with riociguat in CHEST-1 continued to increase for at least 18 months. In addition to providing evidence of a durable effect, the CHEST-2 data for the cohort of patients who had been treated with placebo in CHEST-1 provide additional support for the efficacy of

riociguat. These patients, who had only a small mean change in 6MWD in CHEST-1, were observed to have significant improvements in 6MWD following 12 weeks of open-label riociguat treatment in CHEST-2. Differences between these 2 cohorts need to be interpreted with caution due to the different sizes of the cohorts of former riociguat and former placebo subjects; that is, the unbalanced randomization in CHEST-1, discontinuations over time in CHEST-2, and ongoing patients not yet reaching later time points resulted in fewer than 50 patients in the former placebo cohort after 6 months in CHEST-2.

Mean change from baseline in CHEST-2 was 56.5 meters at 6 months (n=149), 54.0 meters at 9 months (n=113), 47.6 meters at 12 months (n=93), and 60.7 meters at 18 months (n=63).

Figure 4: Mean Change From Baseline in 6MWD by Visit in Studies CHEST-1 and CHEST-2 Combined (Long-term Safety Population, Observed Cases)



Definition of abbreviations: 6MWD = 6-minute walking distance; BL = baseline; IDT = individual dose titration; m = meters.

Patients with inoperable CTEPH had a consistently higher mean increase in 6MWD through month 6 to 18 (month 6: +58.6 meters, month 12: +49.5 meters, month 18: +64.9 meters) compared to patients with postoperative CTEPH (month 6: +50.7 meters, month 12: +42.3 meters, month 18: +52.3 meters).

The findings for NT-proBNP, WHO functional class, Borg CR 10 score, and EQ-5D in CHEST-2 were consistent with the findings for 6MWD, namely that clinically relevant improvements seen in CHEST-1 were maintained in CHEST-2, with an indication of long-term maintenance of the riociguat treatment effect and improvement in those patients treated with placebo in CHEST-1.

At week 12 in CHEST-2, 39.9% of patients showed an improvement from baseline in WHO functional class while 3.6% showed deterioration in functional class. Improvement/deterioration was 47.1%/4.5% at 6 months (n=155), 47.8%/3.5% at 9 months (n=115), 50.0%/2.1% at 12 months (n=96), and 50.0%/3.1% at 18 months (n=64).

PAH Efficacy Findings in PATENT-1

PATENT-1 was one of the largest studies completed in patients with PAH (445 randomized patients). The study enrolled patients who were naïve to PAH-specific therapies, and patients receiving 1 background (approved) PAH-specific medication (ERA or non-intravenous prostacyclin analogue). PATENT-1 met its primary endpoint. In addition, several clinically relevant secondary endpoints were met. No randomized, placebo-controlled studies had been previously conducted in PAH patients demonstrating a statistically significant benefit by the addition of an oral drug to existing ERAs.

PATENT-1 was a phase III, double-blind, randomized, multicenter, multinational, placebo-controlled 12-week study of the efficacy and safety of oral riociguat in patients with symptomatic PAH (Section 5.2.1, page 109). To be eligible for inclusion, patients had to have a diagnosis of symptomatic PAH and a baseline 6MWD test between 150 meters and 450 meters (inclusive), PVR >300 dyne*second*cm^{-5}, and mPAP >25 mmHg. Both treatment-naïve patients and patients on stable pre-treatment with an ERA or a non-intravenous prostacyclin analogue could be included.

After a pre-treatment phase of up to 2 weeks, eligible patients were randomized in a 4:2:1 ratio to receive riociguat TID with IDT (from 1.0 mg to 2.5 mg TID), placebo TID, or riociguat TID with CT (from 1.0 mg to 1.5 mg TID). Dose titration occurred during an 8-week titration phase (Figure 16, page 90), which was followed by a 4-week main study phase. Riociguat and placebo were administered orally as film-coated tablets with or without food. The starting dose was 1.0 mg riociguat or placebo TID. The respective single daily doses were to be taken 6 to 8 hours apart. To ensure the blinding of the treatment groups, the treatment group allocation and the dose titration were performed with the aid of an interactive voice response system.

The titration scheme for the riociguat IDT group was similar to the one applied in CHEST-1 (Figure 1, page 22). If during the titration phase for the riociguat CT group, the patient reached the 1.5 mg dose level, no further titration was possible. From that point in time on, the patient underwent a sham titration that only allowed dose maintenance or decrease. To ensure blinding, patients allocated to the placebo group underwent a sham titration that followed the rules of the individual dose titration scheme.

The titration phase was followed by a 4-week main study phase (from Visit 5 to Visit 6). During the main study phase, all patients were to remain on their optimal dose of riociguat or placebo, as decided by the titration scheme at Visit 5, the end of the titration phase. Dose reductions for safety reasons were allowed, but a subsequent re-increase during the main study phase was not.

At the end of the treatment period of 12 weeks, eligible patients had the option to enter an open-label extension trial (PATENT-2) where all patients were to be treated with an individual optimal dose of riociguat. Patients who did not enter the open-label extension trial or who stopped the study medication prematurely at any time during the study entered a 30-day safety follow-up phase.

There were 586 patients enrolled in PATENT-1 at 124 study centers in 30 countries worldwide. Of these 586 patients, 141 failed screening criteria (primarily due to hemodynamic measurements, performance of 6-minute walk, and lung function/pulmonary disease) and 443 of the 445 randomized patients received study medication. The completion rate for the treatment phase was high (91.0% of randomized patients) and similar among the treatment groups (Table 17, page 111). All 443 randomized, treated patients were included in the Safety/ITT population (254 riociguat IDT, 126 placebo, 63 riociguat CT).

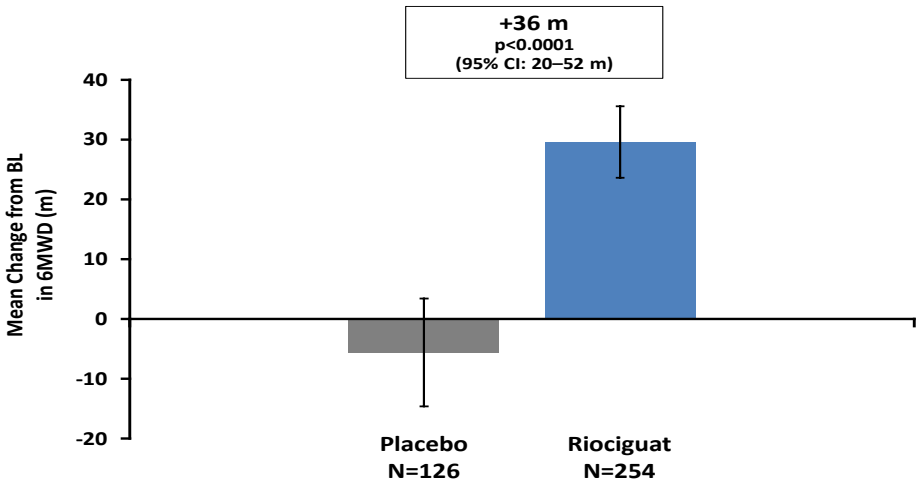
The treatment groups were comparable with respect to demographic and baseline characteristics (Table 18, page 112). Almost 80% of patients were female. The majority of patients in each treatment group were white (52 to 63%). Very few patients were classified as black (<2%). Mean age was similar in all 3 treatment groups (51.1 years riociguat IDT, 50.7 years placebo, 48.8 years riociguat CT). Between 22% and 26% of patients in each treatment group were aged ≥65 years. The majority of patients in each treatment group had never smoked (62% to 67%) and the majority of patients reporting no alcohol consumption (58% to 67%).

Most patients in the Safety/ITT population had a primary diagnosis of idiopathic PAH (58.7% to 66.7%) or PAH due to connective tissue disease (19.8% to 28.0%). More than 90% of patients in each treatment group had a WHO functional class of II or III. About half of the patients in each treatment group were treatment-naïve and half were pre-treated for PAH. Most of the pre-treated patients were receiving an ERA. The frequency of patients pre-treated with a prostacyclin analogue (inhaled, subcutaneous or oral) was less than 10% in all treatment groups.

In the primary efficacy analysis, treatment with riociguat IDT resulted in a statistically significant and clinically relevant improvement in 6MWD from baseline to week 12 (last observation until week 12) as compared to placebo in the Safety/ITT population (Figure 5). Rather unexpectedly, patients randomized to the riociguat CT group improved their 6MWD to the same magnitude as patients randomized to the riociguat IDT group (mean change to final visit of 31.1 meters and 29.6 meters in the riociguat CT and IDT groups, respectively). Results for the riociguat CT group are summarized in Table 19 (page 113). The capped dose titration (1.0 to 1.5 mg) has been analyzed in a purely exploratory manner.

Sensitivity analyses indicated that there was clear evidence of a treatment effect regardless of the method used to take account for missing data.

Figure 5: Primary Endpoint: Mean (with Standard Error Bar) Change in Mean 6MWD From Baseline to Last Visit in PATENT-1 for the Placebo and Riociguat IDT Groups (Safety/ITT population)



Definition of abbreviations: 6MWD = 6-minute walking distance; BL = baseline; CI = confidence interval; IDT = individual dose titration; ITT = intent-to-treat; m = meters.
Baseline means: 361.4 meters riociguat IDT; 367.8 meters placebo.
Least squares mean treatment difference between riociguat IDT and placebo for change from baseline = 35.78 with 95% confidence interval of 20.06 to 51.51 ($p<0.0001$ for stratified Wilcoxon test).

The point estimate of the treatment difference for change the 6MWD from baseline to last visit suggested benefit in the majority of pre-defined subgroups (Figure 6). The 95% CI excluded zero in most subgroups with larger sample sizes. Consistent results with respect to improvement of the 6MWD for riociguat over placebo were also seen for other subgroups of weight, renal function, and cardiac function (not shown).

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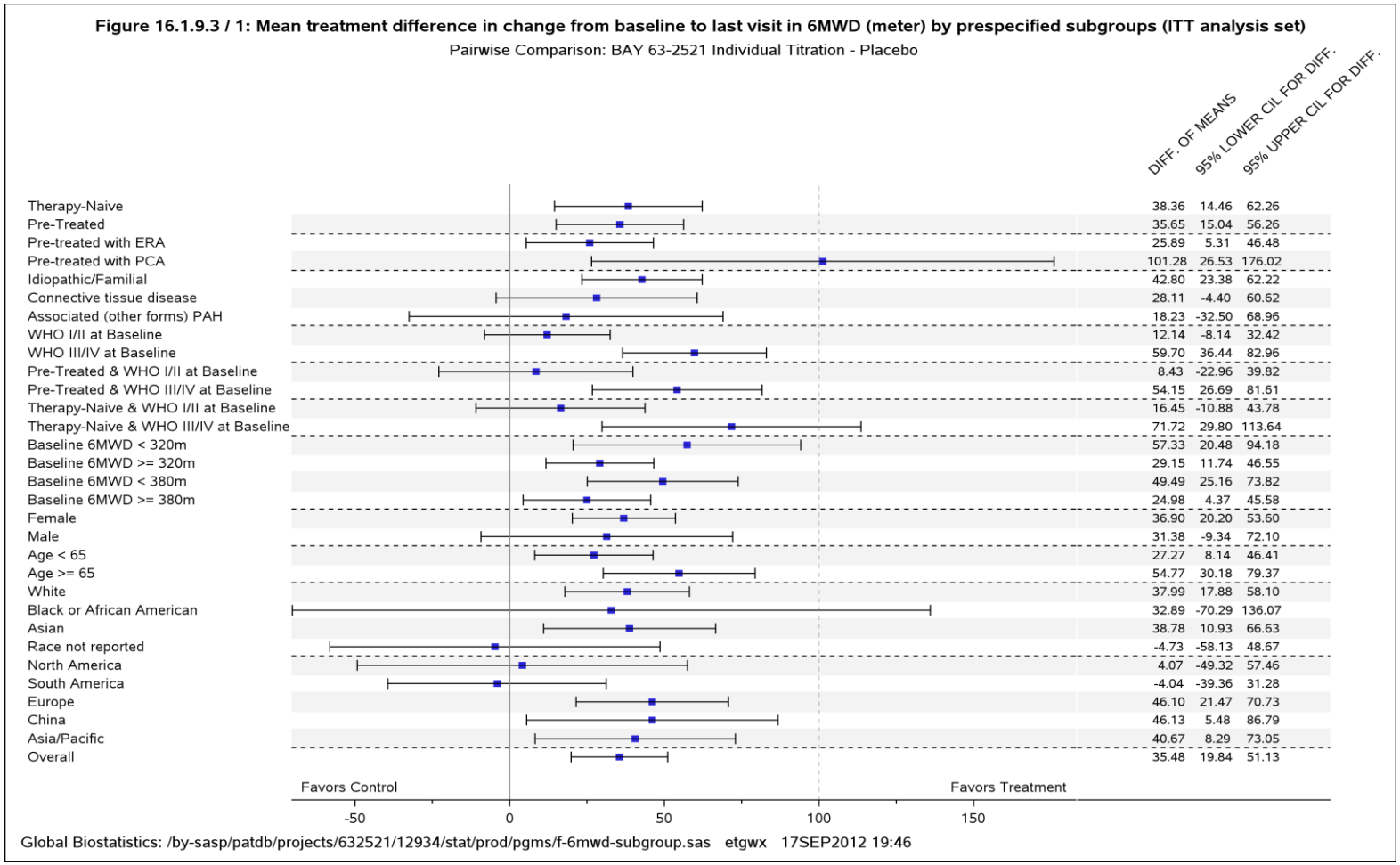
Figure 6: Subgroup Analysis: Mean Treatment Difference in Change From Baseline to Last Visit in 6MWD by Pre-specified Subgroups in Study PATENT-1 (Safety/ITT population)



Definition of abbreviations: 6MWD = 6-minute walking distance; CIL = confidence interval limit; ERA = endothelin receptor antagonist; ITT = intent-to-treat; PCA = prostacyclin analogue; WHO = World Health Organization.

Number of patients (riociguat IDT/placebo) in each subgroup:

- Pre-treatment: therapy naive (n = 123/66), pre-treated patients (n = 131/60), pre-treated with ERA (n = 113/54), and pre-treated with PCA (n = 20/7)
- Type of PAH: idiopathic / familial (n = 156/85), connective tissue disease (CTD, n = 71/25), and associated (other forms) (n = 27/16)
- WHO functional class at baseline: I/II (n = 113/64) and III/IV (n = 141/61)
- Pre-treatment and WHO functional class: Naïve and WHO I/II (n = 68/39), naïve and WHO III/IV (n = 55/27), pre-treated and WHO I/II (n = 45/25), and pre-treated and WHO III/IV (n = 86/34)
- Baseline 6MWD: <320 meters (n = 67/27), <380 meters (n = 139/53), ≥320 meters (n = 187/99), and ≥380 meters (n = 115/73)
- Sex: female (n = 203/98) and male (n = 51/28)
- Age: <65 years (n = 188/94) and ≥65 years (n = 66/32)
- Race: White (n = 161/78), Asian (n = 79/38), Black (n = 4/1), and not reported (n = 9/8)
- Region: North America (n = 24/11); Europe (n = 118/59), Asia/Pacific (n = 46/18), South America (n = 23/14) and China (n = 43/24)

Treatment with riociguat IDT also resulted in a consistent improvement across the secondary efficacy variables of PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg CR 10 score, EQ-5D questionnaire, and LPH questionnaire. Based on the hierarchical testing procedure, secondary endpoints with a statistically significant improvement for the riociguat IDT group compared to placebo were PVR, NT-proBNP, WHO functional class, time to clinical worsening, and Borg CR 10 score. Mean change in secondary efficacy variables from baseline to last visit is summarized in Table 3. Results for the percentage of patients with changes in WHO functional class and for time to clinical worsening are presented following the table of mean changes.

Table 3: Mean Change in Secondary Variables From Baseline to Last Visit in Study PATENT-1 (Safety/ITT population)

	Mean (Standard Deviation) Change From Baseline			Riociguat IDT Versus Placebo
Variable	Placebo (N=126)	Riociguat IDT 1.0 to 2.5 mg (N=254)	Riociguat CT 1.0 to1.5 mg (N=63)	Stratified Wilcoxon p-value
PVR (dyne*second*cm^{-5})	–8.9 (316.6)	–223.3 (260.1)	–167.8 (320.2)	<0.0001
NT-proBNP (pg/mL)	232.4 (1011.1)	–197.9 (1721.3)	–471.5 (913.0)	<0.0001
Borg CR 10 score	0.09 (2.05)	–0.44 (1.72)	–0.33 (1.47)	0.0022
EQ-5D utility score	–0.032 (0.304)	0.033 (0.235)	0.078 (0.311)	0.0663
LPH total score	0.36 (18.15)	–5.99 (17.76)	–10.21 (21.27)	0.0019

Definition of abbreviations: CT = capped titration; IDT = individual dose titration; ITT = intent-to-treat; LPH = Living with Pulmonary Hypertension; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PVR = pulmonary vascular resistance.
Shaded p-values are not considered statistically significant per hierarchical testing procedure.

A larger proportion of patients in the riociguat IDT group than in the placebo group had an improvement of at least 1 class in WHO functional class (20.9% versus 14.4%; Table 22, page 120) and a smaller proportion had a deterioration of at least 1 class (3.5% versus 14.4%). The difference between the riociguat IDT and placebo groups for the distribution of changes was statistically significant (p=0.0033).

The difference in time to clinical worsening between the riociguat IDT group and the placebo group in the Safety/ITT population was statistically significant (p=0.0046, stratified log-rank test). The overall frequency of clinical worsening was lower in both riociguat treatment groups than in the placebo group (1.2% riociguat IDT, 6.3% placebo, 3.2% riociguat CT). All individual components of the combined endpoint were reported less frequently in the riociguat IDT group than in the placebo group.

PAH Efficacy Findings in PATENT-2

PATENT-2 is an ongoing phase III, open-label, multicenter, multinational, extension study of the long-term safety and efficacy of oral riociguat in patients with symptomatic PAH. The study included patients who had completed 12 weeks of treatment in the double-blind PATENT-1 (Section 5.2.2, page 121). Of the 405 patients who completed PATENT-1, 396 entered PATENT-2. All patients received riociguat TID, as in PATENT-1. The respective single daily doses were to be taken 6 to 8 hours apart.

In order to maintain the blind of PATENT-1, PATENT-2 included an 8-week titration phase for each patient, in which riociguat study medication was blinded with respect to dose. During the titration phase, riociguat study medication was titrated for formerly placebo-treated patients from a starting dose of 1.0 mg TID by the investigators in steps of 0.5 mg TID every 2 weeks via the interactive voice response system in accordance with the same individual dose titration scheme as used in PATENT-1. Patients formerly treated with riociguat IDT underwent sham titration and remained on the dose they were receiving at the end of PATENT-1, while patients formerly treated with riociguat who had reached 1.5 mg at the end of PATENT-1 were titrated.

The titration phase ended at day 56 (Visit 5). At this visit, the actual dose of the patients was unblinded by the interactive voice response system while maintaining the blind for treatment assignments in PATENT-1.

During the subsequent main study phase, investigators openly modified the riociguat dose in a range between 0.5 mg TID and 2.5 mg TID according to the clinical circumstances of the individual patient. For all patients stopping study treatment at any time, a safety follow-up visit was to be performed 30 days after the last dose of riociguat.

Concomitant ERAs and prostanoids could be administered (treatment-naïve patients) or modified (pre-treated patients) starting after day 56 (Visit 5).

PATENT-2 is currently ongoing. The interim analysis (data cut-off date 16 Apr 2012) included 363 patients (long-term safety population): 215 patients from the former riociguat IDT group, 96 from the former placebo group, and 52 from the former riociguat CT group. There were 55 patients who had prematurely discontinued study medication at the time of the cut-off for the interim analysis (Table 24, page 124).

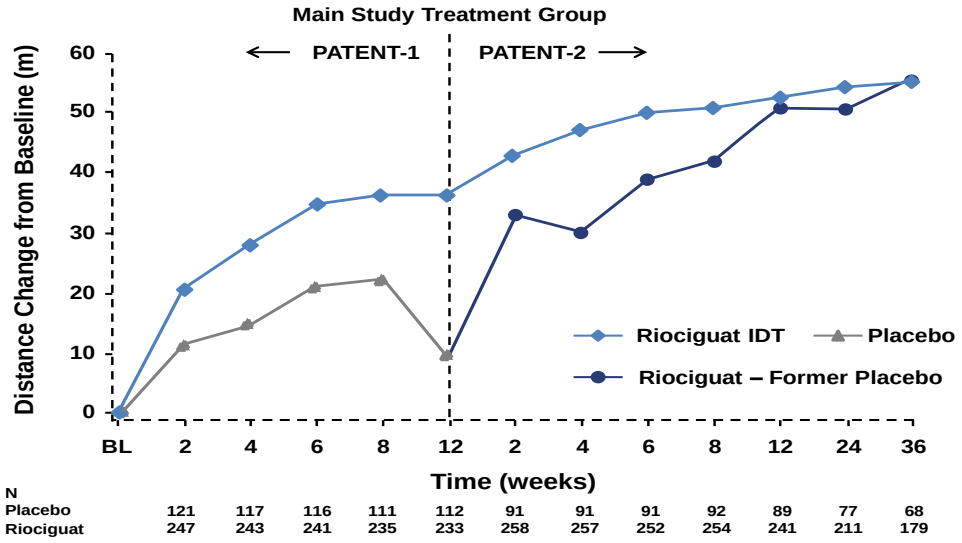
Almost 80% of the 363 patients were female, 62.8% were white, and 32.0% were classified as Asian (Table 25, page 125). Very few patients were classified as black (<1%). Mean age was 49.4 years and 22.6% were ≥65 years of age. The majority of patients (63.9%) had never smoked, and the majority of patients (62.5%) reported no alcohol consumption.

Mean changes in 6MWD from baseline for patients in PATENT-2 are displayed over time in Figure 7. The data available from PATENT-2 to-date suggest that the beneficial effects of riociguat observed in PATENT-1 are durable. During PATENT-2, the mean 6MWD for the

cohort of patients who had been treated with riociguat in PATENT-1 continued to increase for at least 18 months. In addition to providing evidence of a durable effect, the PATENT-2 data for the cohort of patients who had been treated with placebo in PATENT-1 provide additional support for the efficacy of riociguat. These patients, who had only a small mean change in 6MWD in PATENT-1, were observed to have significant improvements in 6MWD following 12 weeks of open-label riociguat treatment in PATENT-2. Differences between these 2 cohorts need to be interpreted with caution due to the different sizes of the cohorts of former riociguat and former placebo subjects; that is, the unbalanced randomization in PATENT-1, discontinuations over time in PATENT-2, and ongoing patients not yet reaching later time points result in few patients in the former placebo cohort after 6 months in PATENT-2.

Mean change from baseline in PATENT-2 was 51.2 meters at 6 months, 53.7 meters at 9 months (n=247), 48.4 meters at 12 months (n=214), and 47.3 meters at 18 months (n=151).

Figure 7: Mean Change From Baseline in 6MWD by Visit in Studies PATENT-1 and PATENT-2 (Long-term Safety Population, Observed Cases)



Definition of abbreviations: 6MWD = 6-minute walking distance; BL = baseline; IDT = individual dose titration; m = meters.

The findings for NT-proBNP, WHO functional class, Borg CR 10 score, and EQ-5D were consistent with the key findings for 6MWD, namely that clinically relevant improvements seen in

PATENT-1 were maintained in PATENT-2, with an indication of long-term maintenance of the riociguat treatment effect and improvement in those patients treated with placebo in PATENT-1.

Safety Results

Data from the placebo-controlled CHEST-1 and PATENT-1 studies were pooled for analyses of safety; in addition, the riociguat IDT and CT groups were combined for the pooled safety analysis. The main rationale for pooling was to improve signal detection in 2 rare patient populations (CTEPH and PAH). Additionally, when the safety data were evaluated from the individual studies, the AE profile was consistent between studies, supporting that there were no safety issues that were unique to either population. Safety during long-term exposure is based on patients who entered the CHEST-2 and PATENT-2 extension studies from the respective placebo-controlled CHEST-1 and PATENT-1 studies.

The safety database from the double-blind pivotal studies comprises 490 riociguat-treated patients and 214 placebo-treated patients who were treated for 12 weeks in PATENT-1 and 16 weeks in CHEST-1. In the pooled ongoing long-term extension studies, median treatment duration was 369 days at the cut-off time for the NDA; 402 patients had been treated for at least 180 days and 288 patients had been treated for at least 360 days (Table 28, page 134).

The Safety/ITT population of CHEST-1 and PATENT-1 included a large number of elderly patients (>30% were older than 65 years), and more women than men. The largest ethnic group was white (approximately 65%), followed by Asian (>25%), and black (2%). Patients had a mean age of 54 years (Table 29, page 136).

Overview of Adverse Events (Section 6.3.1, page 137)

In the pooled data from the placebo-controlled studies CHEST-1 and PATENT-1(Table 4), the incidence of AEs was higher in the riociguat group (90.6% of patients) than in the placebo group (86.0% of patients). The incidence of AEs was lower in the riociguat group than the placebo group for clinically important events such as SAEs (15.1% versus 17.3%), AEs resulting in discontinuation of study medication (2.9% versus 5.1%), and AEs leading to death (1.0% versus 3.3%). Note that 1 of the placebo-treated patients who died was diagnosed with metastatic malignant melanoma on day 76 of PATENT-1, received riociguat during the long-term extension, and subsequently died on day 134 of PATENT-2. If this patient is excluded, 2.8% of patients in the placebo group died.

Table 4: Overall Summary Adverse Events in Pooled Studies CHEST-1 and PATENT-1 (Main Phase, Safety/ITT Population)

Adverse Events	Number (%) of Patients CHEST-1 and PATENT-1 Placebo (N=214)	Number (%) of Patients CHEST-1 and PATENT-1 Riociguat (N=490)
Any	184 (86.0)	444 (90.6)
Any serious	37 (17.3)	74 (15.1)
Any leading to discontinuation of study medication	11 (5.1)	14 (2.9)
Any leading to death	7 [a] (3.3)	5 (1.0)

Note: Sample size for the pooled riociguat group includes the capped dose treatment group in PATENT-1, but N for the riociguat group in PATENT-1 reflects only the individual dose titration group.

a One AE leading to death, included here, was included in the source tables of the study report of PATENT-1, although the patient had died after 134 days in the extension study PATENT-2. This patient died from metastatic malignant melanoma; the case was assessed as a post-treatment death.

In the pooled long-term extension studies (CHEST-2 and PATENT-2), AEs were reported in 91.0% of patients, SAEs in 35.7% of patients, AEs leading to discontinuation in 5.6% of patients, and AEs leading to death in 4.1%. The most common SAEs by preferred term were summarized per 100 patient-years for the pooled CHEST-2 and PATENT-2 studies. Using this incidence rate adjusts for differences in exposure among patients in these ongoing studies. The total population includes those patients treated with placebo in the main controlled study who began riociguat treatment in the long-term extension study. The long-term extension studies were not controlled. After adjusting for duration of exposure, the number of SAEs per 100 patient-years of exposure was lower in the pooled long-term extension studies (65) than in the pooled controlled studies (92 and 102 for the riociguat and placebo groups, respectively).

Common Adverse Events (Section 6.3.2, page 138)

Adverse events reported by a larger proportion of riociguat-treated than placebo-treated patients (≥5% difference) included headache, dizziness, dyspepsia, and hypotension (Table 31, page 138). Adverse events reported by a smaller proportion of riociguat-treated than placebo-treated patients (≥5% difference) included cough and dyspnea.

The overall rate of AEs in this population was 668 events per 100 patient-years (Table 32, page 139). This rate is lower than those observed for the pooled controlled phase III studies: 1944 events per 100 patient-years for the riociguat group and 1771 events per 100 patient-years for the placebo group.

Deaths (Section 6.3.3.1, page 139)

There were 11 deaths (5 [1.0%] riociguat, 6 [2.8%] placebo) in the controlled phase III studies CHEST-1 and PATENT-1. An additional placebo-treated patient was diagnosed with metastatic malignant melanoma on day 76 of PATENT-1, received riociguat during the long-term extension, and subsequently died on day 134 of PATENT-2. The patient was considered to have died post-treatment in the long-term extension study. In the long-term safety population of CHEST-2, 5 patients died within the study period (Table 33, page 140). In the long-term safety population of PATENT-2, 18 patients died within the study period (Table 34, page 142) and 4 patients died post-treatment (Table 35, page 143).

Other Serious Adverse Events in CHEST-1 and PATENT-1 (Section 6.3.3.2, page 143)

The most common SAEs by preferred term for each treatment group (Table 36, page 144) were as follows:

- Riociguat treatment group: right ventricular failure (2.2% of patients), syncope (1.4%), hemoptysis (1.0%), gastritis (0.8%), pneumonia (0.8%), chest pain (0.6%), gastroenteritis (0.6%), renal failure acute (0.6%), and pulmonary hypertension (0.6%)

- Placebo treatment group: syncope (3.7% of patients), right ventricular failure (1.9%), pulmonary arterial hypertension (0.9%), dyspnea (0.9%), and cardiac arrest (0.9%)

Other Serious Adverse Events in CHEST-2 and PATENT-2 (Section 6.3.3.2, page 143)

The most common SAEs by preferred term in the pooled long-term extension studies were syncope (5.4% of patients), pulmonary arterial hypertension (4.5%), right ventricular failure (4.1%), pulmonary hypertension (2.9%), catheterization cardiac (2.7%), pneumonia (2.0%), hemoptysis (1.3%), bronchitis (1.1%), and dyspnea (1.1%). These are generally consistent with the most common SAEs for the controlled phase III studies.

Adverse Events Resulting in Discontinuation (Section 6.3.4, page 145)

In the pooled controlled studies, AEs leading to discontinuations were reported in 14 patients (2.9%) in the riociguat group and 11 patients (5.1%) in the placebo group. The most frequent AEs leading to discontinuations in the riociguat group across both studies were in the primary system organ classes of cardiac disorders (3 patients), gastrointestinal disorders (2 patients), general disorders and administration site conditions (2 patients) and nervous system disorders (2 patients). The most frequent AEs leading to discontinuations in the placebo group across both studies were in the primary system organ classes of cardiac disorders (2 patients) and respiratory, thoracic and mediastinal disorders (5 patients).

In the pooled long-term extension studies, AEs leading to discontinuations were reported in 31 patients (5.6%). The profile of AEs leading to discontinuations was similar to that seen in CHEST-1 and PATENT-1.

Pre-specified Safety Topics of Special Interest

Based on observations made in the phase II proof-of-concept study, and given the mechanism of action of riociguat, syncope and hypotension were pre-defined as safety topics of special interest for phase III:

Syncope (Section 6.6.1.1, page 151)

Syncope in PAH is associated with worsening right heart function and is an independent predictor of poor prognosis. Occurrence of syncope in patients treated with riociguat was not found to be related to dose or riociguat plasma concentrations. Overall, treatment-emergent syncope events were reported in 16 patients (3.3%) in the pooled riociguat group and 10 patients (4.7%) in the pooled placebo group. Two patients discontinued study medication because of syncope AEs (1 with riociguat and 1 with placebo).

Hypotension (Section 6.6.1.2, page 152)

Hypotension is a known AE of medications used for treatment of pulmonary hypertension. The evaluation of hypotension as a AE of special interest was performed for associated preferred terms (blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic

decreased, blood pressure orthostatic decreased, blood pressure systolic decreased, blood pressure systolic inspiratory decreased, hypotension, orthostatic hypotension, and diastolic hypotension).

As expected, AEs of hypotension were more frequently reported in the riociguat group compared to the placebo group (10.0% versus 3.7%) in pooled controlled studies. Only 1 patient in each treatment group experienced a severe event of hypotension. Hypotension of moderate severity was reported for 4.1% and 1.4% of patients in the riociguat and placebo groups, respectively. Two patients in the riociguat group had an SAE of hypotension, 1 patient in the riociguat discontinued due to hypotension, and no patient died due to hypotension. No patients in the placebo group had an SAE of hypotension or discontinued due to hypotension.

Where hypotension was reported, the event was frequently when the patient had their first exposure to riociguat, or during early titration (Table 39, page 154). The vast majority of events were non-serious, had an outcome of resolved, and did not result in discontinuation of riociguat. Hypotension was not linked to syncope and was presumably asymptomatic in the majority of patients.

Safety Topics Based on Mechanism of Action

Based on riociguat's mechanism of action, gastrointestinal motility disturbances, bone metabolism, and fetal toxicity are discussed.

Gastrointestinal Motility Disturbances (Section 6.6.2.1, page 156)

The observed gastrointestinal AEs were principally related to riociguat's mechanism of action (relaxation of smooth muscle). Overall, treatment-emergent gastrointestinal disorders were reported in 52.0% of patients in the pooled riociguat group and 33.6% of patients in the pooled placebo group. The most frequent treatment-emergent gastrointestinal disorders (as defined by Standardized MedDRA Query [SMQ]) by preferred term for each treatment group in the pooled controlled studies were:

- **Riociguat**: dyspepsia (17.8%), nausea (14.1%), diarrhea (11.8%), vomiting (10.2%), chest pain (5.9%), gastro-esophageal reflux disease (5.1%), constipation (4.5%), abdominal pain upper (3.3%), abdominal pain (2.9%), and gastritis (2.9%).

- **Placebo**: nausea (10.7%), diarrhea (7.9%), dyspepsia (7.9%), chest pain (7.0%), vomiting (6.5%), abdominal pain upper (3.7%), gastro-esophageal reflux disease (1.9%), abdominal discomfort (1.4%), abdominal pain (1.4%), and constipation (1.4%).

Most of these events were non-serious; gastrointestinal disorders were reported as SAEs in 1.6% of patients in the pooled riociguat group and 0.9% of patients in the pooled placebo group. Gastrointestinal AEs leading to discontinuation were reported in 2 patients (0.4%) in the pooled riociguat group and 1 patient (0.5%) in the pooled placebo group. Most of the events were located in the upper gastrointestinal tract. Notably, use of concomitant gastric pH-increasing medications

was more frequent in the pooled riociguat group than in the pooled placebo group (56.1% versus 35.0%). Long-term exposure to riociguat during the extension studies did not increase the incidence of these AEs.

Bone Metabolism (Section 6.6.2.2, page 157)

After repeated administration to juvenile and adolescent rats, riociguat induced morphological effects (widening of the growth plates) on long bones in growing rats at systemic exposure levels clearly above the therapeutic range. Treatment of full-grown rats at comparable exposure levels did not result in morphological changes on the bone. It is generally accepted that the NO-sGC-cGMP and the natriuretic peptide- particulate (membrane-bound) guanylate cyclase (pGC)-cGMP pathway play a role in regulation of bone and cartilage homeostasis and the stimulation of these pathways results in activation of bone formation rather than in bone resorption. This provides evidence that the effects are related to the pharmacological mechanism of action of riociguat.

The exploratory biomarker type I collagen C-telopeptides (carboxy-terminal collagen crosslinks [CTX]) was evaluated in CHEST-1 and PATENT-1. CTX is a sensitive marker to assess the potential for increasing or decreasing bone resorption (23, 24, 25). The analyses of CTX gave no indication of an impact of riociguat on bone metabolism. Additionally, rates of fractures in all completed phase II and phase III clinical studies were similar in the all riociguat group (5/754 [0.7%]) and in the placebo group (1/289 [0.3%]).

Based on the absence of morphological effects on bone in riociguat-treated adult rats and dogs, and the further re-assuring clinical data from CHEST-1 and PATENT-1, the findings in growing rats are considered to be of no relevance for adult patients with CTEPH and PAH.

Fetal Toxicity

Embryo-fetal toxicity was observed in preclinical data (Section 3.3, page 65).

During the clinical trials program, patients were counseled to use contraception, and regular pregnancy testing was performed. Three patients had a positive pregnancy test during the long-term extension studies. The outcomes of these pregnancies resulted in 1 spontaneous abortion, 1 elective abortion, and 1 ectopic pregnancy.

Pulmonary hypertension is associated with high morbidity and mortality during pregnancy in all clinical divisions of the disease (26). There is general consensus that women with PH should currently be advised to avoid pregnancy. A REMS program to minimize the risk of fetal exposure has been proposed (Section 8, page 180).

Safety Topics Based on Observations in Phase III

Based on observations from phase III studies, the following safety topics are discussed: decreases in hemoglobin and hematocrit, bleeding, and renal function.

Decreases in Hemoglobin and Hematocrit (Section 6.6.3.1, page 159)

The only consistent finding in hematology and clinical chemistry results was decreased hemoglobin and hematocrit in the riociguat group. Mean changes from baseline to Week 12 were small in both treatment groups:

- Hemoglobin: riociguat group: –0.58 g/dL, placebo group: 0.13 g/dL
- Hematocrit: riociguat group: –1.66%, placebo group: 0.45%

The observed decrease in mean hemoglobin in the riociguat group appeared to be independent from the occurrence of bleeding events. Overall, there was no increased risk for clinically relevant anemia for pulmonary hypertension patients treated with riociguat.

Bleeding (Section 6.6.3.2, page 161)

Overall, the incidence of bleeding events in CHEST-1 and PATENT-1 was similar for the riociguat and placebo treatment groups, but an increased rate in respiratory tract bleeding events was observed in the riociguat group compared to placebo. No temporal or dose-related pattern was identified. Respiratory bleeding events with a higher rate in the riociguat group were epistaxis (2.9% riociguat versus 1.4% placebo) and hemoptysis (2.0% riociguat versus 0.9% placebo). After adjusting for duration of exposure, the numbers of epistaxis events per 100 patient-years of exposure in pooled controlled studies were 14.8 and 5.6 for the riociguat and placebo groups respectively. The number of events per 100 patient-years of exposure in the pooled extension studies was 8.7. The numbers of hemoptysis events per 100 patient-years of exposure in pooled controlled studies were 9.0 and 5.6 for the riociguat and placebo groups respectively. The number of events per 100 patient-years of exposure in the pooled extension studies was 5.0.

Serious AEs of respiratory tract bleeding in pooled controlled studies consisted of 5 patients (1.0%) reporting hemoptysis in the riociguat group. After adjusting for duration of exposure, the numbers of serious hemoptysis events per 100 patient-years of riociguat exposure was 4.93 in pooled controlled studies and 1.24 in pooled long-term extension studies. In CHEST-1, 3 patients experienced 1 instance each of serious hemoptysis. Onset was between day 22 and day 78 of the study, severity was mild or moderate, and none was related to study medication in the investigator's judgment. All events resolved spontaneously without treatment or intervention after 1 to 2 days duration. One of the 3 patients reported a history of hemoptysis prior to study enrollment. In PATENT-1, 2 patients experienced hemoptysis. One patient was hospitalized for hemoptysis due to coughing; the event was of moderate severity. The other patient was

hospitalized twice for hemoptysis and died as a result of the second episode of hemoptysis. The patient with a fatal outcome had a medical history of hemoptysis, with the most recent episode occurring 2 weeks prior to randomization in PATENT-1.

Published literature indicates that in some patients, especially those with more advanced pulmonary hypertension, hemoptysis may be regarded as complication of the underlying disease (21, 22). In a recent publication focused on anticoagulation treatment in pulmonary hypertension (21), it was noted that the bleedings occurred independent from vitamin K antagonist international normalized ratio (INR) target. More than 90% of the patients in the CHEST-1 trial and more than 50% of the patients in the PATENT-1 trial were anticoagulated. Notably, hemoptysis was described by the authors to be well known for patients with pulmonary hypertension, but hardly reported in patients using vitamin K antagonists for atrial fibrillation or venous thromboembolism.

Importantly, no further pattern or bleeding site was identified from the pooled CHEST-1 and PATENT-1 studies. No excess serious bleeding risk at other sites prone to bleeding (typically the gastrointestinal tract in an anticoagulated population) was identified, with plausible alternative explanations in all cases. The serious bleeding events are thus consistent with expectations for an anticoagulated patient population with pulmonary hypertension. However, hemoptysis is regarded as a potential risk, especially in patients with a history of lung bleeding, and will be addressed in labeling.

Renal Function (Section 6.6.3.3, page 164)

During double-blind treatment in CHEST-1 and PATENT-1, SAEs labeled as renal and urinary disorders were numerically more frequent in the riociguat group than in the placebo group (6 [1.2%] versus 1 [0.5%] of patients). The patient in the placebo group experienced renal impairment. Events classified as renal failure included acute renal failure (3 patients in riociguat group), chronic renal failure (2 patients in riociguat group), and renal failure (1 patient in riociguat group). After adjusting for duration of exposure, the number of serious renal events per 100 patient-years of exposure was lower in the pooled long-term extension studies (0.93) than in the pooled controlled studies (5.75 and 1.87 for the riociguat and .placebo groups, respectively).

Overall, events of renal impairment were associated with other medical conditions, including a medical history of renal impairment. In all cases of serious adverse renal events, concomitant events were reported which confounded interpretation of the data. The majority of patients with a serious renal event had no temporal relationship to a hypotensive event.

In contrast to the numerically small increase in the incidence of renal AEs, the laboratory parameters of creatinine, creatinine clearance, and urea in CHEST-1 and PATENT-1 were stable over the course of 3 to 4 months of treatment in riociguat- and placebo-treated patients. Based on mean change from baseline to week 12, a trend was observed toward improvement of renal function in the riociguat group when compared with placebo for cystatin C (8.0 ng/mL versus

43.3 ng/mL), creatinine (0.013 mg/dL versus 0.033 mg/dL), creatinine clearance (1.96 mL/min versus -2.29 mL/min), estimated glomerular filtration rate (2.58 mL/min/1.73m^2 versus -2.72 mL/min/1.73m^2), potassium (-0.131 mmol/L versus -0.014 mmol/L), urate (-0.39 mg/dL versus 0.24 mg/dL), and urea (-0.80 versus 0.74 mg/dL).

Therefore, despite the observed imbalance of events, a specific signal for a potential negative impact of riociguat on renal function could not be identified.

Safety Conclusions

In summary, the AE profile for riociguat was generally similar in the 2 placebo-controlled studies with the majority of AEs being mild to moderate in severity and consistent with riociguat's mechanism of action. The profile during the long-term extension studies was similar to the placebo-controlled studies. Although the rates of some AEs were increased relative to placebo, the events did not result in increased rates of death, SAEs, or discontinuations due to AEs. Hypotension is consistent with the mechanism of action, but was generally mild to moderate in severity and asymptomatic, with fewer events once the patient's dose had been optimized. Hemoptysis is known to occur in patients with pulmonary hypertension. There was a numerical increase in serious events of hemoptysis in riociguat-treated patients but causality could not be established. Hemoptysis will be carefully monitored. Riociguat was generally safe and well-tolerated in the patients enrolled in the clinical development program.

Pharmacokinetic Data (Section 4, page 67)

Studies in the world-wide phase I development program were performed in healthy white, black, Hispanic, and Asian (Chinese and Japanese) volunteers as well as in patients with renal or hepatic impairment; an evaluation of important drug-drug interactions was included in the program. Pharmacokinetic and pharmacodynamic evaluations were performed for all patients in phase II and III studies. Moreover, a proof-of-concept study was performed in patients with suspected pulmonary hypertension due to PAH, CTEPH, chronic obstructive pulmonary disease, or interstitial lung disease.

Key pharmacokinetic findings include:

- Oral bioavailability of riociguat is high with or without food. The absolute bioavailability as a 1.0 mg immediate release tablet was 94%.
- Median peak concentrations were observed 1.0 to 1.5 hours after dosing with the immediate release tablet. Riociguat terminal half-life in patients is about 13 hours with high inter-individual variability.
- Due to underlying disease, riociguat exposure in patients with pulmonary hypertension is approximately 2- to 3-fold higher at steady state compared to healthy subjects.
- Riociguat pharmacokinetics behaved dose-proportionally with increasing tablet doses.

- Changes in gastric pH (e.g., induced by concomitant medication of antacids or proton pump inhibitors) reduced exposure to riociguat by 34% or 26%, respectively.
- Plasma protein binding for riociguat in human plasma is high and other medications have not been observed to displace riociguat. The binding of riociguat to plasma proteins is fully reversible.
- Riociguat is eliminated via 3 routes in man: 27% to 71% of the dose was subject to oxidative biotransformation while 13% (up to 44%) was excreted as unchanged drug in feces, and 6% (up to 19%) was excreted as unchanged drug in urine via glomerular filtration.
- Riociguat is metabolized via cytochrome P_{450} (CYP) pathways of CYP1A1, CYP2C8, CYP2J2, and CYP3A4 to metabolite M-1 in the liver, intestine and lung. Biotransformation of riociguat is much more pronounced in lung microsomes of smokers.
- Due to its multipathway clearance, riociguat has a low risk for clinically relevant drug-drug interactions.
- Riociguat and its primary metabolite have been characterized *in vitro* to be both a substrate of the active transporter P-glycoprotein (P-gp) and the multi-drug transport 'breast cancer resistance protein' (BRCP).

Benefit-Risk Assessment (Section 9, page 182)

In the assessment of a new pharmacotherapy, every effort must be made to weigh the benefits provided by this therapy against the risks brought by it.

For CTEPH, clinically meaningful improvements compared to placebo were observed across multiple efficacy endpoints (including patient-reported quality-of-life measures) in patients with inoperable CTEPH or with residual pulmonary hypertension following pulmonary endarterectomy. The safety profile of riociguat has been characterized in phase III studies, and riociguat was well-tolerated in this rare disease. Riociguat is a safe and effective treatment for this rare, progressive, life-threatening disease for which no approved pharmacotherapy exists.

For PAH, clinically meaningful improvements compared to placebo were observed across multiple efficacy endpoints in patients naïve to treatment and patients pre-treated with PAH-specific drugs. The safety profile of riociguat has been characterized in phase III studies. Riociguat was well-tolerated in this population, with an AE profile broadly similar to other drugs approved for PAH and thus familiar to physicians managing patients with PAH.

Bayer is proposing a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of riociguat outweigh the potential risk of embryo-fetal toxicity in females of reproductive potential. This proposal is based on discussions with the FDA and data from non-clinical studies suggesting a potential risk of fetal harm. The proposed riociguat REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for REMS Assessments.

Weighing the risks and benefits for riociguat is informed by the entire clinical development program of this product, comprising the data from the phase III trials, the well-documented pathophysiology of CTEPH and PAH, the mechanism of action, and clinical pharmacology knowledge base. Balanced against the risk factors associated with these life threatening conditions, the benefit-risk for patients treated with riociguat is positive in the populations of CTEPH and PAH.

1. Introduction

Bayer HealthCare has submitted an NDA for the use of riociguat to treat adult patients with CTEPH and PAH. This briefing document is provided for the advisory committee meeting scheduled for 06 August 2013 as part of the ongoing review by the Division of Cardiovascular and Renal Products of the FDA.

This briefing document summarizes key aspects of the riociguat development program, including:

- Limitations of current pharmacotherapy for patients with CTEPH and PAH
- Relevant non-clinical results
- Pharmacokinetic and pharmacodynamic properties of riociguat
- Efficacy results from clinical studies
- Safety results from clinical studies
- Overall benefit/risk profile

1.1 Pharmacological Class and Mechanism of action

Riociguat is the first-in-class of a new group of compounds, sGC stimulators. Soluble guanylate cyclase is present in vascular cells and platelets, and it is a key enzyme in the cardiopulmonary system and the receptor for NO. Both CTEPH and PAH are associated with endothelial dysfunction, leading to an imbalance in circulating levels of endogenous vasodilators and vasoconstrictors. Impaired synthesis of NO, and insufficient stimulation of the NO-sGC-cGMP pathway has been well-described in PAH.

Riociguat directly stimulates sGC, thereby increasing levels of the signaling molecule cGMP. The cGMP molecule plays a pivotal role in regulating cellular processes, such as vascular tone, proliferation, fibrosis, and inflammation. Two key features of riociguat are (i) it directly stimulates sGC independently of NO, and (ii) it sensitizes sGC to low levels of NO. Collectively, these dual effects restore the NO-sGC-cGMP pathway. Impairments of the NO-sGC-cGMP pathway provoke acute and chronic vascular injury, including endothelial dysfunction, vasoconstriction, and vascular remodeling in the pulmonary circulation.

Accumulating data suggest that some patients with CTEPH and PAH may have NO deficiency that limits the efficacy of PDE5 inhibitors. The PDE5 inhibitors also act on the NO pathway by

preventing cGMP degradation; however, these compounds are dependent on cGMP synthesis and the presence of NO. Riociguat's ability to direct stimulate sGC independently of NO makes it unique in the setting of pulmonary hypertension. The sGC stimulators have not yet been evaluated in patients with CTEPH or PAH. Based on its mechanism of action, riociguat is different from all other drugs currently approved for PAH.

1.2 Key Pharmacological and Pharmacokinetic Properties of Riociguat

Riociguat exhibits the following key properties:

- Direct stimulation of sGC (independent of NO), sensitization of sGC to low levels of NO, and collectively, restoration of the NO-sGC-cGMP pathway via these dual effects
- Nearly complete bioavailability (94%)
- Variable clearance and metabolism due to multiple CYP pathways
    - Low risk for clinically relevant drug-drug interactions
    - High between-patient variability (approximately 60% coefficient of variation) and low within-patient variability (35%) in pharmacokinetics
    - Mean half-life of 13 hours (68% coefficient of variation, with a range from 4 to 29 hours)
    - Renal and hepatic impairment: approximately 2-fold and 1.5-fold increase in exposure, respectively.
- No dynamic or kinetic interaction with Aspirin® or warfarin.

Riociguat is metabolized via the pathways of CYP1A1, CYP2C8, CYP2J2, and CYP3A4 to metabolite M-1 in the liver, intestine and lung. Biotransformation of riociguat is much more pronounced in lung microsomes of smokers.

Metabolite M-1 exhibits pharmacological activity as a sGC stimulator but at 3- to 10-fold lower potency than riociguat. It has a terminal half-life of approximately 20 hours and accumulates in a predictable fashion to stable and constant concentrations.

1.3 Proposed Indications and Dose

The proposed indications for riociguat are the treatment of adult patients with:

CTEPH with inoperable CTEPH or with persistent or recurrent CTEPH after surgical treatment to improve exercise capacity and WHO functional class, and

PAH to improve exercise capacity, WHO functional class, and to delay clinical worsening.

1.4 Overview of Clinical Development Program

Riociguat was discovered in-house by Bayer scientists. A combination of pre-clinical investigations in animal models, together with early signs of efficacy studies in patients, suggested that sGC was a valid therapeutic target for patients with pulmonary hypertension. An open-label, phase II study (Study 12166) demonstrated the potential clinical effectiveness of riociguat in the setting of CTEPH and PAH. For the 6MWD, clinically relevant improvements were observed: for subjects with PAH (+73 meters) and CTEPH (+64 meters). These improvements in 6MWD were sustained during the long-term extended treatment phase (now ongoing for 4.5 years).

The observations from phase II led to the design of the international phase III clinical development program for riociguat that consists of separate efficacy and safety studies in patients with CTEPH and PAH. Primary evidence for efficacy in patients with CTEPH is provided by randomized, double-blind, placebo-controlled, multicenter Study 11348 (CHEST-1). This is the largest randomized, placebo-controlled study in this patient population to-date. Supportive evidence is provided by open-label, non-controlled, long-term extension Study 11349 (CHEST-2).

Primary evidence for efficacy in patients with PAH is provided by randomized, double-blind, placebo controlled, multicenter Study 12934 (PATENT-1). This study was one of the largest studies conducted to-date in this patient population. Supportive evidence is provided by open-label, non-controlled, long-term extension Study 12935 (PATENT-2).

CHEST-1 and PATENT-1 were designed and conducted in consultation with the FDA and in accordance with the international guidelines for the diagnosis and treatment of patients with pulmonary hypertension. Guidelines for the classification, diagnosis, and treatment of pulmonary hypertension were developed by an international group of disease area experts and are refined on a periodic basis. They were last defined at the 4th World Symposium of Pulmonary Hypertension in Dana Point (1), and recently refined at the 5th World Symposium of Pulmonary Hypertension in Nice (not yet published). Additionally, regional consensus statements and/or guidelines in both the United States and Europe have been written in accordance with the Dana Point guidelines (6, 27).

Steering committees for both studies were made up from experts who helped define these guidelines and represented an international group of experts, including the United States. The inclusion/exclusion criteria of the PATENT-1 study were similar with respect to other large international clinical trials studying other PAH compounds that have been approved for this indication. The inclusion/exclusion criteria for the CHEST-1 study were similar to the only other large, international trial conducted in CTEPH (11).

In both PATENT-1 and CHEST-1, background therapy for patients was in line with standard treatments as recommended by international guidelines. Hemodynamics, the gold standard for the diagnosis of all forms of pulmonary hypertension, was confirmed at baseline in both PATENT-1 and CHEST-1, further reinforcing that the patient population enrolled in both studies strictly adhered to international guideline definitions. Moreover, the CHEST-1 operability assessment criteria were defined according to input from international experts. The studies were conducted in accordance with Good Clinical Practices and with the ethical principles set forth in the Declaration of Helsinki.

A summary of all studies of riociguat in patients is provided in Table 5.

Table 5: Studies of Riociguat in Patients

Study	Description
CHEST-1	A phase III, double-blind, randomized, multicenter, multinational, placebo-controlled study of the efficacy and safety of oral riociguat in patients with CTEPH.
CHEST-2	An ongoing, phase III, open-label, multicenter, multinational, extension study of the long-term safety and efficacy of oral riociguat in patients with CTEPH. The study included patients who had completed 16 weeks of treatment in the double-blind study CHEST-1.
PATENT-1	A phase III, double-blind, randomized, multicenter, multinational, placebo-controlled study of the efficacy and safety of oral riociguat in patients with symptomatic PAH.
PATENT-2	An ongoing, phase III, open-label, multicenter, multinational, extension study of the long-term safety and efficacy of oral riociguat in patients with symptomatic PAH. The study included patients who had completed 12 weeks of treatment in the double-blind study PATENT-1.
11874	A phase II, single-dose, proof-of-concept study that evaluated invasive hemodynamics in 19 patients with PAH, CTEPH, and interstitial lung disease-associated pulmonary hypertension. Study 11874 is not presented in this document as supportive evidence because the riociguat formulation used (oral solution) was not used in subsequent phase II and phase III studies.
12166	A phase II, 12-week, open-label study (described above) that assessed safety, tolerability, and pharmacodynamics including invasive hemodynamics of riociguat at doses of 1.0 to 2.5 mg TID in 75 evaluable patients with PAH or CETPH. Efficacy results for this study are summarized in Section 5.3 (page 127); SAEs and AEs resulting in discontinuation are summarized in Section 6.3.3 (page 139) and Section 6.3.4 (page 145), respectively.
11917	A phase II, open-label study that assessed potential interactions between riociguat and sildenafil and tested the starting dose of 1 mg for Study 15096. Single doses of 0.5 and 1 mg riociguat were administered to 7 patients with pulmonary hypertension who received treatment with sildenafil at a stable dose of 20 mg TID. Key safety results are summarized in Section 6.6.4.1 (page 169).

Table 5: Studies of Riociguat in Patients

15096	A randomized, double-blind, placebo-controlled, multicenter, interaction study to evaluate changes in blood pressure following 1, 1.5, 2, and 2.5 mg riociguat TID (i.e., the IDT regimen) compared to placebo treatment on the background of stable sildenafil pre-treatment in patients with symptomatic PAH. Key safety results are summarized in Section 6.6.4.1 (page 169).
12915	A phase II, single-dose (1 or 2.5 mg riociguat) proof-of-concept study of hemodynamic effects in patients with pulmonary hypertension associated with chronic obstructive pulmonary disease. Study 12915 is not presented in this document because of differences in the study population.
12916	A phase II, multicenter, non-randomized, non-blinded, non-controlled study to investigate the effects of multiple doses of riociguat on safety, tolerability, and efficacy parameters in 22 patients with pulmonary hypertension due to interstitial lung disease. Study 12916 is not presented in this document because of differences in the study population.
14308	A phase II, randomized, double-blind, placebo-controlled study that evaluated treatment with 3 different doses of riociguat in subjects with symptomatic pulmonary hypertension associated with left ventricular systolic dysfunction. Study 14308 is not presented in this document because of differences in the study population.

Additional details on the phase II studies are provided in Appendix 11.5.1 (page 202).

Studies in the world-wide phase I development program were performed in healthy white, black, Hispanic, and Asian (Chinese and Japanese) volunteers as well as in patients with renal or hepatic impairment; an evaluation of important drug-drug interactions was included in the program. Pharmacokinetic and pharmacodynamic evaluations were performed for all patients in phase II and III studies. Moreover, phase II studies were performed in patients with suspected pulmonary hypertension due to PAH, CTEPH, chronic obstructive pulmonary disease, or interstitial lung disease. A tabular listing of the phase I studies is provided in Appendix 11.5.2 (page 203).

2. Rationale for Product Development

Pulmonary hypertension has been classified into 5 types (1):

- Group 1: PAH, which includes subtypes of idiopathic, heritable, and association with other diseases (e.g., connective tissue disease, infection with human immunodeficiency virus, portal hypertension, congenital heart disease);;
- Group 2: Pulmonary hypertension associated with left heart disease, which includes atrial, ventricular, and valvular diseases;
- Group 3: Pulmonary hypertension associated with lung diseases and/or hypoxemia, which includes chronic obstructive pulmonary disease, interstitial lung disease, and sleep-disordered breathing;
- Group 4: Pulmonary hypertension due to chronic thrombotic and/or embolic disease, which includes CTEPH;
- Group 5: Miscellaneous

There is a high medical need for patients with different forms of pulmonary hypertension. Approved therapies only address one form of pulmonary hypertension, namely PAH. Despite available therapies, mortality in patients with PAH remains high. There are currently no approved pharmacotherapies for patients with CTEPH.

The shared pathology, signs and symptoms of CTEPH and PAH, and the common mechanism of mortality (right ventricular failure due to increased pulmonary hypertension) provided the rationale for investigating potential pharmacological treatments of both CTEPH and PAH.

The histopathological hallmark of all forms of pulmonary hypertension, regardless of the specific etiology, is the presence of structural changes to the pulmonary arterial vasculature, principally due to medial and adventitial thickening of the arteries and arterioles, a process termed vascular remodeling (9). This remodeling process is frequently observed in tandem with intimal proliferation, *in situ* thrombi, deposition of extracellular matrix (fibrosis) and inflammation. Despite having different clinical classifications (1), CTEPH and PAH share a common microvasculopathy, considered to be a main component of disease progression. A comparison of features and treatment responses for CTEPH and PAH is provided in Table 6.

Table 6: Comparison of Features and Treatment Responses for CTEPH and PAH

Feature	CTEPH	PAH
Gross pathology	Organized, central thrombi	Some thrombotic pathology (e.g., terminus technicus: thrombosis *in situ*)
Histopathology	Plexogenic arteriopathy	Plexogenic arteriopathy
Symptoms	Shortness of breath	Shortness of breath
Signs	Pulmonary hypertension and right heart failure	Pulmonary hypertension and right heart failure
Treatment responses	Pulmonary endarterectomy/lung transplant Anticoagulants Advanced therapies[a] Reduced vasodilator response	Lung transplant Vasodilator therapy Anticoagulants Advanced therapies[a]

Definition of abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension.
Reference: 28.
a Including prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors.

2.1 Chronic Thromboembolic Pulmonary Hypertension

CTEPH is characterized by non-resolving thromboemboli that are located proximal or more distal in the pulmonary arterial tree. The true incidence of CTEPH is unknown. The estimates are in the range between 1.5% and 4% within 2 years after acute symptomatic pulmonary embolism (6), but do not cover the true estimate as CTEPH also occurs in patients that did not present with a history of a symptomatic venous thromboembolism event (29, 30). Fischler reported an estimated 85% 1-year survival rate for a mixed CTEPH population of their registry including patients with and without pulmonary endarterectomy (31). From data contained in the publication of Bonderman it can be derived that the 1-year survival probability in patients not suitable for pulmonary endarterectomy is in the range of 80% and the one of patients with pulmonary endarterectomy is in the range of 90% (32).

Pulmonary endarterectomy surgery is the treatment of choice for patients with symptomatic, operable CTEPH. Currently, there are no approved pharmacotherapies for CTEPH. A substantial proportion of patients with CTEPH are deemed inoperable by surgeons, mainly due to criteria such as non-accessibility of thrombi, non-beneficial relation of PVR and anticipated thrombus mass, existing co-morbidities, CTEPH-associated medical conditions, or lack of decrease of pulmonary artery pressure after administration of inhaled NO at the diagnostic right heart catheterization (3).

In addition, approximately 30% of patients who underwent surgery were found to have persistent or recurrent pulmonary hypertension (4). Postoperative persistent or recurrent pulmonary hypertension has been identified as the most important predictor of death. Of particular

importance is the finding by Saouti et al (5) that baseline 6MWD was the only independent predictor of survival in inoperable CTEPH patients.

2.2 Pulmonary Arterial Hypertension

PAH is a uniformly fatal disease that affects adults and children, for which there is no cure. In 1984, the National Institute of Health compiled the first large registry of PAH patients confirming poor survival as the estimated median survival of these patients was 2.8 years (7, 8). While there have been improvements in PAH therapies, PAH remains a progressive and fatal disease.

Despite advances in diagnosis and an increased awareness of the disease, data from regional registries on incidence and prevalence of the disease indicate that the disease still is under-diagnosed because it is diagnosed in the late stages (19, 33, 34, 35). The prevalence of PAH is estimated to be in the range of 15 per million adults based on European registries (19, 33). Advances in the understanding of the pathophysiology of PAH have led to introduction of specific treatments, including PDE5 inhibitors, ERAs, and prostacyclin/prostacyclin analogs. These vasodilator agents provide important symptomatic benefits to patients, and may in some patients also improve long term outcomes.

2.3 Role of Riociguat

Several lines of evidence support the hypothesis that worsening of pulmonary hypertension in CTEPH patients may involve a similar remodeling process to what has been historically described in PAH. First, there is a low correlation between the extent of central obstruction and the degree of pulmonary hypertension. Secondly, pulmonary hypertension progresses in CTEPH patients in the absence of recurrent thromboembolism. Despite satisfactory pulmonary endarterectomy, some patients develop residual pulmonary hypertension (36).

The shared pathology, signs and symptoms of CTEPH and PAH, and the common mechanism of mortality (right ventricular failure due to worsening pulmonary hypertension) provided the rationale for investigating potential pharmacological treatments of both CTEPH and PAH. Riociguat's ability to directly stimulate sGC and synergize with NO, thus restoring the NO-sGC-cGMP pathway, provided the rationale for investigating riociguat in these indications. Importantly, riociguat exerts its biological effects independently of NO, which is present in low levels in some patients with CTEPH and PAH.

This approach was further supported by non-clinical data indicating that besides hemodynamic effects, riociguat has beneficial effects on anti-remodeling processes as shown in several non-clinical pulmonary hypertension models.

2.4 Rationale for Riociguat Dosing Regimen in Phase III

The Sponsor proposes dose titration of riociguat to establish an individualized dose per patient. The use of titration to safely increase dose to efficacious levels is an accepted and common practice in many therapeutic areas and is analogous to the treatment of PAH with parenteral prostanoids and of systemic hypertension (e.g., captopril which is initiated at 25 mg twice daily or 3 times daily [TID] and increased to 50 mg twice daily or TID). We make this proposal for riociguat based on the following:

- Pathophysiology of patients with pulmonary hypertension
- High between-patient variability in pharmacokinetics
- Certain intrinsic and extrinsic factors that affect riociguat exposure

It is well established that patients with CTEPH and PAH are characterized by chronic exposure to high pulmonary resistance, high pulmonary pressure, low cardiac output, and tendency to right heart failure resulting in low systolic blood pressure. The long-term persistence of these characteristics may make patients more sensitive to treatment, resulting in rapid and strong hemodynamic responses.

Early in development, pharmacokinetic/pharmacodynamic analyses demonstrated a close relationship between riociguat plasma concentrations and hemodynamic effects such as decreases in systemic and pulmonary vascular resistance, decrease in systolic blood pressure, and increase in cardiac output. Importantly, high between-patient variability in pharmacokinetics (coefficient of variation of approximately 60% across all doses) was observed, suggesting that a fixed dose of riociguat for all patients was not possible. The close relationship of riociguat exposure to its intended effect, coupled with between-patient variability, was anticipated to result in high between-patient variability in the efficacy response at a given dose.

Intrinsic factors such as severe renal and hepatic dysfunction, advanced age, and disease state, as well as extrinsic factors like co medication with strong multi-pathway inhibitors, and metabolic induction from smoking affect riociguat exposure.

Based on these biologic characteristics we developed an individual dose titration (IDT) scheme to be evaluated in our clinical program. Early in the program, a single dose hemodynamic study that showed that 1.0 mg elicited clinically relevant changes in hemodynamic variables as measured by right heart catheter in patients with pulmonary hypertension and was the minimal effect dose in healthy subjects.

Study 11874 was a single-dose, proof-of-concept study that evaluated invasive hemodynamics in 19 patients with PAH, CTEPH, and interstitial lung disease-associated pulmonary hypertension. Riociguat proved to be safe and well tolerated and showed efficacy based on invasive hemodynamic measurements. Individual titration seemed necessary due to the pronounced

between-patient variability for the maximum plasma concentration of riociguat and overall drug exposure. Mean change from baseline for the 2.5 mg dose group was -5.1 mmHg for mPAP, -168 dyne*second*cm^{-5} for PVR, -546 dyne*second*cm^{-5} for systemic vascular resistance, and +0.95 L/min/m^2 for cardiac index.

This information provided the rationale to start with a low dose of riociguat, then titrate slowly (2-week intervals), with the possibility to titrate to a dose of 2.5 mg TID. Indeed, this gradual IDT from 1 mg TID up to 2.5 mg TID, guided by monitoring of systolic blood pressure and signs/symptoms of hypotension, was developed in phase II, and provided the rationale for its use in phase III. Low within-patient variability (coefficient of variation of approximately 35%) was anticipated to provide consistent efficacy across time for an individual patient once an appropriate dose was established during titration. This was demonstrated successfully for CTEPH and PAH patients in Study 12166 (including long-term follow-up), and has been validated in phase III, with the majority of patients in the long-term extension studies being maintained on 2.5mg TID. A single dose of 5 mg riociguat caused a pronounced reduction in systolic blood pressure in patients with pulmonary hypertension and relevant symptomatic orthostatic hypotension in healthy subjects. A single dose of 2.5 mg was tolerated. This was confirmed in the multiple dose studies such as phase II Study 12166. Therefore, the 2.5 mg TID dose was chosen as the highest dose for phase III studies.

Individual dose titration ensures adequate therapeutic exposure in patients, and prevents underdosing of patients. The goal of IDT in phase III was to safely maximize the clinical benefits (exercise capacity and hemodynamics) for each patient with CTEPH or PAH by titrating each individual patient to the highest tolerated dose.

Choice of Dosing Interval

A TID regimen was chosen instead of a twice daily regimen to increase tolerability and reduce the incidence of symptomatic hypotension. Riociguat has a close and direct relationship between plasma concentrations and blood pressure. Riociguat has a mean half-life of about 13 hours with high inter-patient variability, and a range of 4 to 29 hours. Therefore, in order to bring all patients to effective riociguat plasma concentrations while preventing symptomatic blood pressure drops associated with peak concentrations, the TID regimen was considered preferable.

The TID dosing interval was successfully implemented in phase II Study 12166.

Choice of Titration Interval

Dose increases of 0.5 mg TID every 14 days at the discretion of the treating physician was considered appropriate based on phase II results. Dose decreases based on tolerability could be made at any time. Pharmacokinetic steady-state was demonstrated after 3 days and pharmacodynamic steady-state (blood pressure) after 10 to 14 days. This slow and stepwise titration allows for adaptation to the altered hemodynamic state with decreasing PVR and increasing cardiac output compensating for the simultaneous decrease in systemic vascular resistance.

The 14-day titration interval was successfully implemented in phase II Study 12166.

Tablet Strengths

Five tablet strengths of riociguat (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg) were used in the phase III clinical program so that patients took 1 tablet TID, regardless of dosage. The Sponsor is requesting that all 5 tablet strengths of riociguat be approved in order to facilitate titration with minimal confusion for the patient

Phase III Dosing Regimens

In response to a request from the FDA, PATENT-1 included 2 regimens of riociguat, the primary IDT regimen with a maximum dose of 2.5 mg TID and the exploratory CT regimen with a maximum dose of 1.5 mg TID. A riociguat CT group was not included in CHEST-1. Dosing considerations based on PATENT-1 results are summarized in Section 7 (page 176).

3. Overview of Non-clinical Development

Riociguat is an NO-independent direct stimulator of the sGC and may present a novel therapeutic principle for the treatment of CTEPH and PAH.

3.1 Pharmacodynamics

A set of primary and secondary pharmacodynamic studies was performed to characterize and assess the efficacy and specificity of riociguat.

Primary pharmacodynamic studies

As shown *in vitro* with isolated recombinant sGC, sGC-overexpressing cell line, and vascular endothelial cells, riociguat has a dual mechanism of action: It sensitizes sGC to low levels of NO, and directly stimulates sGC, thereby increasing cGMP levels independently of NO.

In vitro, riociguat is a potent relaxing agent of arteries, coronary arteries, veins, and corpus cavernosum. It also dilated arteries taken from nitrate-tolerant rabbits. In the Langendorff heart preparation, riociguat potently reduced coronary perfusion pressure without influencing left ventricular pressure and heart rate.

In anesthetized normotensive rats, conscious spontaneously hypertensive and normotensive rats, as well as in anesthetized and conscious dogs, riociguat produced a dose-dependent decrease in blood pressure. After multiple dosing, riociguat did not cause tachyphylaxis.

A study in anesthetized dogs demonstrated that riociguat causes a dose-dependent decrease in mean arterial blood pressure, increase in coronary blood flow, increase in oxygen saturation in the coronary sinus blood, and a modest increase in heart rate.

Riociguat showed beneficial effects both in the hypoxia-induced experimental pulmonary hypertension in mice and in rats with monocrotaline-induced pulmonary hypertension after chronic administration.

For induced pulmonary hypertension in rats, riociguat suppressed pulmonary vascular remodeling and improved right ventricular function.

The interaction with the sGC by riociguat was highly specific as shown in different enzyme and radioligand binding assays, in various phosphodiesterase assays as well as in particulate guanylate cyclase assays.

The main metabolite M-1 of riociguat was investigated in a separate study, in which a complete pharmacological characterization was performed.

Overall, in different isolated organs M-1 was about 10-fold less potent than riociguat with regard to its vasorelaxing effect *in vitro*. The comparison of the hemodynamic effects of riociguat and M-1 in anesthetized dogs after intravenous infusion showed that M-1 is about 3 times less potent than riociguat. Overall, M-1 revealed the same pharmacological *in vitro* and *in vivo* profile as riociguat.

Secondary pharmacodynamic studies

Riociguat is a weak inhibitor of platelet aggregation *in vitro* at concentrations about 50-fold above the observed maximum concentration (C_{max}) after 2.5 mg TID. No clinically relevant increase in rat tail transection bleeding time was observed.

Riociguat showed positive effects in various models of cardio-renal protection. Riociguat improved cardio-renal function in a diabetic nephropathy model in eNOS knockout mice, in a low-NO, high-renin rat model of hypertension, and in rat models of chronic renal failure and of pressure and volume overload.

Safety pharmacology studies

Riociguat did not exhibit signs for an arrythmogenic potential *in vitro* and *in vivo*. *In vitro* studies with the human ether-a-go-go related gene (hERG) K+ voltage clamp assay, no effects on hERG K+ current up to 10 µM were observed. In the isolated Purkinje fiber assay (rabbit), only a slight and biologically not-relevant APD_{90} prolongation (+14%) at 10 µM was measured. In studies of anesthetized and conscious (telemetry) dogs, no biologically relevant QTc effects were observed up to doses causing ≥25% blood pressure.

As expected from its pharmacological mechanism of action, effects on gastro-intestinal motility were seen.

Pharmacodynamic interactions

Simultaneous administration of riociguat and glycerol trinitrate, nifedipine, and the PDE5 inhibitors vardenafil and sildenafil showed additive effects on blood pressure and heart rate.

3.2 Pharmacokinetics and Drug Metabolism

The absolute bioavailability of riociguat was moderate in rat (35% to 65%) and higher in dog (50% to 80%). After repeated administration of riociguat to rat and dog in safety studies, M-1 exposure in dog was similar to parent drug exposure, whereas the exposure of M-1 was about 10% of parent drug exposure in rat. The protein binding of riociguat and M-1 was low to moderate and species-dependent. The elimination of riociguat occurred rapidly from rat and dog plasma with half-lives of about 1 to 3 hours.

The distribution of [^{14}C]riociguat and labeled metabolites to organs and tissues was largely homogenous in rat. Blood/brain and blood/testes penetration of radioactivity was low. Highest exposure of radioactivity in terms of area under the curve (AUC) was found for thyroid, liver, and kidney outer medulla. The [^{14}C]riociguat associated radioactivity penetrated the placental barrier to a moderate extent in pregnant rat.

Major biotransformation pathway in liver microsomes of riociguat in rat, dog, and human was the N-demethylation of the drug leading to M-1. No human-specific metabolic pathways and no major species differences in the *in vitro* metabolism of riociguat were found in all species investigated.

In vitro incubations with human liver microsomes and recombinant CYP isoforms revealed several CYP isoforms capable to form M-1 (CYP1A1, 2C8, 2J2, 3A4/5). CYP1A1 is regarded as an important enzyme of riociguat metabolism in liver and lung. N-glucuronidation of M-1 to give metabolite M-4 was catalyzed by human UGT1A1 and UGT1A9.

Riociguat and M-1 were major components in plasma of all species, including human. Metabolite M-4, N-glucuronide of M-1, was a major component in human plasma (6% to 26% of radioactivity AUC) but was not detected in plasma of the other species.

Excretion occurred via both renal and fecal/biliary routes in animal species and in human.

In *in vitro* investigations, riociguat and its main metabolite M-1 exhibited no inhibitory and no inductive potential on major human CYP isoforms, but revealed an inhibitory potency on CYP1A1. Furthermore, no inhibitory potency towards human glucuronosyl transferases (UGTs) or sulfotransferases (SULTs) was observed. Riociguat and M-1 are classified as P-gp and BCRP

substrates *in vitro*, but are not inhibitors of P-gp, BCRP, and organic cationic transporters at relevant therapeutic concentrations. In addition, riociguat is no inhibitor of OATP1B1, OATP1B3, OAT1 and OAT3.

Therefore, the risk of clinically relevant drug-drug interactions by riociguat and M-1 is regarded to be low. Clinically relevant drug-drug interactions with co-medications that are significantly cleared by CYP1A1 cannot be ruled out.

3.3 Toxicology

The toxicological program included studies to investigate the systemic toxicity as well as exaggerated pharmacodynamic effects after single and repeated administration up to 26 weeks in rats and up to 52 weeks in dogs, reproductive toxicity studies, genotoxicity studies and carcinogenicity studies as well as studies addressing specific questions (phototoxicity studies, toxicity of impurities, mechanistic investigation and studies in juvenile animals). The toxicological program was designed to support the chronic use of riociguat in humans.

The toxicological profile after repeated administration was characterized by effects secondary to the intracellular cGMP increase. In all species tested, effects subsequent to an exaggerated smooth muscle cell relaxation were observed. After administration of riociguat, no toxicities of specific interest (e.g., renal, hepatic toxicity) or findings unrelated to the pharmacological mechanism of action were observed.

In mice, in addition to hemodynamic effects, gastro-intestinal intolerability due to motility reduction following smooth muscle cell relaxation was found. As a consequence of this chronically reduced motility, intestinal dysbiosis and chronic inflammation associated with mucosal degeneration and regeneration were observed.

In rats, the toxicological profile of riociguat was characterized by hemodynamic effects and sequelae thereof, as well as by changes on bone metabolism and morphology in juvenile and adolescent rats. The bone findings are considered to be related to the pharmacological mechanism of action, as the NO-sGC-cGMP pathway is involved in bone metabolism. However, since no findings on bones were seen in adult rats, as well as in full-grown dogs, and the findings were restricted to areas undergoing rapid turnover during bone growth, the findings in fast growing animals are not considered relevant for the adult patient population.

In dogs, as a consequence of the pharmacological mechanism of action, blood pressure lowering, reflex tachycardia and as a consequence morphological changes as known from other vasodilative drugs were observed. In addition, gastro-intestinal smooth muscle relaxation resulted in increases of vomitus and diarrhea.

In experimental animals, riociguat treatment has revealed no impact on fertility and early embryonic development.

Maternal tolerability and embryo-fetal, as well as pre- and early postnatal, development was influenced by the pharmacological properties of riociguat. In rats, an increase of cardiac malformations was seen, and is considered a consequence of the hemodynamic effects of riociguat and potential anti-proliferative effects on undifferentiated mesenchymal cells during cardiac development.

Juvenile animal testing revealed the same target organs of toxicity as in adult rats with no new findings. Bone findings were more pronounced than in adolescent rats.

Riociguat was negative in a battery of *in vitro* and *in vivo* genotoxicity tests and revealed no evidence for a genotoxic risk.

In 2-year lifetime bioassays in rats and mice, no drug-related neoplasms were observed under riociguat treatment, and an absence of a carcinogenic risk for humans is deduced.

Metabolite M-1 was tested in a comprehensive toxicological program. Overall, the toxicological profile of M-1 is comparable to the non-clinical safety profile of riociguat. At high exposure levels starting at about 40-fold of human exposure, evidence for adverse effects of M-1 on the kidneys was identified. No renal effects were seen up to 13-fold of human therapeutic exposure in terms of AUC corrected for inter-species differences in protein binding for M-1.

In summary, single and repeat-dose toxicity studies in rats, mice and dogs, which fulfill the requirements for non-clinical safety evaluation, revealed no unexpected toxicity of riociguat. The non-clinical safety profile is characterized by exaggerated pharmacological activity of riociguat subsequent to an increase of intracellular cGMP levels. Studies on genotoxicity, juvenile toxicity and carcinogenicity did not yield any specific concern. Developmental toxicity revealed an increase of cardiac malformations in rats. This effect is seen to be due to a mechanism of action related to hemodynamic and potential anti-proliferative effect on the developing heart.

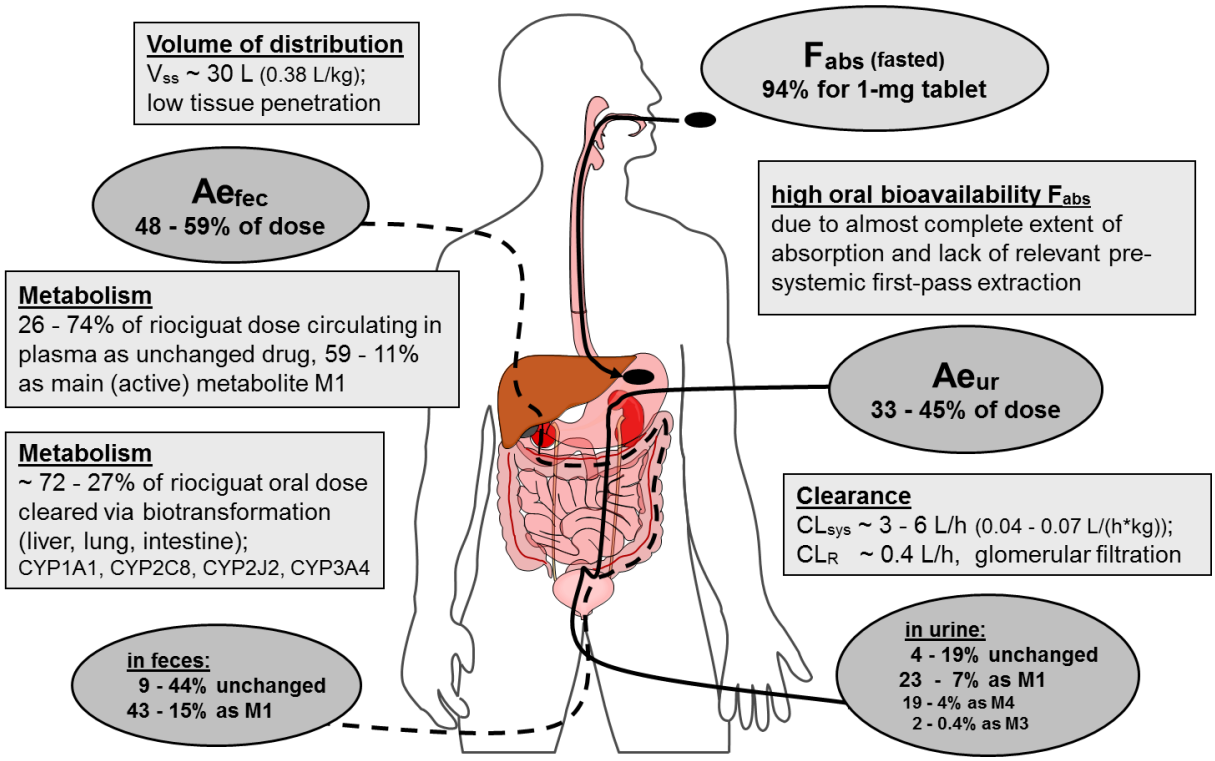
4. Overview of Clinical Pharmacology Program

The clinical pharmacology program for riociguat is comprised of 33 studies, including 768 healthy subjects or patient-volunteers (with renal or hepatic impairment, respectively), and 26 patients with pulmonary hypertension. In addition, population models for riociguat pharmacokinetics, pharmacodynamics, and pharmacokinetic/pharmacodynamic relationships were developed, based on sparse sampling in all riociguat-treated patients enrolled in phase II and III trials, to support interpretation of clinical results. Pooled analyses of riociguat exposure/response in patients treated with riociguat in phase III for the pursued indications support the efficacy/safety conclusions.

4.1 Pharmacokinetics

Figure 8 provides an overview of the clinical pharmacokinetic profile of riociguat to be reviewed in the subsequent sections:

Figure 8: Summary of Riociguat Mass Balance, Excretion Pattern, Distribution and Clearance Properties in Humans



Ae_{ur}	amount excreted into urine
Ae_{fec}	amount excreted into bile/feces
CL_{sys}	systemic (plasma) clearance
CL_R	renal clearance (via glomerular filtration)
CYP	cytochrome P_{450}
F_{abs}	absolute bioavailability
M-1, M-3, M-4	metabolites M-1, M-3 and M-4
V_{ss}	volume of distribution at steady-state

All numbers are approximate; sum of percentages is 90 to 95% (recovery in human mass balance study).
Percentages separated by a hyphen indicate minimum - maximum observed in Study 11911.
The assay methodology for riociguat is described in Appendix 11.6 (page 207).

4.1.1 Rate and Extent of Absorption

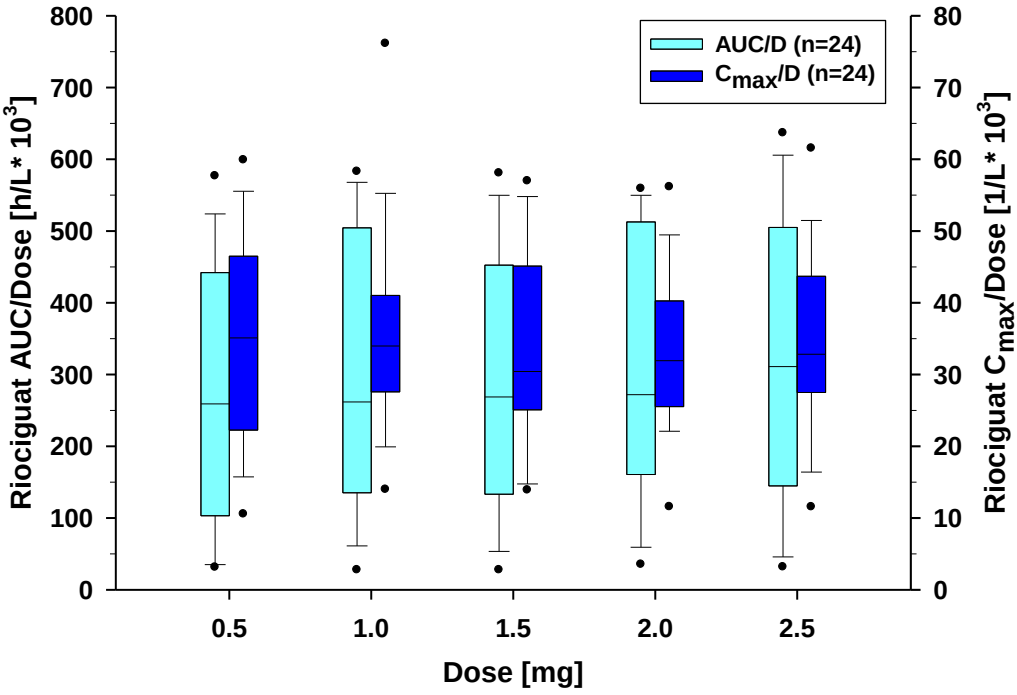
In accordance with its *in vitro* characteristics and *in vivo* animal data, oral bioavailability of riociguat is high due to almost complete absorption with or without food (up to the highest

therapeutic dose of 2.5 mg) and lack of relevant pre-systemic first-pass extraction of this low-clearance drug. The absolute bioavailability as a 1.0 mg immediate release tablet was 94% (90% CI: 83%; 107%) in comparison to 1.0 mg riociguat as a 60-minute intravenous infusion.

Riociguat is readily absorbed after oral administration as immediate release tablet with median C_{max} observed after 1.0 to 1.5 hours after dosing.

Riociguat pharmacokinetics behaved dose-proportionally with increasing tablet doses (Figure 9).

Figure 9: Riociguat Dose-normalized AUC and C_{max} (AUC/Dose, C_{max}/Dose) Following Administration of Riociguat Tablet Doses 0.5 mg to 2.5 mg Under Fasting Conditions



Note: Box-Whisker plot with 5, 10, 25, 50, 75, 90, and 95 percentiles; n=24 per dose.
Definition of abbreviations: AUC = area under the curve; C_{max} = maximum observed concentration.

Lack of relevant food effect could be demonstrated for the 2.5 mg immediate release tablet dose.

Consistent with its basic nature, riociguat is highly soluble in aqueous acidic medium; solubility in pure water at neutral pH is low (4 mg/L at 25°C). Changes in gastric pH (e.g., induced by concomitant medication of antacids or proton pump inhibitors) reduced AUC of riociguat by 34 or 26%, respectively.

In conclusion, based on the data presented above, it can be inferred that oral absorption of riociguat is almost complete and oral bioavailability is high (94%) for riociguat immediate release

tablets. Dose-proportionality was demonstrated for the dose range of 0.5 to 2.5 mg riociguat tablets.

Absence of a clinically relevant food effect was demonstrated and supported the mode of administration recommended in the pivotal clinical phase III trials where riociguat as 0.5 to 2.5 mg tablets were allowed to be taken irrespective of food intake.

4.1.2 Distribution, Binding with Plasma Proteins

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

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

Displacement studies in human plasma revealed that the unbound fraction of riociguat remains unchanged *in vitro* after co-incubation with ibuprofen, warfarin, nifedipine, digitoxin, atorvastatin, furosemide, sildenafil, and bosentan. There was a 1.5-fold increase of the unbound fraction after addition of 200 mg/L salicylic acid (approximately corresponding to a C_{max} of single oral doses of 4 to 5 grams of acetylsalicylic acid). In a phase I study employing riociguat 2.5 mg co-administered with Aspirin® 500 mg, no relevant pharmacokinetic interaction was observed.

The volume of distribution at steady-state is 30 L (0.38 L/kg) for riociguat, indicating a low affinity to tissues.

Riociguat penetration across the blood-brain-barrier and placental barrier is of low and moderate extent in the respective rat studies. The estimated amount of radioactivity excreted with milk of lactating rats is 2.2% of the dose within 32 hours after administration.

4.1.3 Metabolism

Riociguat is eliminated by both metabolic degradation as well as direct excretion of unchanged active compound (Figure 8, page 67).

The major biotransformation pathway is oxidative N-demethylation of the drug leading to metabolite M-1 and subsequently, catalyzed by UGT1A1 and UGT1A9, the N-glucuronide M-4. N debenzylation of riociguat (leading to metabolite M-3) is of minor importance.

CYP reaction phenotyping approaches applying human liver, intestinal and lung microsomes revealed that CYP2C8, CYP2J2, and CYP3A4 contribute to a similar extent to M-1 formation in the liver, whereas CYP3A4 and CYP2J2 almost equally catalyze M-1 formation in the intestine. In addition, CYP1A1 significantly contributed to the N-demethylation of riociguat as demonstrated with microsomes from human liver and lung tissue in the presence of CYP1A1 inhibitors like α-naphthoflavone, ketoconazole and quercetin.

Biotransformation of riociguat was much more pronounced in lung microsomes of smokers. This significant difference in enzymatic activity can be explained by induction of CYP1A1 in smokers, and discrepancies in the expression of this enzyme according to the smoking status of patients most likely explain the 2- to 3-fold difference of riociguat clearance between smokers and non-smokers.

In terms of exposure, riociguat (with 26% to 74%) and M-1 represented the majority of the radioactivity present in plasma (11% to 59%). Metabolite M-4 accounted for 6 to 26 % of the total radioactivity present in plasma. Metabolite M-1 exhibits pharmacological activity as an sGC stimulator but at 3- to 10-fold lower potency; M-4 has been shown to be pharmacologically inactive.

4.1.4 Excretion

Total riociguat (parent compound and metabolites) is excreted via both renal (33% to 45%) and biliary/fecal routes (48% to 59%). Approximately 4% to 19% of the administered dose was excreted as unchanged riociguat via the kidneys, pre-dominantly via (passive) glomerular filtration. Seven to 23% of the administered dose was recovered in urine as M-1, excreted via both glomerular filtration and active transporter-mediated secretion. Parent drug and M-1 were also the major constituents in fecal extracts in man, at varying extents (riociguat: 9% to 44%; M-1: 15 to 43%).

Riociguat and M-1 have been characterized *in vitro* to be both a substrate of P-gp and the multi-drug transport protein BCRP. Considering that active renal secretion is not a major route of elimination for riociguat, the major involvement of P-gp and BCRP is most likely its biliary and/or extra-biliary excretion into feces.

In summary, riociguat is eliminated via 3 routes in man: 27% to 71% of the dose was subject to oxidative biotransformation (as metabolites M-1, M-3 and M-4), 13% (up to 44%) was excreted as unchanged drug in feces, and 6% (up to 19%) was excreted as unchanged drug in urine via glomerular filtration. The quantitative contribution to these elimination/ clearance pathways considerably varies between individuals, mainly dependent on the individual metabolic activity status (e.g., CYP1A1 due to smoking habits).

With an average systemic clearance after intravenous administration of 3.2 L/hour (0.04 L/[h*kg]) in non-smoking subjects (6.0 L/hour (0.07 L/[h*kg]) in smokers) riociguat can be classified as low-clearance drug, lacking relevant first-pass. Elimination of riociguat in healthy subjects is associated with a mean terminal half-life of 6.8 hours with high inter-individual variability (coefficient of variation: 74%). In elderly healthy subjects, mean half-lives are prolonged to 12 hours. Due to the underlying disease affecting riociguat clearance, riociguat terminal half-life in patients is about 13 hours on average.

4.1.5 Comparative PK in Healthy Subjects and Patients

Riociguat pharmacokinetics is linear up to 2.5 mg TID in both healthy subjects and patients with pulmonary hypertension. Absorption of riociguat is comparable between healthy subjects and patients with peak concentrations reached after 0.25 to 1.5 hours. The elimination phase is prolonged in patients with mean terminal half-lives of approximately 12 hours. The resulting exposure (AUC) in patients is approximately 2- to 3-fold higher at steady state compared to healthy subjects.

Some of the intrinsic factors, such as age, with known reductions in renal and hepato-biliary clearance processes as normal physiological changes may contribute to increased riociguat exposure. Moreover, the underlying pulmonary hypertension *per se* alters renal and/or hepato-biliary elimination of riociguat due to reduced cardiac output, liver shunts, worsening renal function, etc.

Table 7 provides key data for riociguat exposure at steady state for CTEPH and PAH patients following multiple dosing (individualized dose titration up to 2.5 mg TID) at last day of PATENT-1 (Day 84) and CHEST-1 (Day 112). Figure 10 depicts the respective plasma concentration versus time profile (post-hoc estimates) for the riociguat IDT group in PATENT-1 and CHEST-1.

Table 7: Riociguat Exposure Data at Steady State Following Multiple Doses (Individual Dose Titration up to 2.5 mg TID) of Riociguat in PATENT-1 and CHEST-1

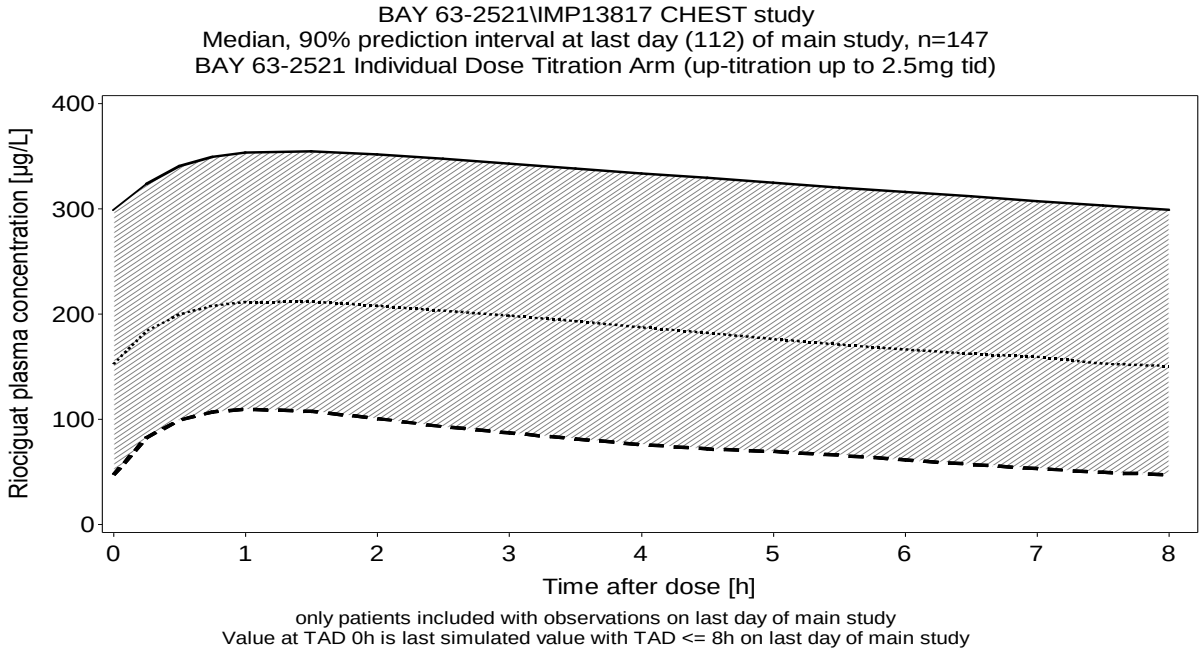
Riociguat		PAH patients PATENT-1 Study (N=228)	CTEPH patients CHEST-1 Study (N=153)
AUC [µg*h/L]	Geometric mean (CV)	1174 (55.0)	1433 (45.2)
	Median	1226	1475
C_{max} [µg/L]	Geometric mean (CV)	176 (47.8)	207 (38.9)
	Median	178	213
C_{trough} [µg/L]	Geometric mean (CV)	113 (69.6)	145 (58.4)
	Median	124	152

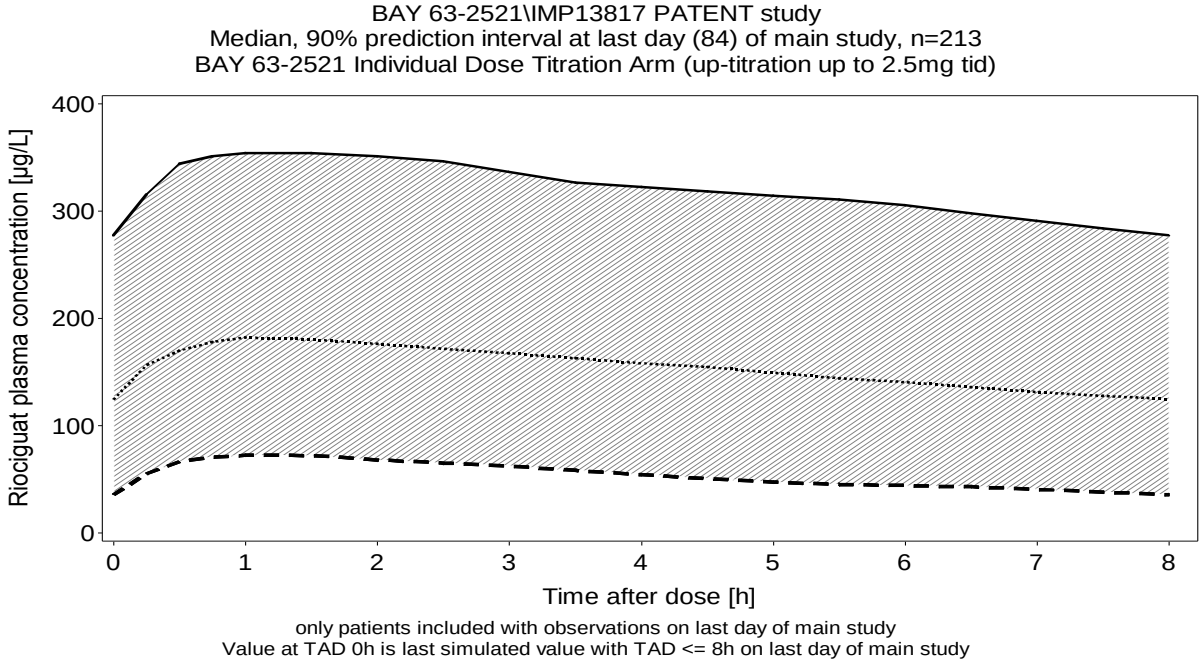
Definition of abbreviations: AUC = area under the curve; C_{max} = maximum concentration; CTEPH = chronic thromboembolic pulmonary hypertension; C_{trough} = trough concentration; CV = coefficient of variation (%); PAH = pulmonary arterial hypertension.

Variability in riociguat exposure (AUC) in patients is high with inter-individual variability (geometric coefficient of variation of approximately 60%) across all doses. The intra-individual variability is considerably lower with 35% for riociguat trough plasma concentration (for instance, over the close to 4-year extension period of phase II Study 12166).

Riociguat plasma-concentration versus time profiles after multiple dosing TID were rather flat without pronounced peak-to-trough fluctuation.

Figure 10: Riociguat Plasma Concentration Versus Time Profile for Riociguat IDT Group Within One Dosing Interval at Last Day of CHEST-1 and PATENT-1





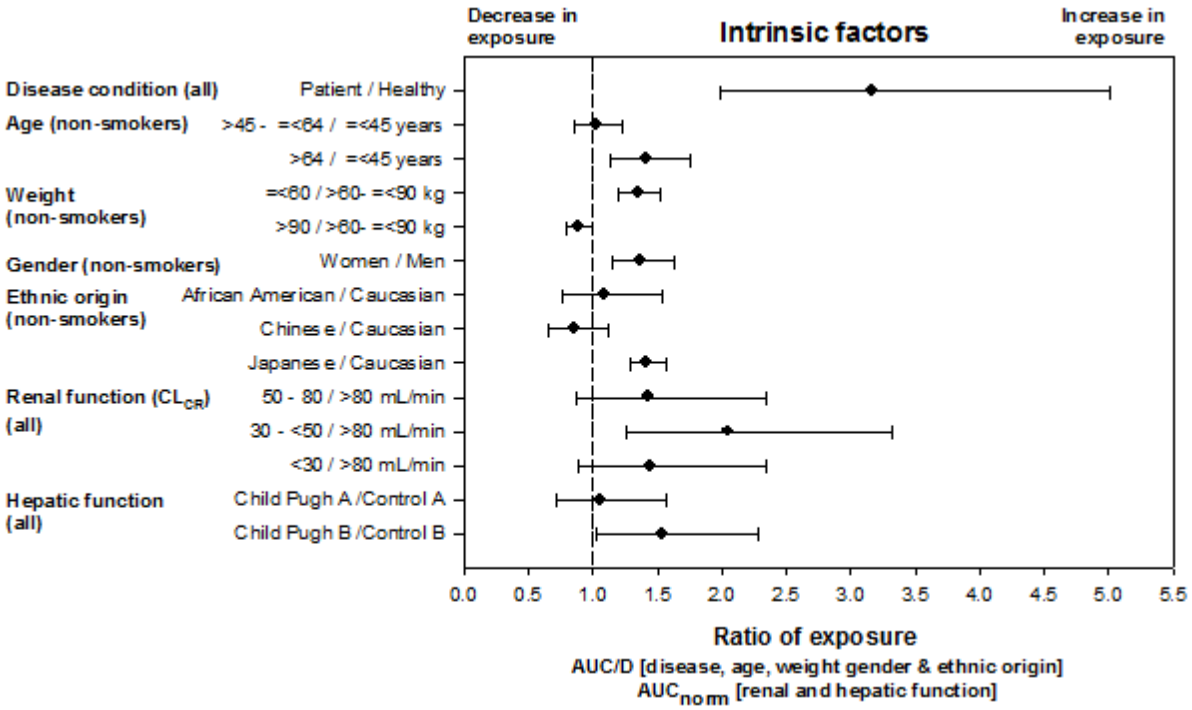
Definition of abbreviations: BAY 63-2521 = riociguat; IDT = individual dose titration.
Upper panel CHEST-1; lower panel PATENT-1 population pharmacokinetic post-hoc estimates. median and 5/95 percentiles of individually post-hoc estimated plasma concentration/time curves; n= 228/153]

4.1.6 Pharmacokinetics Related to Intrinsic Factors

All relevant covariates, such as age, gender, body weight, renal and hepatic function as well as ethnicity, have been investigated in detail in independent clinical-pharmacological studies and via population approaches in the phase II and III studies.

Figure 11 shows a summary of riociguat exposure data (AUC/Dose) in relation to intrinsic factors potentially affecting riociguat plasma concentrations. Results are derived from a pooled analysis of phase I studies and include all subjects and non-smokers only, and from a pooled analysis (all subjects) of studies on renal and hepatic impairment.

Figure 11: Impact of Intrinsic Factors on Riociguat Exposure (AUC/Dose for Disease, Age, Body Weight, Gender and Ethnic Origin; Normalized AUC for Renal and Hepatic Function) (Including Subjects Valid for Pharmacokinetic Analysis)



Definition of abbreviations: AUC = area under the curve; CLcr = creatinine clearance.

Elderly subjects have a 40% prolonged terminal half-life and subsequently higher AUC compared to younger subjects. No notable age-related change in C_{max} was observed. An exploratory across-study analysis of all phase I trials confirmed this effect of age on riociguat

pharmacokinetics. Subjects aged 65 years and older show prolonged riociguat half-lives (by approximately 30%) and increases in riociguat exposure (by approximately 40%).

The influence of **body weight** was assessed in the context of studying ethnic influences. In this combined analysis of 4 studies, a minor-to-moderate impact of body weight on dose-normalized AUC and C_{max} of riociguat was apparent. The exploratory across-study analysis of all phase I trials showed that AUC and C_{max} of riociguat are approximately 35% and 40% higher, respectively, at body weights below 60 kg compared to normal weight (>60 to 90 kg). Exposure at body weights >90 kg is approximately 11% lower compared to normal weight.

The AUC and half-life values are similar for men and women. The C_{max} values are on average 35% higher in women than in men ($p<0.05$). This difference is explained at least partly by body weight, as body weight-normalized C_{max} values were on average 20% higher in women. The exploratory across-study analysis of all phase I trials confirmed this moderate effect of gender, mainly driven by differences in body weight, on riociguat exposure (approximately 35% higher AUC, 30% higher C_{max} for women compared to men).

Within the range of high inter-subject variability observed independently for all **ethnic groups**, riociguat exposure in Japanese subjects tends to be at the higher end of the range, especially with respect to C_{max} when compared to whites (i.e., Caucasians). The differences in body weight-normalized exposure are less pronounced (12% for normalized AUC, 23% for normalized C_{max}).

Differences in riociguat exposure observed between the other investigated ethnic groups (black [i.e., African-American] and Chinese) are within the magnitude of inter-individual variability described for white subjects.

The influence of **renal impairment** on riociguat pharmacokinetics was investigated in a pre-specified pooled analysis of 2 studies including smokers and non-smokers. In accordance with prior knowledge and expectation, mean renal clearance of riociguat decreased by 33% in subjects with mild renal impairment, by 67% in subjects with moderate renal impairment, and by about 82% in subjects with severe renal impairment compared to the group of healthy controls. However, riociguat overall exposure increased in all groups of renal impairment, but did not increase proportionally to decreasing renal function as expected. Overall, mean dose- and weight-normalized AUC of riociguat was 43% higher in subjects with mild renal impairment, 104% higher in subjects with moderate renal impairment, and 44% higher in subjects with severe renal impairment compared to subjects with normal renal function. Exposures observed in subjects with renal impairment were highly variable and the ranges of exposures overlapped with those observed in healthy controls.

The pre-specified pooled analysis of 2 studies (including smokers and non-smokers) investigating the influence of **hepatic impairment** on riociguat pharmacokinetics showed that apparent (total) body clearance of riociguat decreases in subjects with hepatic impairment (by 6% for the Child Pugh A group and by 35% for the Child Pugh B group when compared to their healthy controls).

Due to the rapid absorption of riociguat with median time to maximum concentration of ≤1.5 hours in both hepatically impaired patients and healthy controls, mean weight-normalized C_{max} values of riociguat are similar in all 4 groups. Mean half-life of riociguat is prolonged in Child Pugh B subjects (13.7 hours; geometric mean) compared to Child Pugh A subjects (9.2 hours) and healthy controls (9.0 hours and 7.5 hours). As a result, mean exposure to riociguat (normalized AUC) is significantly increased by approximately 50% (total) to 70% (unbound) in Child Pugh B subjects compared to their matched healthy controls with the rank order of exposure Child Pugh B subjects > Child Pugh A subjects ≥ healthy controls. Exposures (normalized AUC) observed in subjects with hepatic impairment are highly variable and the ranges of exposures observed in Child Pugh A and Child Pugh B subjects are overlapping with those observed in healthy controls.

4.1.7 Pharmacokinetics Related to Extrinsic Factors

Figure 12 (page 78) summarizes riociguat exposure data in relation to various extrinsic factors potentially affecting riociguat plasma concentrations in dedicated clinical-pharmacological studies.

CYP1A1 catalyzes the formation of riociguat's main metabolite M-1 in liver and lungs and is known to be inducible by polycyclic aromatic hydrocarbons, for instance, present in cigarette smoke.

While absorption and distribution of riociguat remains unaffected by smoking status, induction of CYP1A1 in smokers increases mean clearance by 2- to 3-fold in healthy subjects, markedly reduces mean elimination half-life, and significantly contributes to the overall variability of drug exposure.

This effect leading to reduced riociguat exposure in smoking patients (by 2.3-fold on average) at high variability is consistent in all studies with participation of smokers, including clinical phase II and III trials. No difference is apparent between white, Japanese or Chinese subjects.

4.1.8 Time-Dependent Changes in Pharmacokinetics

Riociguat pharmacokinetics is linear with no relevant undue accumulation beyond steady-state after multiple doses up to 2.5 mg TID. Morning and evening pharmacokinetic profiles within the TID dosing regimens are comparable and do not indicate any diurnal alteration in riociguat absorption or elimination behavior.

Inter-individual variability in riociguat pharmacokinetics is high with total variability of 77% for half-life, 90% for AUC/Dose, and moderate with 42% for C_{max}/Dose in healthy subjects, including smokers and non-smokers. Intra-individual variability in various crossover studies is consistently lower with 18% for AUC/Dose and 24% for C_{max}/Dose.

Examination of a panel of 1069 genetic variations in 172 drug metabolizing genes and transporters did not reveal genetic factors contributing to the pharmacokinetic variability of riociguat in healthy male white (n=147) and Japanese (n=12) subjects.

One main factor contributing to variability of riociguat exposure is smoking in subjects and patients. Riociguat clearance was approximately 2- to 3-fold higher in smokers compared to non-smokers in populations of healthy subjects and patients with pulmonary hypertension. Inter-individual variability in smokers and non-smokers alone may still be considerably high due to other environmental/diet factors possibly accounting for induction of CYP1A1, but also due to imprecisions when assessing smoking status and quantitative smoking habits in clinical practice.

4.1.9 Variability in Pharmacokinetics

Inter-individual variability in riociguat pharmacokinetics is high with total variability of 77% for half-life, 90% for AUC/Dose, and moderate with 42% for C_{max}/Dose in healthy subjects, including smokers and non-smokers. Intra-individual variability in various crossover studies is consistently lower with 18% for AUC/Dose and 24% for C_{max}/Dose.

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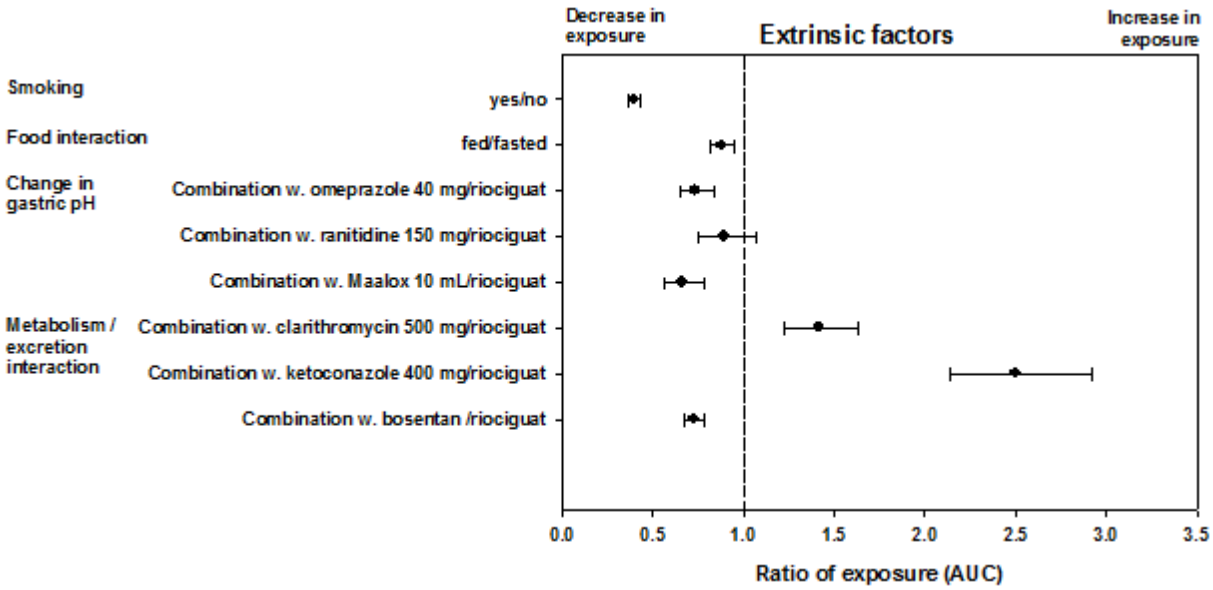
Inter-individual variability (% coefficient of variation) in population pharmacokinetic estimates for clearance from the phase III trials, when correcting for the relevant intrinsic and extrinsic factors as potential sources of variability, were in the range of 45%. Inter-individual variability in exposure (AUC) across all doses is approximately 60% in the patient populations of phase III trials. The intra-individual variability in patients is considerably lower with 35% for trough concentrations, for instance, over the close to 4-year extension period of phase II Study 12166.

4.1.10 Clinically Relevant Pharmacokinetic Interactions with Other Medicinal Products or Other Substances

Figure 12 summarizes riociguat exposure data in relation to various extrinsic factors potentially affecting riociguat plasma concentrations in dedicated clinical-pharmacological studies.

Figure 12: Impact of Extrinsic Factors on Riociguat Exposure (AUC for Smoking Habits, Influence of Food, Co-medications Affecting Absorption or Metabolism/ Elimination) with 90% Confidence Interval (Including Subjects Valid for Pharmacokinetic Analysis)



Definition of abbreviations: AUC = area under the curve; w. = with.

Smoking reduced riociguat exposure (AUC/Dose) by 60% compared to AUC/Dose of non-smokers via induction of CYP1A1.

Lack of relevant **food effect** was demonstrated for the 2.5 mg riociguat immediate release tablet. Dosing in the pivotal clinical phase III trials with riociguat tablets (all dose strengths from 0.5 up to 2.5 mg) was allowed irrespective of food intake.

Pre- and co-treatment with the **proton pump inhibitor omeprazole** 40 mg once daily reduced riociguat bioavailability with a mean C_{max} decrease of 35% and a corresponding AUC decrease of 26%. Co-treatment with an **antacid** (10 mL of aluminum hydroxide/ magnesium hydroxide [Maalox®]) reduced riociguat bioavailability with a mean C_{max} decrease of 56% and a mean AUC decrease of 34%. Co-treatment with the **H_2-antagonist ranitidine** (150 mg once daily) reduced riociguat bioavailability with a mean C_{max} decrease of approximately 15% and a mean AUC

decrease of approximately 10%. These results confirm lower bioavailability of riociguat in neutral versus acidic medium as expected from *in vitro* solubility data.

Co-administration of **acetylsalicylic acid** (500 mg) or **warfarin** (25 mg), respectively, did not affect riociguat pharmacokinetics.

According to mechanistic investigations, the main elimination pathways for riociguat are CYP-mediated oxidative metabolism, direct biliary/fecal excretion of unchanged drug, and renal excretion of unchanged drug via glomerular filtration.

Riociguat and its main human metabolite M-1 are neither inducers (CYP1A2, CYP3A4) nor inhibitors (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2, and 3A4) of any major CYP isoforms or human UGTs or SULTs *in vitro* at therapeutic plasma concentrations.

No clinically relevant drug-drug interactions due to inhibition of transporters such as P-gp or BCRP, OATP1B1, OATB1B3, OAT1, OAT3, or OCTs by riociguat are expected. Furthermore, metabolite M-1 is not an inhibitor of P-gp, BCRP and OCTs at relevant therapeutic concentrations.

Lack of mutual pharmacokinetic interaction between riociguat and the **CYP3A4 co-substrates midazolam and sildenafil** could be demonstrated *in vivo*.

Riociguat and M-1 revealed an inhibitory potency on CYP1A1 *in vitro* with a K_i value of 0.6 µM, each. Clinically relevant drug-drug interactions with co-medications that are significantly cleared by CYP1A1-mediated biotransformation (such as erlotinib or granisetron) cannot be ruled out.

Based on *in vitro* studies, CYP1A1, CYP3A4/3A5, CYP2C8 and CYP2J2 are known to be involved in riociguat biotransformation and P-gp/BCRP in its active excretion processes. Thus, riociguat was classified as potentially susceptible to pharmacokinetic interaction when co-medicated with inhibitors or inducers of these enzymes and/or transporter proteins.

To evaluate the drug-drug interaction potential for riociguat as victim, a series of 87 drugs from various compound classes (e.g., anticancer drugs, analgesics, antiviral drugs, antibiotics, and antifungal azoles) were part of a broad *in vitro* screening with common co-medications tested regarding their potential to affect riociguat microsomal (hepatic) oxidative metabolism *in vitro*:

- N-demethylation (i.e., metabolite M-1 formation) in human liver microsomes was considerably inhibited by human immunodeficiency virus protease inhibitors (ritonavir, atazanavir > indinavir, inhibitory concentration$_{50}$ (IC_{50}) values of 5.3 to 11.7 µM) and antifungal azoles (ketoconazole > clotrimazole, miconazole, IC_{50} values of 0.6 to 5.7 µM).

- Pronounced inhibition of recombinant human CYP1A1, an important CYP isoenzyme in riociguat metabolism, especially in smokers, was observed by the antifungal azoles ketoconazole, clotrimazole and miconazole (IC_{50} values of 0.3 to 0.6 µM), as well as carvedilol, ebastine, quercetin (IC_{50} values of 0.6 to 2.5 µM) and tyrosine kinase inhibitors like erlotinib, gefitinib, imatinib, sorafenib and sunitinib (IC_{50} values of 0.2 to 4.2 µM).

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

- Co-administration of **clarithromycin** 500 mg twice daily, classified as a strong and selective CYP3A4 and weak-to-moderate P-gp inhibitor, moderately increases riociguat exposure with a mean AUC increase by 41% at no significant change in C_{max}.
- **Ketoconazole** is classified as a strong CYP3A4 and P-gp inhibitor according to the FDA guidance. *In vitro*, ketoconazole could be established as a potent 'multi-pathway CYP and P-gp/BCRP inhibitor' for riociguat metabolism and excretion. As expected from these *in vitro* data, concomitant administration of 400 mg once daily ketoconazole leads to a 150% (range up to 370%) increase in riociguat mean AUC and a 46% increase in mean C_{max}. Mean terminal half-life increases from 7.3 to 9.2 hours and mean apparent (total) body clearance decreased from 6.1 to 2.4 L/h.

The pharmacokinetic interaction observed for ketoconazole covers the high end of expected magnitude of interaction due to the potential of ketoconazole to inhibit a wide range of isozymes of the CYP class and transporters such as P-gp and BCRP. Extending the results of the ketoconazole study, a similar increase of exposure might be expected with other strong CYP3A4 inhibitors within the class of azole antimycotics with a potential to inhibit additional CYP isozymes or P-gp/BCRP (e.g., itraconazole) or with drugs of the class of human immunodeficiency virus protease inhibitors, such as ritonavir.

Co-medications that inhibit single pathways such as tyrosine kinase inhibitors like erlotinib and gefitinib (potent inhibitors of CYP1A1) or P-gp inhibitors/BCRP inhibitors such as cyclosporine A may potentially increase riociguat exposure. However, based on the totality of *in vitro* and *in vivo* information, the extent of interaction is not expected to exceed the magnitude observed for the ketoconazole interaction.

Bosentan, a common PAH-specific co-medication that is reported to be a pronounced inducer of CYP3A, led to a decrease of riociguat steady-state plasma concentrations in patients by 27% on average.

The concomitant use of riociguat with strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbitone, or St. John's Wort) may also lead to decreased riociguat plasma concentrations. No information on the potential effect of inducers of the transporter proteins P-gp or BCRP alone on riociguat pharmacokinetics can be provided due to lack of known selective inducers.

4.2 Pharmacodynamics

Riociguat is a direct stimulator of sGC *in vitro* and *in vivo*, which is independent of NO, the endogenous stimulator of the enzyme, but enhances the effects of NO when present.

4.2.1 Primary and Secondary Pharmacological Effects

In healthy subjects the measurement of the heart rate over 1 minute is a sensitive and non-invasive parameter for the effect on systemic vascular resistance, especially if placebo-corrected and baseline-adjusted by statistical methods. This parameter is more sensitive to indicate a systemic vascular effect than the measurement of systolic blood pressure in the supine position.

In phase I dose-escalation studies, riociguat had significant dose-dependent effects on heart rate over 1 minute at single doses of 1.0 to 5.0 mg when compared with placebo ($p<0.01$). For the effect on heart rate over 1 minute after multiple oral doses of 0.5, 1.0, 1.5, or 2.5 mg riociguat TID for 10 days, mean placebo-corrected differences were 3.0, 3.8, 6.9, 6.7, and 10.9 beats per minute on the first day, and 1.0, 3.0, 7.0, 4.8, and 4.4 beats per minute on the last day for the 5 dose steps, respectively. This increase in heart rate is seen as a reflex to the reduced systemic vascular resistance and blood pressure, and was observed at all doses. The effect on heart rate was more pronounced after the first dose and attenuated at steady state on the last day. This increase in heart rate, observed particularly after the first dose in healthy subjects, was not observed in patients with CTEPH or PAH after 3 months of treatment.

After multiple oral doses of 0.5, 1.0, 1.5, or 2.5 mg riociguat TID for 10 days, mean placebo-corrected changes in diastolic blood pressure were -0.8, -2.4, -2.0, -3.7, and -3.3 mmHg on the first day, and -2.6, -3.1, -0.7, -4.9, and -5.4 mmHg on the last day for the 5 dose steps, respectively. A consistent and significant decrease in systolic blood pressure was observed for the highest doses 2.5 mg twice daily and 2.5 mg TID. The mean placebo-corrected changes in systolic blood pressure were -3.0, and -1.9 mmHg on the first day, and -5.6, and -8.0 mmHg on the last day for the 2.5 mg twice daily and 2.5 mg TID doses, respectively.

Vasoactive hormones were investigated to assess the effect of riociguat on important pressure control mechanisms, thus demonstrating the extent of compensational efforts. Following single dosing, riociguat produced a statistically significant increase in **noradrenaline** levels at only the 5.0 mg dose ($p=0.0006$ versus placebo). A statistically significant and dose-dependent increase in **plasma renin activity** was observed at doses of 1.0 mg ($p=0.0064$), 2.5 mg (solution) ($p=0.003$), and 5.0 mg ($p<0.0001$) compared with placebo. Riociguat also produced a statistically significant increase in **plasma cGMP** concentrations at doses of 2.5 mg (solution) ($p=0.0024$) and 5.0 mg ($p<0.0001$) compared with placebo. In doses up to 5.0 mg, riociguat did not have significant effects on plasma **aldosterone** and **angiotensin II** concentrations.

After multiple oral doses of 0.5, 1.0, 1.5, or 2.5 mg riociguat TID for 10 days, statistically significant and dose-dependent changes versus placebo in **plasma renin activity** were observed starting at the 0.5 mg riociguat dose after 10 days of dosing. Starting at a dose of 1.5 mg TID, increases in plasma renin activity were less pronounced on Day 9 compared to Day 0. For cGMP, statistically significant and dose-dependent changes versus placebo were observed starting at the 1.0 mg riociguat dose after a single dose and after 10 days of dosing. Starting at a dose of 1.5 mg TID, increases in cGMP were more pronounced on Day 9 compared to Day 0.

Patients with pulmonary hypertension due to PAH, CTEPH, or interstitial lung disease, were investigated by right heart catheter according to Swan-Ganz in an open-label, non-placebo controlled study. Riociguat, given at single doses of 1 and 2.5 mg, caused clinically relevant and statistically significant reductions from baseline in mPAP, PVR, systolic blood pressure, and systemic vascular resistance to a similar extent. A clinically relevant and statistically significant increase in cardiac index was also observed at both doses (p-values between 0.0151 and 0.0001), whereas a significant increase in heart rate was observed in the 2.5 mg dose group. Mean change from baseline for the 2.5 mg dose group was -5.1 mmHg for mPAP, -168 dyne*second*cm^{-5} for PVR, -546 dyne*second*cm^{-5} for systemic vascular resistance, and +0.95 L/min/m^2 for cardiac index. The dose of 5 mg caused a large increase in heart rate and a reduction in blood pressure. Therefore, the dose of 5 mg was not evaluated further. Riociguat had a similar effect in patient subgroups with PAH or CTEPH. The minimal hemodynamic effect dose in these patients was not evaluated.

4.2.2 Onset and/or Offset of Action

Due to the close relationship between riociguat plasma concentrations and hemodynamic effects, the time course of (acute) hemodynamic activity following riociguat administration is mainly determined by the plasma concentrations versus time profile of the drug.

Riociguat is rapidly absorbed after oral administration of the riociguat immediate release tablet, releasing micronized drug substance with median peak concentrations observed after 1.0 to 1.5 hours. Elimination of riociguat is associated with a mean terminal half-life of approximately 7 hours in healthy subjects and approximately 13 hours in patients with high inter-individual variability. No undue accumulation is to be expected and therefore no prolonged or even unpredictable elimination half-lives have been observed.

In accordance with the pharmacokinetics, maximum effects of riociguat on heart rate, blood pressure, and vasoactive hormones were observed at 1 to 4 hours after oral administration.

4.2.3 Pharmacokinetic / Pharmacodynamic Relationships

There is a close and direct relationship between riociguat plasma concentrations and hemodynamic effects such as decrease in systemic and pulmonary vascular resistance, decrease in

systolic blood pressure, and increase in cardiac output, in both healthy subjects and patients after administration of a wide range of single doses (0.5 to 5 mg) or at steady state (1.0 to 2.5 mg TID).

4.2.4 Clinically Relevant Pharmacodynamic Interactions with Other Medicinal Products or Substances

Riociguat is intended to be used for the treatment of patients with CTEPH and patients with PAH. Thus, riociguat has the potential to interact with other vasodilators and other drugs forming a standard part of the co-medication in CTEPH and PAH such as warfarin.

Riociguat and NO delivered by **nitroglycerin** act on sGC by increasing the second messenger cGMP. Thus, an additive effect on the systemic circulation may be expected. In a phase I study in healthy subjects, administration of a standard dose of 0.4 mg sublingual nitroglycerin 4 hours after a single oral tablet dose of 2.5 mg riociguat resulted in a pronounced pharmacodynamic interaction leading to significant hypotensive effects. Therefore, concomitant use of riociguat and nitroglycerin cannot be recommended.

Riociguat and the **PDE5 inhibitor sildenafil** act on the NO-sGC-cGMP signaling pathway. Thus, an additive effect on pulmonary and systemic circulation may be expected. In patients with PAH stable for the last 6 weeks and treated with 20 mg sildenafil TID, sildenafil alone reduced mPAP and PVR, and led to pronounced and significant effects on the parameters of the systemic circulation such as systolic and diastolic blood pressure, systemic vascular resistance and cardiac output. When added to sildenafil, single doses of 0.5 mg and 1 mg riociguat had an additive but not significant effect on the parameters of systemic circulation and a less additive effect on the parameters of pulmonary circulation.

For patients with CTEPH and PAH, **warfarin** is part of basic drug therapy. Moreover, warfarin has a small therapeutic window. In an interaction study in healthy subjects, concomitant administration of 2.5 mg riociguat TID at steady state did not influence prothrombin time and factor VII percent activity compared to concomitant administration of placebo. Thus, no pharmacodynamic interaction between riociguat and warfarin (Coumadin®) was detected.

In patients with PAH, **acetylsalicylic acid** (**Aspirin®**) might be administered at a low dose instead of warfarin or at regular doses. Increasing cGMP in platelets by stimulation of sGC via riociguat has an anti-aggregatory effect, at least *in vitro*. Thus, riociguat may have the potential to increase the anti-aggregatory effect of Aspirin®. In a phase 1 study in healthy subjects, no additive effect or interaction of 2.5 mg riociguat co-administered with 500 mg Aspirin® on bleeding time, platelet aggregation measured *ex vivo* after stimulation with collagen and arachidonic acid, or on thromboxane B_2 in serum could be demonstrated. Thus, no pharmacodynamic interaction between riociguat and Aspirin® was detected.

4.2.5 Interpretation of the Results and Implications of Special Studies

In juvenile and adolescent rats, riociguat-related effects on bone morphology were observed. Since intracellular cGMP levels are known to be involved in regulation of bone homeostasis, these findings are considered secondary to the pharmacological mechanism of action.

In order to investigate the potential influence of riociguat and cGMP on bone metabolism in humans, a mechanistic study with riociguat (2.5 mg TID over 14 days) was initiated. Direct effects of riociguat on bone resorption (e.g., CTX) and bone formation markers (e.g., serum procollagen type 1 amino-terminal propeptide) were not demonstrated.

In addition, an effect of riociguat on renal function was observed. This resulted in an increased glomerular filtration rate (GFR) as measured by an increased creatinine clearance. Over the whole 14-day treatment period, riociguat resulted in an increased urinary excretion of calcium of 0.97 mmol (approximately 40 mg) per day compared to placebo. This effect was statistically significant but not clinically relevant, as mean serum calcium values remained within the normal range.

Due to the higher drug exposure in patients than healthy subjects, a thorough QT/QTc study according to pertinent guidelines could not be conducted in healthy subjects. The influence of riociguat on ECG parameters was thoroughly investigated within the phase III trials (Section 6.6.4.3, page 172).

4.3 Pharmacodynamic Support for the Proposed Dose and Dosing Interval

In phase I dose-escalation studies, based on the effects on heart rate over 1 minute, diastolic blood pressure, and plasma renin activity, the minimum effective dose in healthy subjects with respect to hemodynamic parameters was 1 mg riociguat and the maximum tolerated dose due to the hemodynamic effects was 2.5 mg riociguat given as a single dose or as TID multiple doses.

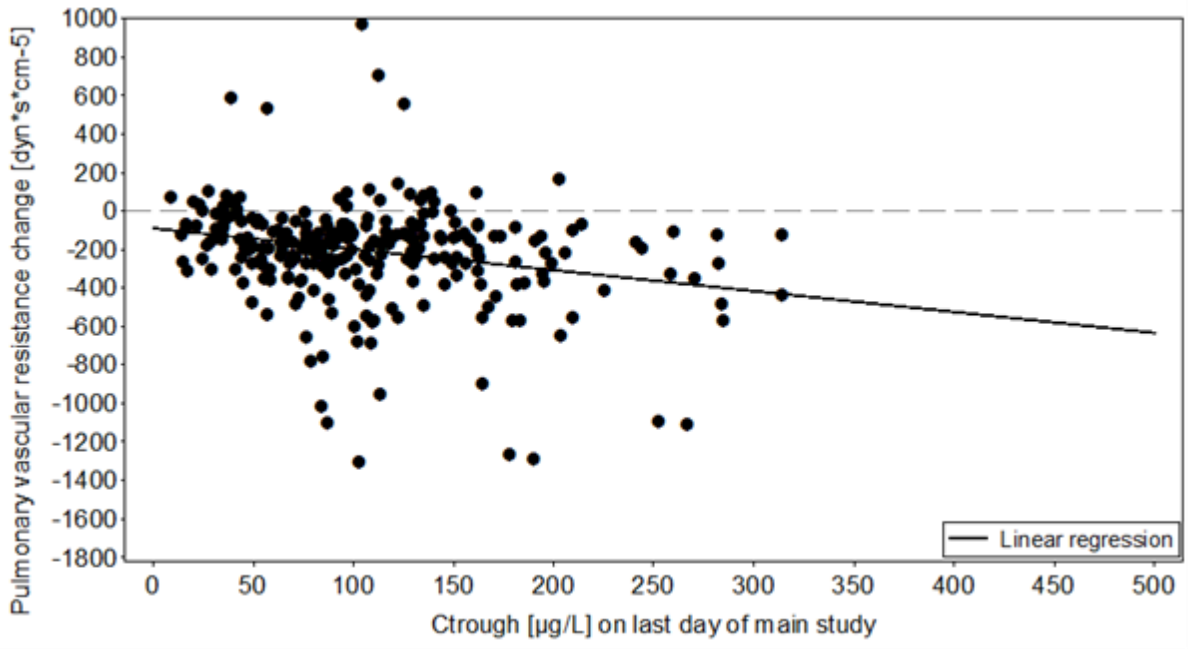
In a non-randomized, open-label, non-placebo-controlled, group comparison study in adult patients with pulmonary hypertension due to PAH, CTEPH, or interstitial lung disease, riociguat at single doses of 1 and 2.5 mg caused clinically relevant and statistically significant reductions from baseline in mPAP, PVR, systolic blood pressure, and systemic vascular resistance to a similar extent. A clinically relevant and statistically significant increase in cardiac index was also observed at both doses (p-values between 0.0151 and 0.0001), whereas a significant increase in heart rate was observed in the 2.5 mg dose group. The dose of 5 mg caused a high increase in heart rate and a reduction in blood pressure. Therefore, the dose of 5 mg was not further evaluated. Riociguat had a similar effect in the subgroups with PAH or CTEPH. The minimum effective dose in these patients was not evaluated. The hemodynamic effects observed in this study lasted for more than 5 hours, supporting the proposed 7- to 8-hour dosing interval

corresponding to a TID dosing regimen. The proposed dosing interval is in accordance with the pharmacokinetics of riociguat.

Blood sampling for pharmacokinetics was done in all patients in phase II and III studies. Population pharmacokinetic / pharmacodynamic approaches to describe riociguat exposure and hemodynamic effects were prospectively implemented into the overall clinical development program so that a detailed exposure-response analysis could be conducted.

Overall a close and direct correlation between riociguat exposure and the hemodynamic effects was observed. Figure 13 illustrates the correlation between trough concentrations of riociguat and PVR.

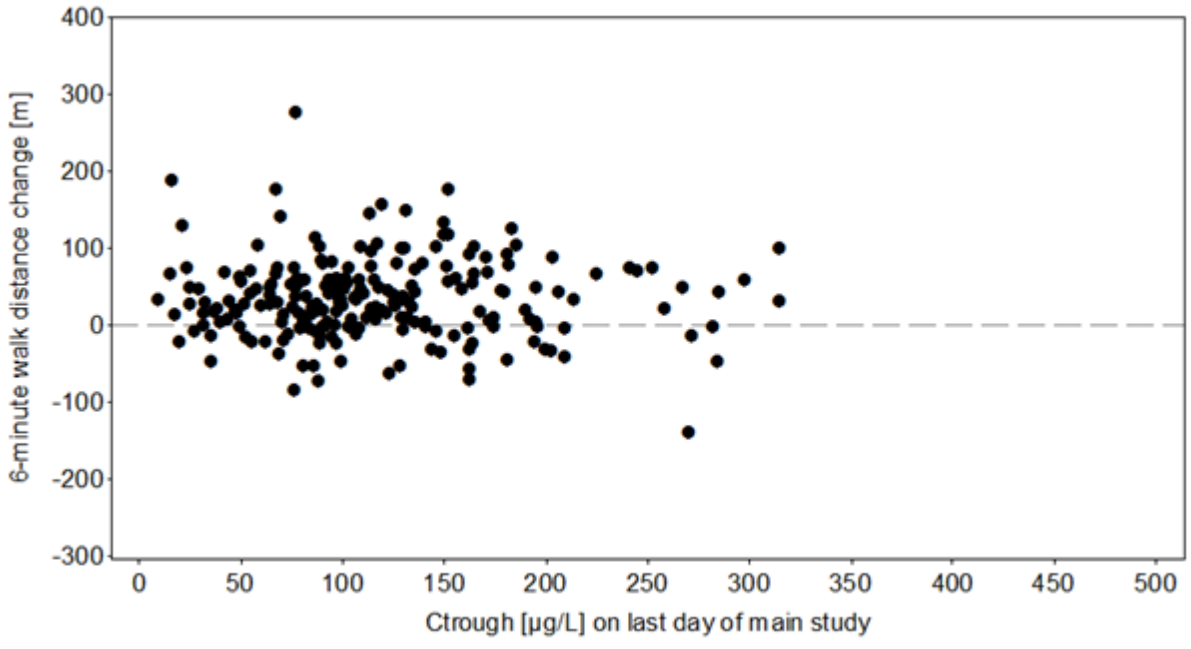
Figure 13: Correlation Between Trough Concentration of Riociguat and Pulmonary Vascular Resistance



Definition of abbreviations: Ctrough = trough concentration.

However, probably due to the high variability in both riociguat exposure and 6MWD, a weak correlation was observed between trough concentration of riociguat and 6MWD (Figure 14).

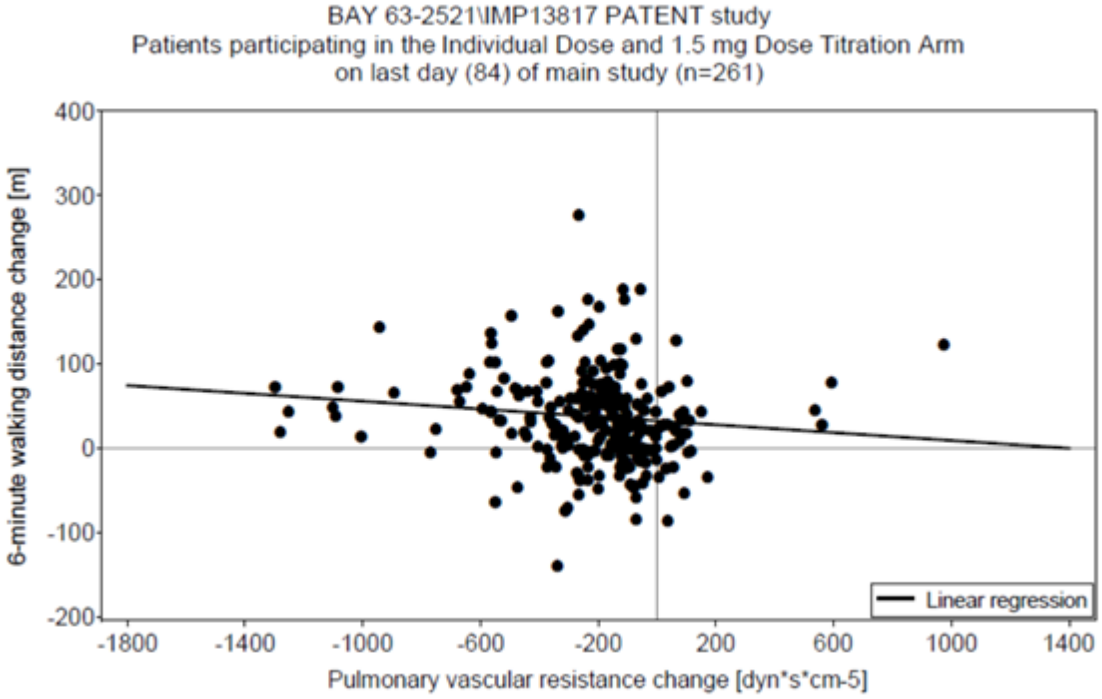
Figure 14: Correlation Between Trough Concentration of Riociguat and 6-minute Walking Distance



Definition of abbreviations: Ctrough = trough concentration.

When collapsing both exposure-response curves (trough concentration versus PVR and trough concentration versus 6MWD, Figure 13 and Figure 14) together, thereby normalizing for the variability in exposure and the variability in disease properties affecting both PVR and 6MWD in a similar way, a correlation between PVR and 6MWD can be observed (Figure 15).

Figure 15: Correlation Between Pulmonary Vascular Resistance and 6-minute Walking Distance



5. Overview of Clinical Efficacy

The efficacy of riociguat for the treatment of CTEPH and PAH is primarily based on 2 phase III randomized, placebo-controlled trials (Study 11348 [CHEST-1] in CTEPH and Study 12934 [PATENT-1] in PAH). Both studies had a similar design and used the same efficacy endpoints, which are widely accepted and used to assess efficacy in patients with pulmonary hypertension (16, 17).

The correspondence between visit and study day follows.

Visit	Study Day
1	0
2	14 ± 2
3	28 ± 2
4	42 ± 2
5	56 ± 2 (end of titration)
6	84 ± 2 (end of main phase for PATENT-1)
7	112 ± 2 (end of main phase for CHEST-1)

Both studies included an 8-week titration phase, during which the dose of study medication was titrated from a starting dose of 1.0 mg TID by the investigators in steps of 0.5 mg every 2 weeks based on the patient's peripheral systolic blood pressure. The dose of riociguat was titrated to a maximum dose of 2.5 mg TID, using dose strengths of 1.5 mg, 2.0 mg, and 2.5 mg. Every dose was given as a single film-coated tablet with or without food.

To ensure the blinding of the treatment groups in each study:

- The treatment group allocation and the dose titration were performed with the aid of an interactive voice response system.
- Patients allocated to the placebo group underwent a sham titration from Visit 1 onwards that followed the rules of the IDT scheme, but the interactive voice response system always allocated blinded placebo medication.
- Study medication and packaging were identical for the treatment groups.
- For patients who continued into the long-term extension study, study medication titration in extension study was blinded in order to preserve blinding in the corresponding controlled study.
- Key efficacy measurements (6MWD, Borg CR 10, and WHO functional class) were performed by another member of the site study team who was not involved in the titration process and was not aware of patient's immediate reaction (e.g., blood pressure and heart rate) after dosing.
- Investigators and Bayer safety monitors were instructed to unblind treatment for individual cases only for emergencies when the treatment assignment was important for acute treatment of the emergency.
- Treatment assignments were not revealed to investigators, patients, or other study personnel (except for medical emergencies) until the study database was closed following resolution of data queries.

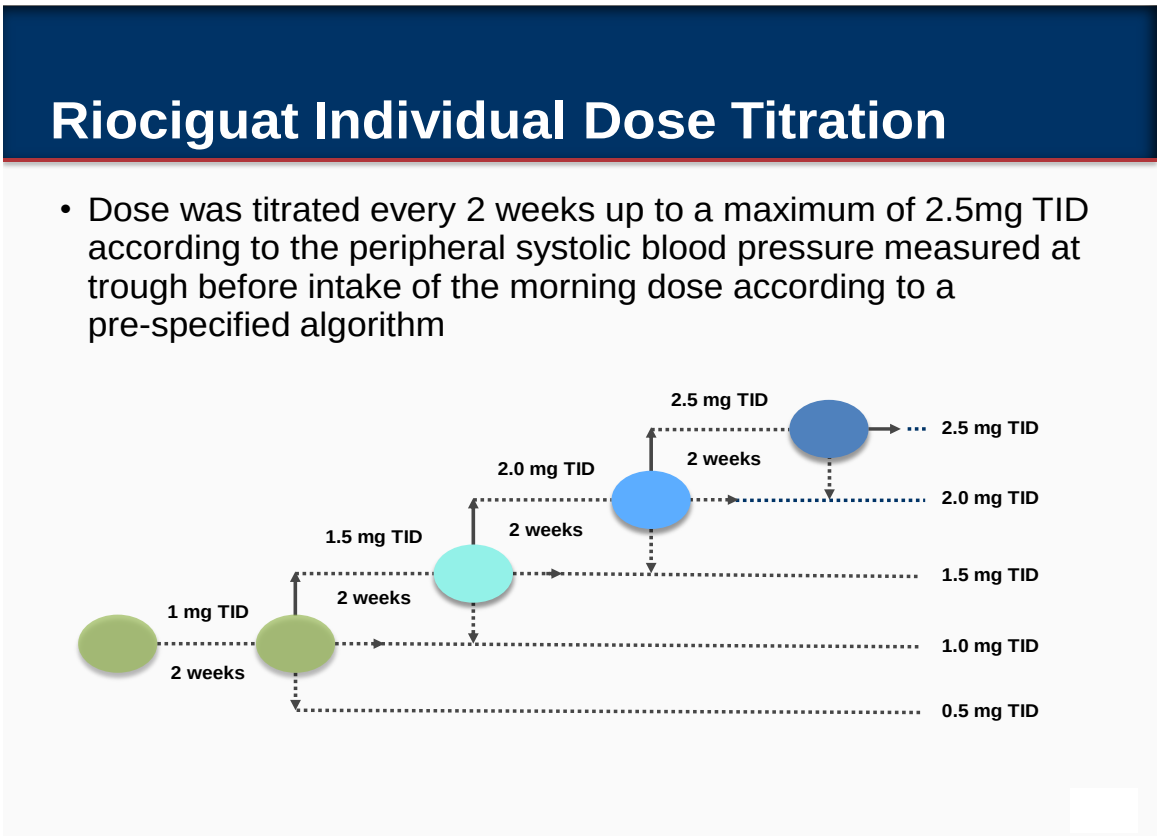
- An independent statistician provided unblinded safety data to the Independent Data Monitoring Committee so that the study statisticians remained blind to treatments.

Blood pressure and heart rate were measured after the patient had been at rest for 10 minutes in a supine position. The same arm was to be used for these measurements. The non-invasive measurement was preferably with a mercury sphygmomanometer or a validated electronic device in accordance with published guidelines. The peripheral systolic blood pressure was measured at trough before intake of the morning dose under consideration of the following IDT scheme:

- If trough systolic blood pressure ≥95 mmHg, increase dose by 0.5 mg TID.
- If trough systolic blood pressure 90 to 94 mmHg, maintain dose.
- If trough systolic blood pressure <90 mmHg without symptoms of hypotension, reduce dose by 0.5 mg TID.
- If any systolic blood pressure <90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, stop study treatment; restart after 24 hours with dose reduced by 0.5 mg TID.

Modifications were permitted in the case of side effects (e.g., symptomatic hypotension), including down-titration to 0.5 mg TID. The IDT scheme for CHEST-1 is illustrated in Figure 16. The IDT was the same in PATENT-1; however, total study duration was only 12 weeks.

Figure 16: Individual Titration Dosing Scheme for Study medication in CHEST-1



PATENT-1 included an exploratory riociguat group with capped dose titration (titration from 1.0 mg to 1.5 mg TID). After reaching the 1.5 mg dose level, patients in the riociguat CT group underwent a sham titration that only allowed dose maintenance or decrease.

The primary endpoint in both studies was the change from baseline in 6MWD until end of study (after 16 weeks in CHEST-1 and after 12 weeks in PATENT-1). The 6MWD is widely acknowledged in the expert community to be clinically meaningful as it reflects the ability of patients with pulmonary hypertension to perform usual activities of living; it is routinely used in clinical practice to assess response to therapy and clinical status of the patient. Moreover, the 6MWD correlates with disease severity and is a prognostic indicator of survival in patients with PAH (18). Data from the REVEAL Registry (12) and the French Registry demonstrate that the baseline 6MWD is predictive of outcome (19). Additionally, work by Saouti and co-workers (5) as well as Reesink et al.(20) reported a positive correlation between the 6MWD and survival in patients with CTEPH.

Secondary efficacy endpoints were:

- Change from baseline in PVR until end of study. Elevated levels of PVR have been associated with increased mortality (37, 38).

- Change from baseline in NT-proBNP until end of study. A decrease indicates cardiac improvement (39).

- Change from baseline in WHO functional class (Appendix 11.1, page 196) until end of study. A higher functional class (e.g., III versus II) indicates less functional ability.

- Time to clinical worsening defined as time to the first occurrence of death (all-cause mortality), heart/lung transplantation, atrial septostomy, non-transient hospitalization due to persistent worsening of pulmonary hypertension, start of new pulmonary hypertension specific therapy or change of pre-existing ERA or prostacyclin analogue treatment due to worsening pulmonary hypertension, decrease in 6MWD at 2 consecutive visits due to worsening pulmonary hypertension and persistent (2 consecutive visits) worsening of WHO functional class due to deterioration of pulmonary hypertension.

- Change from baseline until end of study in Borg CR 10 score (Appendix 11.2, page 197) measured at the end of the 6MWD test. A score of 0 indicates no exertion is perceived by the patient (e.g., no breathing difficulties) and a score of 10 indicates that absolute maximum exertion is perceived.

- Change from baseline in EQ-5D questionnaire (Appendix 11.3, page 199) until end of study. The EQ-5D is a standardized health outcome instrument. For the analysis, the answers to the 5 questions (each with 3 categories) were combined to a score which has a range of possible values from -0.594 (worst outcome, all 5 questions answered with 3) to 1.00 (best outcome, all 5 questions answered with 1). An increase in the utility score represents an improvement in quality of life.

- Change from baseline in LPH questionnaire total score (Appendix 11.4, page 200) until end of study. The LPH questionnaire is a validated quality of life instrument with a total score of 0 (no effect of pulmonary hypertension) to 105 (maximal effect of pulmonary hypertension). A decrease in score is associated with an improved quality of life.

The primary analysis set for efficacy analyses in both studies was the Safety/ITT population, which included all randomized patients who received at least 1 dose of study medication. This set corresponds to the full analysis set in the International Conference on Harmonisation E9 statistical guidance document.

The primary efficacy analysis was the analysis of the change in 6MWD from baseline to last observation until end of the treatment period (week 16 in CHEST-1 and week 12 in PATENT-1) in patients valid for the Safety/ITT population.

The riociguat IDT and placebo groups were compared using analysis of covariance (ANCOVA). The ANCOVA for CHEST-1 included baseline 6MWD as a covariate with treatment group and region (North America, South America, Europe, China, Asia/Pacific) as main effects. The ANCOVA for PATENT-1 included baseline 6MWD as a covariate with treatment group, stratification group (therapy-naïve or add-on), and region (North America, South America, Europe, China, Asia/Pacific) as main effects. If the Shapiro-Wilk test for normality of residuals was statistically significant, the stratified Wilcoxon test was used as the primary statistical method instead of the ANCOVA. Least squares (LS) mean and 95% CIs of the treatment difference were calculated based on the ANCOVA. Superiority of the riociguat IDT group over the placebo group was to be declared if the 2-sided significance level was less than or equal to 0.05.

Missing values were imputed with last observation carried forward, except imputation with worst value (e.g., 0 meters for 6MWD) for patients who died or withdrew due to clinical worsening without a 6MWD being measured at a termination visit.

The secondary efficacy variables were to be formally tested for statistical significance of a difference between the riociguat IDT group and the placebo group only if the primary comparison was statistically significant at the 2-sided 5% level. A sequential testing procedure was to be performed for the 7 secondary efficacy variables, strictly in the order: PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg CR 10 score, EQ-5D, and LPH.

Statistical methods were the same, except given the WHO functional class and Borg CR 10 scales are categorical, the stratified Wilcoxon test was applied and time to clinical worsening was analyzed using the stratified log-rank test.

Additional details for statistical methods are provided in Appendix 11.7 (page 208).

5.1 Riociguat Treatment in Patients with Chronic Thromboembolic Pulmonary Hypertension

5.1.1 Phase III Study CHEST-1

Study CHEST-1 was a phase III, double-blind, randomized, multicenter, multinational, placebo-controlled study of the efficacy and safety of oral riociguat in patients with CTEPH.

To be eligible for inclusion, patients had to have a diagnosis of inoperable or postoperative CTEPH and a baseline 6MWD test between 150 meters and 450 meters, inclusive. Patients with

inoperable CTEPH had to have a PVR >300 dyne*second*cm^{-5} measured at least 90 days after start of full anticoagulation and mPAP >25 mmHg; inoperability was adjudicated by an experienced surgeon or a central adjudication committee. Patients with postoperative CTEPH (persisting or recurrent pulmonary hypertension after pulmonary endarterectomy) had to have a PVR >300 dyne*second*cm^{-5} measured at least 180 days after surgery. Patients were to be therapy-naïve with respect to PAH-specific medications. Patients pre-treated with NO donors in the 90 days prior to Visit 1 (randomization) or with ERAs, prostanoids, or specific (e.g., sildenafil or tadalafil) or unspecific phosphodiesterase inhibitors were not eligible for the study. Concomitant intake of such medications was not permitted during the treatment phase of the study.

After a pre-treatment phase of approximately 4 weeks, eligible patients were randomized in a 2:1 ratio to receive riociguat or placebo TID as an IDT regimen (Figure 16). The starting dose was 1.0 mg riociguat or placebo TID. The respective single daily doses were to be taken 6 to 8 hours apart.

The titration phase was followed by an 8-week main study phase (from Visit 5 to Visit 7). During the main study phase, all patients were to remain on their optimal dose of riociguat or placebo, as decided by the investigator based on the patient's systolic blood pressure at Visit 5 at the end of the titration phase. Dose reductions for safety reasons were allowed, but a subsequent re-increase during the main study phase was not possible.

At the end of the treatment period of 16 weeks, eligible patients had the option to enter an open-label extension trial (CHEST-2) where all patients were to be treated with an individual optimal dose of riociguat. Patients who did not enter the open-label extension trial or who stopped the study medication prematurely at any time during the study entered a 30-day safety follow-up phase.

5.1.1.1 Disposition for Study CHEST-1

There were 446 patients enrolled in 89 study centers in 26 countries worldwide. Of these 446 enrolled patients, 184 failed screening criteria (most frequently due to confirmation of operability) and 261 of the 262 randomized patients received study medication (173 riociguat and 88 placebo). Death was reported for 4 patients prior to randomization. One randomized patient (riociguat IDT group) failed to receive study medication. The completion rate for the treatment phase was high (92.7% of randomized patients) and similar for the 2 treatment groups. Primary reasons for premature discontinuation are summarized in Table 8.

All 261 randomized, treated patients were included in the Safety/ITT population (173 riociguat IDT, 88 placebo).

Table 8: Disposition for Study CHEST-1 (All Randomized Patients)

	Number (%) of Patients	
	Placebo (N=88)	**Riociguat IDT (N=174)**
Completed treatment	83 (94.3)	160 (92.0)
Prematurely discontinued	5 (5.7)	14 (8.0)
Adverse event	2 (2.3)	4 (2.3)
Death	2 (2.3)	2 (1.1)
Lack of efficacy	1 (1.1)	2 (1.1)
Non-compliance with study medication	0	1 (0.6)
Protocol violation	0	3[a] (1.7)
Withdrawal by patient	0	2 (1.1)

Definition of abbreviations: IDT = individual dose titration.
a Including 1 randomized patient who did not receive study medication.

5.1.1.2 Demographic and Baseline Characteristics in Study CHEST-1

In the Safety/ITT population, the treatment groups were comparable with respect to demographic characteristics (Table 9). More than 60% of patients were female (68% riociguat IDT, 61% placebo). The majority of patients in each treatment group were white (69% riociguat IDT, 74% placebo), and about 20% of patients in each group were Asian. Few patients were classified as black (<5%). Mean age was approximately 59 years in each treatment group and approximately 40% of patients in each treatment group were ≥65 years of age. Body mass index at baseline was comparable between treatment groups (27.1 kg/m^2 riociguat IDT, 27.7 kg/m^2 placebo). The majority of patients in each treatment group had never smoked and approximately half of patients in each treatment group reported no alcohol consumption.

Table 9: Demographic and Baseline Characteristics in Study CHEST-1 (Safety/ITT Population)

Characteristic	Placebo (N=88)	Riociguat IDT (N=173)
Female, n (%)	54 (61.4)	118 (68.2)
Race, n (%)		
White	65 (73.9)	120 (69.4)
Black or African-American	1 (1.1)	7 (4.0)
Asian	20 (22.7)	37 (21.4)
Multiple races	0	1 (0.6)
Hispanic or Latino	2 (2.3)	8 (4.6)
Age, years		
Mean (standard deviation)	59.2 (12.7)	59.3 (13.9)
≥65 years, n (%)	36 (40.9)	74 (42.8)
Never smoked, n (%)	47 (53.4)	113 (65.3)
Abstinent from alcohol, n (%)	45 (51.1)	90 (52.0)
Body mass index, kg/m^2		
Mean (standard deviation)	27.73 (5.30)	27.13 (5.75)

Definition of abbreviations: IDT = individual dose titration; ITT = intent-to-treat.

In both treatment groups, the majority of the patients had a diagnosis of inoperable CTEPH (69.9% riociguat IDT, 77.3% placebo group). More than 60% of patients in each treatment group were in WHO functional class III at baseline (61.8% riociguat IDT, 68.2% placebo). Most of the other patients in each group were in WHO functional class II (31.8% riociguat IDT, 28.4% placebo). The proportion of patients with a baseline 6MWD of less than 320 meters was slightly higher in the riociguat IDT group (34.7% riociguat IDT, 28.4% placebo).

5.1.1.3 Primary Efficacy Endpoint in Study CHEST-1

In the primary efficacy analysis of all treated patients, treatment with riociguat IDT resulted in a statistically significant and clinically relevant improvement in 6MWD from baseline to last visit (scheduled for week 16) as compared to placebo in the Safety/ITT population. The LS mean treatment difference for change from baseline was 45.69 with 95% CI of 24.74 to 66.63. The findings are summarized in Table 10.

Table 10: Primary Efficacy Analysis of Change in 6MWD From Baseline to Last Visit in Study CHEST-1 (Safety/ITT Population)

	Placebo (N=88)	Riociguat IDT (N=173)
Baseline		
Mean (standard deviation)	356.0 (74.7)	342.3 (81.9)
Median (minimum, maximum)	372.0 (152, 474)	360.0 (150, 557)
Change from baseline to last visit[a]		
Mean (standard deviation)	-5.5 (84.3)	38.9 (79.3)
Median (minimum, maximum)	5.0 (-389, 226)	42.0 (-376, 335)
Treatment comparison		
LS mean difference	45.69	
95% confidence interval	24.74, 66.63	
p-value (ANCOVA)[b]	<0.0001	
p-value (stratified Wilcoxon)[c]	<0.0001	

Definition of abbreviations: 6MWD = 6-minute walk distance; ANCOVA = analysis of covariance; IDT = individual dose titration; ITT = intent-to-treat; LS = least squares.

a Last visit was defined as last observed value (not including follow-up) for patients who completed the study or withdrew, except imputed worst value in case of death or clinical worsening without a termination visit or a measurement at that termination visit. Worst value imputation for 6MWD at last visit was performed for 4 patients in the riociguat IDT group and 4 patients in the placebo group.

b ANCOVA model with baseline value, treatment group, and region as fixed effects.

c Wilcoxon test stratified by region. The Shapiro-Wilk test indicated non-normality of residuals (p-value=0.0001).

Sensitivity analyses indicated that there was clear evidence of a treatment effect regardless of the method used to take account for missing data (Table 11).

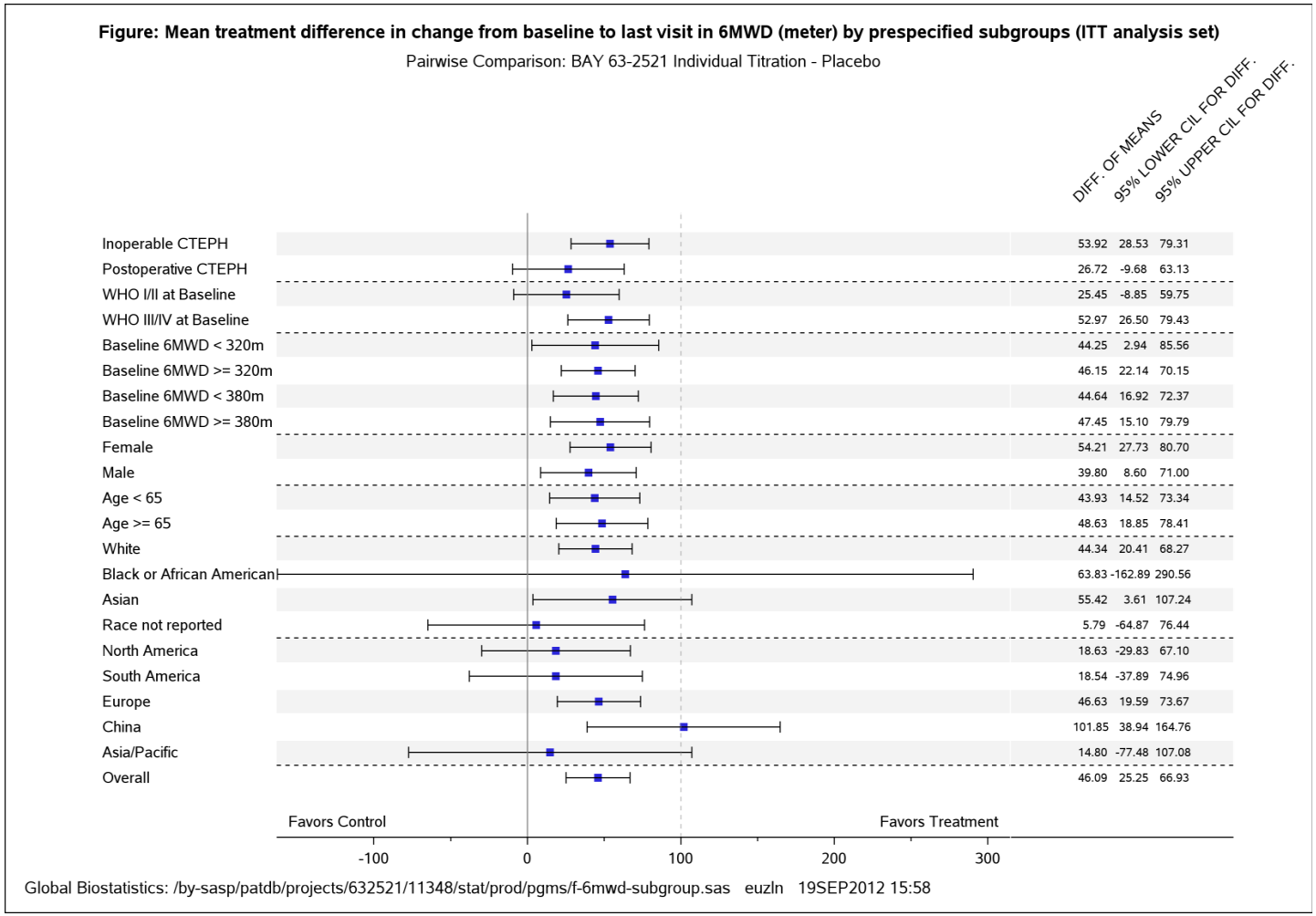
Table 11: Sensitivity Analyses for Change in 6MWD in CHEST-1 (Safety/ITT Population)

Analysis	Estimated Treatment Difference[a]	95% Confidence Interval
Mixed model at Visit 7	44.40	27.94 to 60.85
Multiple imputation (fixed penalty) Riociguat – 60 meters Placebo – 60 meters	43.69	26.25 to 61.13
Multiple imputation (decreasing slope) Riociguat – 20 meters placebo – 20 meters per visit	41.81	24.05 to 59.58
Multiple imputation (fixed penalty) Riociguat – 60 meters placebo – 0 meters	40.07	22.94 to 57.21
Multiple imputation (decreasing slope) Riociguat – 20 meters placebo – 0 meters per visit	38.71	21.27 to 56.15
Robust regression	40.31	25.86 to 54.75

Definition of abbreviations: ITT = intent to treat.
a Riociguat versus placebo

An improvement of the 6MWD from baseline to last visit was observed for the pre-defined subgroups (Figure 17). Consistent results with respect to improvement of the 6MWD for riociguat over placebo were also seen for subgroups defined by weight, renal function, and cardiac function (not shown).

Figure 17: Subgroup Analysis: Mean Treatment Difference in Change in 6MWD From Baseline to Last Visit by Pre-specified Subgroups in Study CHEST-1 (Safety/ITT Population)



Definition of abbreviations: 6MWD = 6-minute walking distance; CIL = confidence interval limit; CTEPH = chronic thromboembolic pulmonary hypertension; ITT = intent-to-treat; WHO = World Health Organization.

Number of patients (riociguat/placebo) in each subgroup:

Type of CTEPH: inoperable CTEPH (n = 121/68) and postoperative CTEPH (n = 52/20)
WHO functional class at baseline: I/II (n = 58/25) and III/IV (n = 115/62)
Baseline 6MWD: <380 meters (n = 109/50) and ≥380 meters (n = 64/38)
Sex: female (n = 118/54) and male (n = 55/34)
Age: <65 years (n = 99/52) and ≥65 years (n = 74/36)
Race: White (n = 120/65), Asian (n = 37/20), Black (n = 7/1), and Not Reported (n = 8/2)
Region: North America (n = 15/9), Europe (n = 104/53), Asia/Pacific (n = 18/9), South America (n = 15/6) and China (n = 21/11)

The lower magnitude of treatment effect observed in North America compared to Europe and China is difficult to interpret due to the small number of patients enrolled in North America (15 riociguat and 9 placebo). This small sample size was also impacted by outliers and imputation of missing values. Baseline characteristics were similar between patients in the North America and Europe.

The data obtained from the international, multicenter, double-blind, placebo-controlled phase III clinical trial CHEST-1 has broad applicability for all regions in the world, including the United States. The rationale for assuming the applicability of foreign data to the United States population/practice of medicine is based on multiple factors. These factors include consistency in pulmonary hypertension expert recommendations for the classification, diagnosis, and treatment of pulmonary hypertension, the design and conduct of the CHEST-1 trial, and the data obtained in the riociguat program. Guidelines for the classification, diagnosis, and treatment of pulmonary hypertension were developed by an international group of disease area experts and are refined on a periodic basis. They were last defined at the 4th World Symposium of Pulmonary Hypertension in Dana Point (1), and recently refined at the 5th World Symposium of Pulmonary Hypertension in Nice (not yet published). The guidelines provide an international consensus recommending:

- How pulmonary hypertension should be classified according to pathophysiology and clinical characteristics
- The appropriate diagnostic algorithm to be used
- The appropriate management and treatment of pulmonary hypertension patients

Additionally, regional consensus statements and/or guidelines in both the United States and Europe have been written in accordance with the Dana Point guidelines (6, 27). Regardless of geographical region, these consensus guidelines recognize that pulmonary hypertension consists of a group of serious, life-threatening cardiopulmonary disorders of various etiologies characterized by vascular remodeling, abnormal pulmonary vascular tone, dysregulation in vascular cell proliferation and *in situ* thrombosis. This common underlying pathophysiology leads to increased pulmonary vascular resistance, progressive right ventricular dysfunction/failure and, ultimately, premature death. The hemodynamic definition of pulmonary hypertension is consistent around the world, as is the confirmation of diagnosing this disease by invasive measurement of hemodynamics via right heart catheterization.

5.1.1.4 Secondary Efficacy Endpoints in Study CHEST-1

Treatment with riociguat IDT also resulted in a consistent improvement across the secondary efficacy variables of PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg CR 10 score, EQ-5D questionnaire, and LPH questionnaire. Based on the hierarchical testing procedure, secondary endpoints with a statistically significant improvement for the riociguat IDT

group compared to placebo were PVR, NT-proBNP, and WHO functional class. Mean and median change in secondary endpoints from baseline to last week of treatment is summarized in Table 12. Results for the percentage of patients with changes in WHO functional class and for time to clinical worsening are presented following the table of mean and median changes.

Table 12: Change in Secondary Endpoints From Baseline to Last Visit in Study CHEST-1 (Safety/ITT Population)

Endpoint Statistic	Placebo (N=88)	Riociguat IDT (N=173)	Stratified Wilcoxon p-value
PVR (dyne*second*cm^{-5})			
n	82	151	
Mean baseline (standard deviation)	779.3 (400.9)	790.7 (431.6)	
Mean change (standard deviation)	23.1 (273.5)	-225.7 (247.5)	<0.0001
Median	14.9	-175.9	
NT-proBNP			
n	73	150	
Mean baseline (standard deviation)	1705.8 (2567.2)	1508.3 (2337.8)	
Mean change (standard deviation)	76.4 (1446.6)	-290.7 (1716.9)	<0.0001
Median	40.6	-184.7	
Borg CR 10 score			
n	88	173	
Mean baseline (standard deviation)	4.44 (2.20)	4.29 (2.25)	
Mean change (standard deviation)	0.17 (2.42)	-0.83 (2.39)	0.0035
Median	0.00	-1.00	
EQ-5D questionnaire			
n	87	172	
Mean baseline (standard deviation)	0.658 (0.246)	0.645 (0.244)	
Mean change (standard deviation)	-0.082 (0.345)	0.062 (0.277)	<0.0001
Median	0.000	0.036	
LPH questionnaire			
n	86	170	
Mean baseline (standard deviation)	46.03 (22.58)	41.48 (21.69)	
Mean change (standard deviation)	-2.09 (19.31)	-6.72 (18.62)	0.1220
Median	-4.00	-6.00	

Definition of abbreviations: IDT = individual dose titration; ITT = intent-to-treat; LPH = Living with Pulmonary Hypertension; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PVR = pulmonary vascular resistance.
Shaded p-values are not considered statistically significant per hierarchical testing procedure.

Categorical change in WHO functional class is summarized in Table 13. A larger proportion of patients in the riociguat IDT group than in the placebo group improved at least 1 class (32.9% versus 14.9%).

Table 13: Categorical Change in WHO Functional Class From Baseline to Last Visit in Study CHEST-1 (Safety/ITT Population)

	Number (%) of Patients	
Change in number of classes	Placebo (N=87)	Riociguat IDT (N=173)
-2 (improved)	0	4 (2.3)
-1 (improved)	13 (14.9)	53 (30.6)
0 (stable)	68 (78.2)	107 (61.8)
1 (deteriorated)	3 (3.4)	7 (4.0)
2 (deteriorated)	3 (3.4)	1 (0.6)
3 (deteriorated)	0	1 (0.6)
Stratified Wilcoxon p-value	0.0026	

Definition of abbreviations: IDT = individual dose titration; ITT = intent-to-treat.

The difference in time to clinical worsening between the riociguat IDT group and the placebo group in the Safety/ITT population was not statistically significant (p=0.1724, stratified log-rank test). This was to be expected because the study sample size was not powered to show statistical significance for this clinical endpoint, the treatment duration of 16 weeks, and the overall low number of events (as expected). However with 4/173 (2.3%) patients with events in the riociguat IDT group and 5/88 (5.7%) patients with events in the placebo group, there was a trend towards an improvement in clinical worsening for the active treatment. Reasons for clinical worsening in the riociguat and placebo groups included hospitalization for pulmonary hypertension (0 and 1 patient, respectively), start of new treatment for pulmonary hypertension (2 and 1 patients, respectively), decrease in 6MWD due to pulmonary hypertension (1 and 2 patients, respectively), persistent worsening of functional class due to pulmonary hypertension (0 and 1 patient, respectively), and death (2 and 3 patients, respectively).

A sensitivity analysis of clinical worsening was performed including all events reported by the investigators: 8 (4.6%) patients with an event of clinical worsening in the riociguat IDT group, as compared to 11 (12.5%) patients in the placebo group. For the sensitivity analysis, both the stratified log-rank test for the treatment difference in time to clinical worsening (p=0.0278) and the Mantel-Haenszel estimate of the difference in incidence of clinical worsening between the treatments (p=0.0451) were nominally statistically significant.

5.1.1.5 Responder Analyses in Study CHEST-1

The number and percent of patients who achieved specific response criteria are summarized in Table 14. A substantially larger proportion of patients in the riociguat IDT group than in the placebo group met each of the response criteria.

Table 14: Responder Analyses at Week 16 in Study CHEST-1 (Safety/ITT Population)

	Percent of Patients			
	Placebo (N=88)		Riociguat IDT (N=173)	
Responder Definition	**Baseline**	**Week 16**	**Baseline**	**Week 16**
PVR <500 dynes*second*cm^{-5}	26.8	25.6	25.2	49.7
Cardiac index ≥2.5 L/min/m^2	28.9	27.7	32.3	58.1
Oxygen saturation ≥65%	41.6	35.1	42.1	54.5
NT-proBNP <1800 ng/L	71.2	63.0	73.3	81.3
6MWD ≥380 meters	43.2	44.3	37.0	58.4
6MWD increase >40 meters		23.9		52.6
Improvement in WHO functional class		14.9		32.9

Definition of abbreviations: 6MWD = 6-minute walking distance; IDT = individual dose titration; ITT = intent-to-treat; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; PVR = pulmonary vascular resistance; WHO = World Health Organization.

5.1.1.6 Efficacy Conclusions for Study CHEST-1

Administration of riociguat in a dosage of 1.0 to 2.5 mg TID as a titration regimen for 16 weeks (8 weeks individual titration to optimal dose and 8 weeks maintenance of optimal dose) resulted in a statistically significant and clinically meaningful improvement in 6MWD as compared to placebo in patients with inoperable or postoperative CTEPH.

In addition, consistent with the effects observed for the 6MWD, riociguat had superior effects over placebo on the predefined secondary efficacy variables of PVR, NT-proBNP, and WHO functional class that were statistically significant and clinically relevant.

5.1.2 Phase III Study CHEST-2

Study CHEST-2 is an ongoing phase III, open-label, multicenter, multinational, extension study of the long-term safety and efficacy of oral riociguat in patients with CTEPH. The study included patients who had completed 16 weeks of treatment in the double-blind study CHEST-1. All patients received riociguat TID, with respective single daily doses to be taken 6 to 8 hours apart.

In order to maintain the blind of CHEST-1, there was an 8-week titration phase for each patient. The CHEST-2 study medication (open-label riociguat) was blinded with respect to the dose during the titration phase, and investigators did not know at which dose level a subject entered the CHEST-2 trial. To allow a blinded individual dose titration, the titration was performed with the

aid of an interactive response system (telephone or web-based, depending on investigational site). At each titration visit (with the exception of Visit 1) the investigator decided, based on the subject's systolic systemic arterial blood pressure, whether the study medication dose should be modified. The respective decision (increase, maintain, or decrease dose) was entered in the interactive response system, which automatically allocated the right dose in accordance with the respective titration scheme. Afterwards, the investigator was informed by the system which of the medication bottles (blinded with respect to the dose) needed to be used for the next titration period (always beginning with the morning dose).

During the titration phase, riociguat study medication was titrated from a starting dose of 1.0 mg TID by the investigators in steps of 0.5 mg TID every 2 weeks in accordance with the IDT scheme as used in CHEST-1:

- Patients from the placebo group of CHEST-1 started with a riociguat dose of 1.0 mg TID. The dose of riociguat was titrated to a maximum dose of 2.5 mg TID, using dose strengths of 1.5 mg, 2.0 mg and 2.5 mg. Every dose was given as a single tablet.
- Patients from the riociguat IDT group of CHEST-1 entered the extension trial on the same dose level as they received on the last day of CHEST-1. Although the investigator applied the same titration rules as for placebo patients, the individual dose was not increased above the dose received on the last day of CHEST-1. If the investigator requested a dose increase above that level via the interactive response system, the patient received a sham titration. However, if the investigator requested a dose decrease (e.g., for safety reasons), dose modifications were possible, but without a subsequent re-increase before Visit 5 (day 56).

The titration phase ended at day 56 (Visit 5). At this visit, the actual dose of the patients was unblinded by the interactive response system while preserving the blind treatment assignment in CHEST-1.

During the subsequent main study phase, investigators openly modified the riociguat dose in a range between 0.5 mg TID and 2.5 mg TID according to the patient's need. For all patients stopping study treatment at any time, a safety follow-up visit was to be performed 30 days after the last dose of riociguat.

If medically indicated, ERAs and prostanoids could be administered starting after day 56 (Visit 5).

As the aim of the long-term extension study was primarily the assessment of safety and tolerability, no single primary efficacy variable was identified.

The following were pre-specified as efficacy variables in CHEST-2:

- Change from baseline in 6MWD test
- Change from baseline in NT-proBNP

- Change from baseline in WHO functional class
- Time to clinical worsening
- Change from baseline in Borg CR 10 score (measured at the end of the 6MWD test)
- Change from baseline in EQ-5D questionnaire
- Change from baseline in LPH questionnaire

All efficacy analyses reported in the study report were pre-specified in the statistical analysis plan for the study. A patient was valid for the long-term efficacy analysis (long-term safety population) if at least 1 dose of study medication was administered in the extension period.

All statistical analyses were exploratory descriptive analyses. Baseline was defined as week 0 of CHEST-1 except for time to clinical worsening for which events in CHEST-2 are summarized.

The summary tables were presented for the overall group of patients, and also separately by former treatment groups in CHEST-1.

5.1.2.1 Disposition of Patients in Study CHEST-2

This study is currently ongoing. Of 243 patients who completed CHEST-1, 237 entered CHEST-2. The interim analysis (data cut-off date 03 May 2012) included 194 patients: 129 patients from the former riociguat IDT group and 65 from the former placebo group. Twelve patients had prematurely discontinued study medication at the time of the data cut-off for the interim analysis. Primary reasons for premature discontinuation of study medication are summarized in Table 15.

Table 15: Disposition for Study CHEST-2 (Long-term Safety Population)

	Number (%) of Patients		
	Former Placebo (N=65)	Former Riociguat IDT (N=129)	Total (N=194)
Prematurely discontinued	5 (7.7)	7 (5.4)	12 (6.2)
AE	0	2 (1.6)	2 (1.0)
Death	2 (3.1)	3 (2.3)	5 (2.6)
Lack of efficacy	1 (1.5)	1 (0.8)	2 (1.0)
Withdrawal by patient	2 (3.1)	1 (0.8)	3 (1.5)

Definition of abbreviations: IDT = individual dose titration

5.1.2.2 Demographic and Baseline Characteristics in Study CHEST-2

The majority of the 194 patients were female (63.9%). The majority of patients were white (69.1%) and 23.7% and were classified as Asian. Mean age was approximately 59 years and 40.7% of patients were ≥65 years of age. Mean body mass index was 26.8 kg/m^2. The majority of patients (60.3%) had never smoked and half of all patients reported no alcohol consumption. There were no important differences between the former treatment groups. Baseline and demographic characteristics are summarized in Table 16.

Table 16: Demographic and Baseline Characteristics for Study CHEST-2 (Long-term Safety Population)

Characteristic	Former Placebo (N=65)	Former Riociguat IDT (N=129)	Total (N=194)
Female, n (%)	38 (58.5)	86 (66.7)	124 (63.9)
Race / Ethnicity, n (%)			
White	47 (72.3)	87 (67.4)	134 (69.1)
Black or African American	1 (1.5)	6 (4.7)	7 (3.6)
Asian	15 (23.1)	31 (24.0)	46 (23.7)
Multiple races	0	1 (0.8)	1 (0.5)
Hispanic or Latino	2 (3.1)	4 (3.1)	6 (3.1)
Age (years)			
Mean (standard deviation)	58.6 (12.9)	58.7 (13.7)	58.6 (13.4)
Age ≥65 years, n (%)	26 (40.0)	53 (41.1)	79 (40.7)
Never smoked, n (%)	33 (50.8)	84 (65.1)	117 (60.3)
Abstinent from alcohol, n (%)	30 (46.2)	67 (51.9)	97 (50.0)
Body mass index (kg/m^2) at baseline			
Mean (standard deviation)	27.73 (5.32)	26.40 (5.18)	26.84 (5.25)

Definition of abbreviations: IDT = individual dose titration

Overall, 74.7% of patients had inoperable CTEPH, while 25.3% had postoperative CTEPH. At the start of CHEST-1, 34% of patients had WHO functional class I or II and 66% had functional class III or IV.

At the time of cut-off, mean and median treatment duration (not including exposure in CHEST-1) was 388 and 336 days, respectively. Mean duration of treatment was similar in the 2 former treatment groups.

5.1.2.3 Efficacy Results in Study CHEST-2

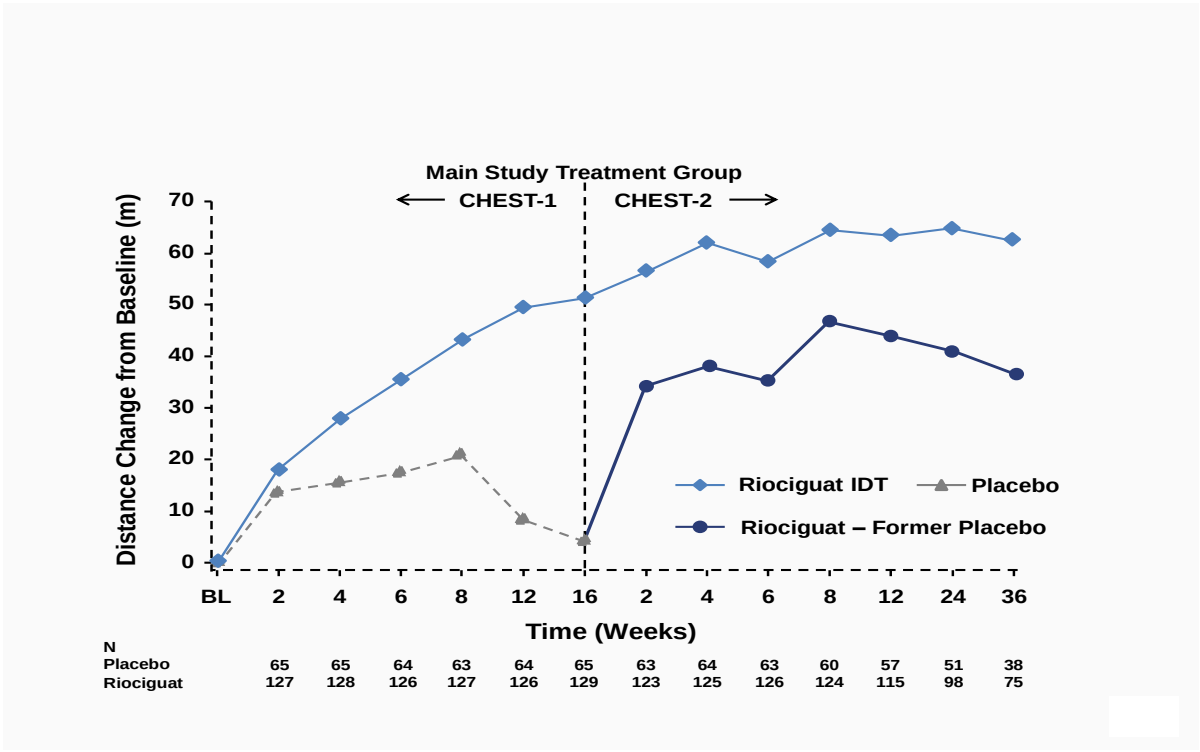
6MWD

Mean changes in 6MWD from baseline for patients in CHEST-2 are displayed over time in Figure 18. The cohort of patients treated with riociguat in CHEST-1 maintained (for at least 18 months) the mean improvement in 6MWD achieved in CHEST-1. The cohort of patients

treated with placebo in CHEST-1 had a small mean change in 6MWD in CHEST-1. However, when this cohort switched to active riociguat treatment in CHEST-2, improvements in 6MWD were observed. Differences between these 2 cohorts need to be interpreted with caution due to the different sizes of the cohorts of former riociguat and former placebo subjects; that is, the unbalanced randomization in CHEST-1, discontinuations over time in CHEST-2, and ongoing patients not yet reaching later time points resulted in fewer than 50 patients in the former placebo cohort after 6 months in CHEST-2.

Mean change from baseline in CHEST-2 was 56.5 meters at 6 months (n=149), 54.0 meters at 9 months (n=113), 47.6 meters at 12 months (n=93), and 60.7 meters at 18 months (n=63). The long-term 6MWD data from CHEST-2 indicate maintenance of the riociguat treatment effect, with clinically relevant improvement in 6MWD observed for at least 18 months.

Figure 18: Mean Change From Baseline in 6MWD by Visit in Studies CHEST-1 and CHEST-2 Combined (Long-term Safety Population, Observed Cases)



Definition of abbreviations: 6MWD = 6-minute walking distance; BL = baseline; IDT = individual dose titration; m = meters.

Patients with inoperable CTEPH had a consistently higher mean increase in 6MWD through month 6 to 18 (month 6: +58.6 meters, month 12: +49.5 meters, month 18: +64.9 meters) compared to patients with postoperative CTEPH (month 6: +50.7 meters, month 12: +42.3 meters, month 18: +52.3 meters).

Analyses of Other Efficacy Variables

The findings for NT-proBNP, WHO functional class, Borg CR 10 score, and EQ-5D in CHEST-2 were consistent with the key findings for 6MWD, namely that clinically relevant improvements seen in CHEST-1 were maintained in CHEST-2, with an indication of long-term maintenance of the riociguat treatment effect and improvement in those patients treated with placebo in CHEST-1.

At week 12 in CHEST-2, 39.9% of patients showed an improvement from baseline in WHO functional class while 3.6% showed deterioration in functional class. Improvement/deterioration was 47.1%/4.5% at 6 months (n=155), 47.8%/3.5% at 9 months (n=115), 50.0%/2.1% at 12 months (n=96), and 50.0%/3.1% at 18 months (n=64).

5.1.2.4 Efficacy Conclusion in Study CHEST-2

Overall, the exploratory analyses of efficacy in CHEST-2 indicate long-term maintenance of the riociguat treatment effect in patients treated with riociguat in CHEST-1 and improvement in those patients treated with placebo in CHEST-1.

5.2 Riociguat Treatment in Patients with Pulmonary Arterial Hypertension

5.2.1 Phase III Study PATENT-1

Study PATENT-1 was a phase III, double-blind, randomized, multicenter, multinational, placebo-controlled study of the efficacy and safety of oral riociguat in patients with symptomatic PAH.

To be eligible for inclusion, patients had to have a diagnosis of symptomatic PAH and a baseline 6MWD test between 150 meters and 450 meters (inclusive), PVR >300 dyne*second*cm^{-5}, and mPAP >25 mmHg. Both treatment-naïve patients and patients on stable pre-treatment therapy with an ERA or a non-intravenous prostacyclin analogue could be included.

After a pre-treatment phase of up to 2 weeks, eligible patients were randomized in a 4:2:1 ratio to receive riociguat TID with IDT (from 1.0 mg to 2.5 mg TID), placebo TID, or riociguat TID with CT (from 1.0 mg to 1.5 mg TID) in an 8-week titration phase (Figure 16). Riociguat and placebo were administered orally as film-coated tablets with or without food. The starting dose was 1.0 mg riociguat or placebo TID. The respective single daily doses were to be taken 6 to 8 hours apart. To ensure the blinding of the treatment groups, the treatment group allocation and the dose titration were performed with the aid of an interactive response system.

The titration scheme for the riociguat IDT group was similar to the one applied in CHEST-1. If during the titration phase for the riociguat CT group, the patient reached the 1.5 mg dose level, no further titration was possible. From that point in time on, the patient underwent a sham titration

that maintained blinding of treatment and only allowed dose maintenance or decrease. To ensure blinding, patients allocated to the placebo group underwent a sham titration that followed the rules of the individual dose titration scheme.

The titration phase was followed by a 4-week main study phase (from Visit 5 to Visit 6). During the main study phase, all patients were to remain on their optimal dose of riociguat or placebo, as decided by the investigator based on the patient's systolic blood pressure at Visit 5 at the end of the titration phase. Dose reductions for safety reasons were allowed, but a subsequent re-increase during the main study phase was not possible.

At the end of the treatment period of 12 weeks, eligible patients had the option to enter an open-label extension trial (study PATENT-2) where all patients were to be treated with an individual optimal dose of riociguat. Patients who did not enter the open-label extension trial or who stopped the study medication prematurely at any time during the study entered a 30-day safety follow-up phase.

5.2.1.1 Disposition in Study PATENT-1

There were 586 patients enrolled in 124 study centers in 30 countries worldwide. Of these 586 patients, 141 failed screening criteria (primarily due to hemodynamic measurements, performance of 6-minute walk, and lung function/pulmonary disease) and 443 of the 445 randomized patients received study medication. The completion rate for the treatment phase was high (91.0% of randomized patients) and similar among the treatment groups. Primary reasons for premature discontinuation are summarized in Table 17.

All 443 randomized, treated patients were included in the Safety/ITT population (254 riociguat IDT, 126 placebo, 63 riociguat CT).

Table 17: Disposition for Study PATENT-1 (All Randomized Patients)

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

Definition of abbreviations: CT = capped titration; IDT = individual dose titration.
a Includes 1 randomized subject who did not receive study medication.

5.2.1.2 Demographic and Baseline Characteristics in Study PATENT-1

In the Safety/ITT population (primary population), the treatment groups were comparable with respect to demographic and baseline characteristics (Table 18). Almost 80% of patients were female. The majority of patients in each treatment group were white (52% to 63%). A third of patients in each group were classified as Asian (30% to 35%). Very few patients were classified as black (<2%). Mean age was similar in all 3 treatment groups (51.1 years riociguat IDT, 50.7 years placebo, 48.8 years riociguat CT). Between 22% and 26% of patients in each treatment group were aged ≥65 years. Body mass index at baseline was comparable in all 3 treatment groups, with a mean body mass index of 26 to 27 kg/m^2 in each treatment group. The majority of patients in each treatment group had never smoked (62% to 67%) and the majority of patients reporting no alcohol consumption (58% to 67%).

Table 18: Demographic and Baseline Characteristics in Study PATENT-1 (Safety/ITT Population)

Characteristic	Placebo (N=126)	Riociguat IDT 1.0 to 2.5 mg (N=254)	Riociguat CT 1.0 to 1.5 mg (N=63)
Female, n (%)	98 (77.8)	203 (79.9)	49 (77.8)
Race / Ethnicity, n (%)			
White	78 (61.9)	161 (63.4)	33 (52.4)
Black or African American	1 (0.8)	4 (1.6)	1 (1.6)
Asian	38 (30.2)	79 (31.1)	22 (34.9)
Multiple races	1 (0.8)	1 (0.4)	0
Hispanic or Latino	8 (6.3)	9 (3.5)	7 (11.1)
Age (years)			
Mean (standard deviation)	50.7 (16.5)	51.1 (16.6)	48.8 (16.1)
Age ≥65 years, n (%)	32 (25.4)	66 (26.0)	14 (22.2)
Never smoked, n (%)	78 (61.9)	171 (67.3)	40 (63.5)
Abstinent from alcohol, n (%)	73 (57.9)	167 (65.7)	42 (66.7)
Body mass index (kg/m^2)			
Mean (standard deviation)	26.26 (5.92)	25.91 (5.48)	26.85 (5.35)

Definition of abbreviations: CT = capped titration; IDT = individual dose titration; ITT = intent-to-treat.

Most patients in the Safety/ITT population had a primary diagnosis of idiopathic PAH (58.7% to 66.7%) or PAH due to connective tissue disease (19.8% to 28.0%). More than 90% of patients in each treatment group had a WHO functional class of II or III. About half of the patients in each treatment group were treatment-naïve and half were pre-treated for PAH. Most of the pre-treated patients were receiving an ERA. The frequency of patients pre-treated with a prostacyclin analogue (inhaled, subcutaneous, or oral) was less than 10% in all treatment groups.

5.2.1.3 Primary Efficacy Endpoint for Study PATENT-1

In the primary efficacy analysis, treatment with riociguat IDT resulted in a statistically significant and clinically relevant improvement in 6MWD from baseline to week 12 (last observation until week 12) as compared to placebo in the Safety/ITT population. The LS mean treatment difference for change from baseline was 35.78 with 95% CI of 20.06 to 51.51. The capped dose titration (1.0 to 1.5 mg) was analyzed in a purely exploratory manner and the results were therefore not

discussed for efficacy and safety in relation to the overall benefit-risk evaluation for riociguat. The findings are summarized in Table 19.

Table 19: Primary Efficacy Analysis of Change in 6MWD From Baseline to Last Visit in Study PATENT-1 (Safety/ITT Population)

Statistic	Placebo (N=126)	Riociguat IDT 1.0 to 2.5 mg (N=254)	Riociguat CT 1.0 to 1.5 mg (N=63)
Baseline			
Mean (standard deviation)	367.8 (74.6)	361.4 (67.7)	363.2 (66.6)
Median	391.0	374.5	385.0
Change from baseline to last visit [a]			
Mean (standard deviation)	–5.6 (85.5)	29.6 (65.8)	31.1 (79.3)
Median	8.5	30.0	32.0
Treatment comparison	**Riociguat IDT – placebo**		
LS mean difference	35.78		
95% confidence interval	20.06 to 51.51		
p-value (ANCOVA)[b]	<0.0001		
p-value (stratified Wilcoxon test)[c]	<0.0001		

Definition of abbreviations: 6MWD = 6-minute walk distance; ANCOVA = analysis of covariance; CT = capped titration; IDT = individual dose titration; ITT = intent-to-treat; LS = least squares.

a Last visit = Last observed value (not including follow-up) for patients who completed the study or withdrew, except imputed worst value in case of death or clinical worsening without a termination visit or a measurement at that termination visit. Worst value imputation for 6MWD at last visit was performed for 2 patients in the riociguat IDT group and 6 patients in the placebo group.

b ANCOVA model with baseline value, treatment group, region, and stratification group as fixed effects.

c Stratified Wilcoxon test by region and stratification group. The Shapiro-Wilk test indicated non-normality of residuals (p-value=0.0001).

Sensitivity analyses indicated that there was clear evidence of a treatment effect regardless of the method used to take account for missing data (Table 20).

Table 20: Sensitivity Analyses for Change in 6MWD in PATENT-1 (Safety/ITT Population)

Analysis	Estimated Treatment Difference[a]	95% Confidence Interval
Mixed model at Visit 6	30.02	16.11 to 43.94
Multiple imputation (fixed penalty) Riociguat IDT –60 meters Placebo –60 meters	33.10	18.49 to 47.71
Multiple imputation (decreasing slope) Riociguat IDT –20 meters placebo –20 meters per visit	35.03	20.49 to 49.57
Multiple imputation (fixed penalty) Riociguat IDT –60 meters placebo –0 meters	26.31	12.32 to 40.30
Multiple imputation (decreasing slope) Riociguat IDT –20 meters placebo –0 meters per visit	27.16	13.36 to 40.96
Robust regression	30.00	18.91 to 41.10

Abbreviations: IDT = individual dose titration; ITT = intent to treat.
a Riociguat IDT versus placebo

An improvement of the 6MWD from baseline to last visit was observed for many of the pre-defined subgroups (Figure 19). Consistent results with respect to improvement of the 6MWD for riociguat over placebo were also seen for other subgroups of weight, renal function, and cardiac function (not shown).

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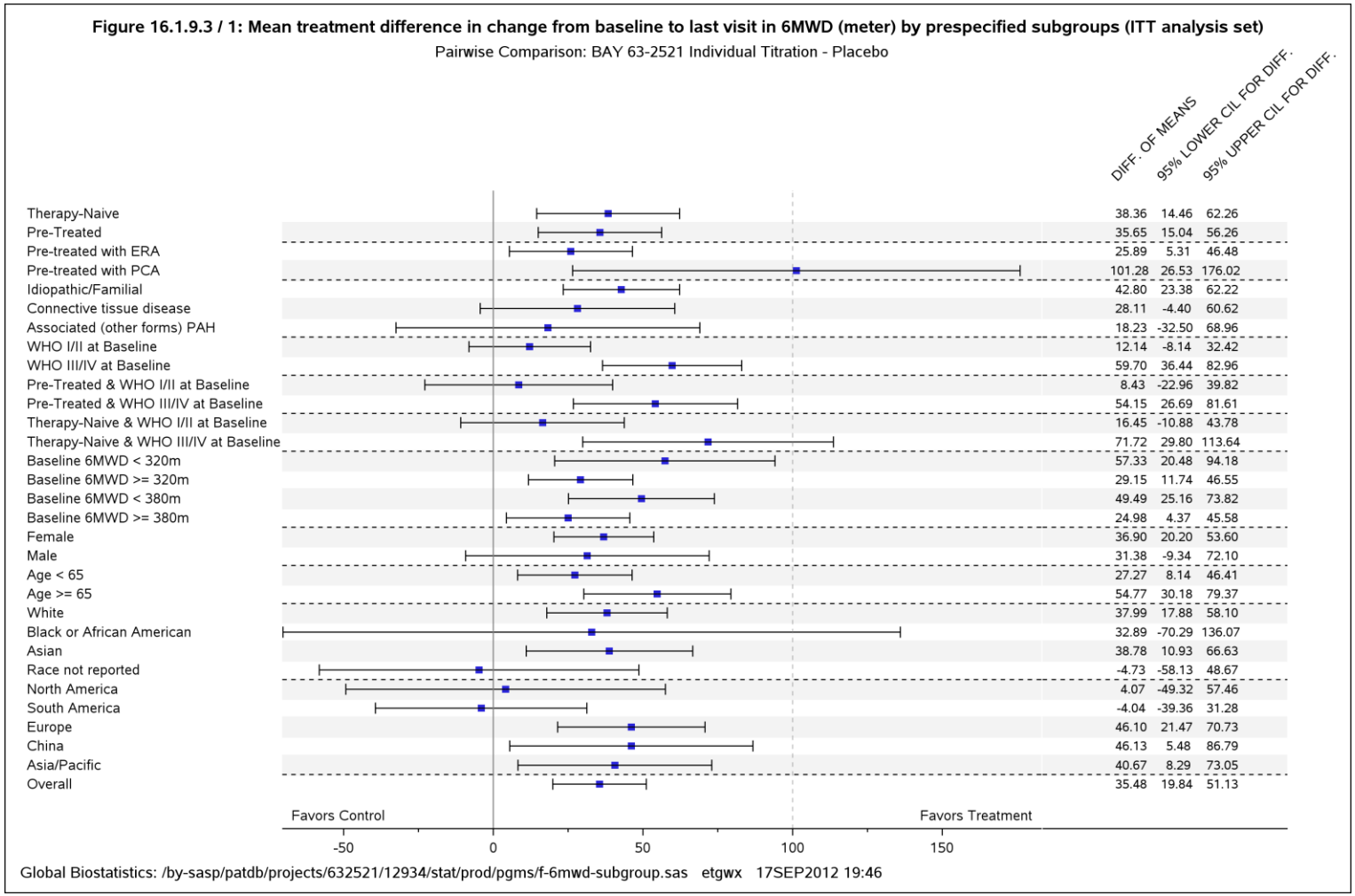
Figure 19: Mean Treatment Difference in Change From Baseline to Last Visit in 6MWD by Pre-specified Subgroups in Study PATENT-1 (Safety/ITT population)



Definition of abbreviations: 6MWD = 6-minute walking distance; CIL = confidence interval limit; ERA = endothelin receptor antagonist; ITT = intent-to-treat; PCA = prostacyclin analogue; WHO = World Health Organization.

Number of patients (riociguat IDT/placebo) in each subgroup:

- Pre-treatment: therapy naive (n = 123/66), pre-treated patients (n = 131/60), pre-treated with ERA (n = 113/54), and pre-treated with PCA (n = 20/7)
- Type of PAH: idiopathic / familial (n = 156/85), connective tissue disease (CTD, n = 71/25), and associated (other forms) (n = 27/16)
- WHO functional class at baseline: I/II (n = 113/64) and III/IV (n = 141/61)
- Pre-treatment and WHO functional class: Naïve and WHO I/II (n = 68/39), naïve and WHO III/IV (n = 55/27), pre-treated and WHO I/II (n = 45/25), and pre-treated and WHO III/IV (n = 86/34)
- Baseline 6MWD: <320 meters (n = 67/27), <380 meters (n = 139/53), ≥320 meters (n = 187/99), and ≥380 meters (n = 115/73)
- Sex: female (n = 203/98) and male (n = 51/28)
- Age: <65 years (n = 188/94) and ≥65 years (n = 66/32)
- Race: White (n = 161/78), Asian (n = 79/38), Black (n = 4/1), and not reported (n = 9/8)
- Region: North America (n = 24/11); Europe (n = 118/59), Asia/Pacific (n = 46/18), South America (n = 23/14) and China (n = 43/24)

The lower magnitude of treatment difference in North America compared to Europe and China is difficult to interpret due to the small number of patients enrolled in North America (24 riociguat and 11 placebo). This small sample size was also impacted by outliers and imputation of missing values. Baseline characteristics were similar between patients in North America and Europe.

The data obtained from the international, multicenter, double-blind, placebo-controlled phase III clinical trial PATENT-1 have broad applicability for all regions in the world, including the United States. The rationale for assuming the applicability of foreign data to the United States population/practice of medicine is based on multiple factors. These factors include consistency in pulmonary hypertension expert recommendations for the classification, diagnosis, and treatment of pulmonary hypertension, the design and conduct of the PATENT-1, and the data obtained in the riociguat program. Guidelines for the classification, diagnosis, and treatment of pulmonary hypertension were developed by an international group of disease area experts and are refined on a periodic basis. They were last defined at the World Symposium of Pulmonary Hypertension in Dana Point (1), and recently refined at a meeting in Nice (not yet published). The guidelines provide an international consensus recommending:

- How pulmonary hypertension should be classified according to pathophysiology and clinical characteristics
- The appropriate diagnostic algorithm to be used
- The appropriate management and treatment of pulmonary hypertension patients

Additionally, regional consensus statements and/or guidelines in both the United States and Europe have been written in accordance with the Dana Point guidelines (6, 27). Regardless of geographical region, these consensus guidelines recognize that pulmonary hypertension consists of a group of serious, life-threatening cardiopulmonary disorders of various etiologies characterized by vascular remodeling, abnormal pulmonary vascular tone, dysregulation in vascular cell proliferation and *in situ* thrombosis. This common underlying pathophysiology leads to increased pulmonary vascular resistance, progressive right ventricular dysfunction/failure and, ultimately, premature death. The hemodynamic definition of pulmonary hypertension is consistent around the world, as is the confirmation of diagnosing this disease by invasive measurement of hemodynamics via right heart catheterization. Supplementing prostacyclin, blocking endothelin, and amplifying cGMP are well accepted pharmacologic targets in PAH across the world.

5.2.1.4 Secondary Efficacy Endpoints in Study PATENT-1

Treatment with riociguat IDT also resulted in a consistent improvement across the secondary efficacy variables of PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg CR 10 score, EQ-5D questionnaire, and LPH questionnaire. Based on the hierarchical testing

procedure, secondary endpoints with a statistically significant improvement for the riociguat IDT group compared to placebo were PVR, NT-proBNP, WHO functional class, time to clinical worsening, and Borg CR 10 score. Mean and median changes in secondary endpoints from baseline to last week of treatment are summarized in Table 21. Results for the percentage of patients with changes in WHO functional class and for time to clinical worsening are presented following the table of mean and median changes.

Table 21: Change in Secondary Variables From Baseline to Last Visit in Study PATENT-1 (Safety/ITT Population)

Variable Statistic	Placebo (N=126)	Riociguat IDT 1.0 to 2.5 mg (N=254)	Riociguat CT 1.0 to 1.5 mg (N=63)
PVR (dyne*second*cm^{-5})			
n	107	232	58
Mean baseline (standard deviation)	834.1 (476.7)	791.0 (452.6)	847.8 (548.2)
Mean change (standard deviation)	–8.9 (316.6)	–223.3 (260.1)	–167.8 (320.2)
Median	–28.6	–183.0	–147.1
Stratified Wilcoxon versus placebo		<0.0001	
NT-proBNP (pg/mL)			
n	106	228	54
Mean baseline (standard deviation)	1228.1 (1774.9)	1026.7 (1799.2)	1189.7 (1404.7)
Mean change (standard deviation)	232.4 (1011.1)	–197.9 (1721.3)	–471.5 (913.0)
Median	27.55	–44.1	–48.1
Stratified Wilcoxon versus placebo		<0.0001	
Borg CR 10 score			
n	126	254	63
Mean baseline (standard deviation)	3.94 (2.45)	3.94 (2.24)	3.43 (1.77)
Mean change (standard deviation)	0.09 (2.05)	–0.44 (1.72)	–0.33 (1.47)
Median	0.00	0.00	0.00
Stratified Wilcoxon versus placebo		0.0022	
EQ-5D utility score			
n	124	253	62
Mean baseline (standard deviation)	0.684 (0.244)	0.678 (0.239)	0.639 (0.268)
Mean change (standard deviation)	–0.032 (0.304)	0.033 (0.235)	0.078 (0.311)
Median	0.000	0.000	0.000
Stratified Wilcoxon versus placebo		0.0663	
LPH total score			
n	122	247	62
Mean baseline (standard deviation)	41.64 (23.16)	42.43 (22.08)	43.40 (22.91)
Mean change (standard deviation)	0.36 (18.15)	–5.99 (17.76)	–10.21 (21.27)
Median	0.00	–4.00	–7.50
Stratified Wilcoxon versus placebo		0.0019	

Definition of abbreviations: CT = capped titration; IDT = individual dose titration; ITT = intent-to-treat; LPH = Living with Pulmonary Hypertension; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PVR = pulmonary vascular resistance.
Shaded p-values are consistent not statistically significant with hierarchical testing procedure.

An improvement in WHO functional class was observed in the riociguat treatment groups (a notably higher proportion of patients with decreases [20.9%] than with increases [3.5%] in class), while decreases and increases in functional class for the placebo group were each reported for the same proportion of patients (18 patients, 14.4% in each case; see Table 22). The difference

between the riociguat IDT and placebo groups for the distribution of changes was statistically significant (p=0.0033).

Table 22: Categorical Change in WHO Functional Class From Baseline to Last Visit in Study PATENT-1 (Safety/ITT Population)

	Number (%) of Patients		
Change in number of classes	Placebo (N=125)	Riociguat IDT 1.0 to 2.5 mg (N=254)	Riociguat CT 1.0 to 1.5 mg (N=63)
–2 (improved)	0	1 (0.4)	0
–1 (improved)	18 (14.4)	52 (20.5)	15 (23.8)
0 (stable)	89 (71.2)	192 (75.6)	43 (68.3)
1 (deteriorated)	15 (12.0)	7 (2.8)	4 (6.3)
2 (deteriorated)	3 (2.4)	1 (0.4)	1 (1.6)
3 (deteriorated)	0	1 (0.4)	0
		p=0.0033[a]	

Definition of abbreviations: CT = capped titration; IDT = individual dose titration; ITT = intent to treat.
a Riociguat IDT versus placebo (stratified Wilcoxon test).

The difference in time to clinical worsening between the riociguat IDT group and the placebo group in the Safety/ITT population was statistically significant (p=0.0046, stratified log-rank test). The overall frequency of clinical worsening was lower in both riociguat treatment groups than in the placebo group (1.2% riociguat IDT, 6.3% placebo, 3.2% riociguat CT).

A sensitivity analysis of clinical worsening was performed including all events entered by the investigators (3.1% riociguat IDT, 7.9% placebo group). For the sensitivity analysis, the stratified log-rank test for the treatment difference in time to clinical worsening (p=0.0346) but not the Mantel-Haenszel test (p=0.0787) were nominally statistically significant.

5.2.1.5 Responder Analyses in Study PATENT-1

The number and percent of patients who achieved specific response criteria are summarized in Table 23. A substantially larger proportion of patients in the riociguat IDT group than in the placebo group met each of the response criteria.

Table 23: Responder Analyses at Week 12 in Patients in Study PATENT-1 (Safety/ITT Population)

	Percent of Patients					
	Placebo (N=126)		Riociguat IDT (N=254)		Riociguat CT (N=63)	
Responder Definition	**Baseline**	**Week 12**	**Baseline**	**Week 12**	**Baseline**	**Week 12**
PVR <500 dynes*second*cm^{-5}	27.1	29.9	30.2	48.7	25.9	44.8
Cardiac index ≥2.5 L/min/m^2	48.1	44.4	45.1	76.4	51.7	67.2
Oxygen saturation ≥65%	61.0	47.0	55.7	73.3	57.1	77.6
NT-proBNP <1800 ng/L	79.2	72.6	81.6	89.5	72.2	87.0
6MWD ≥380 meters	57.9	54.8	45.3	63.0	52.4	66.7
6MWD increase ≥40 meters		23.0		42.9		41.3
Improvement in WHO functional class		14.4		20.5		23.8

Definition of abbreviations: 6MWD = 6-minute walking distance; IDT = individual dose titration; ITT = intent-to-treat; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; WHO = World Health Organization.

5.2.1.6 Efficacy Conclusions in Study PATENT-1

Administration of riociguat in a dosage of 1.0 to 2.5 mg TID as a titration regimen for 12 weeks (8 weeks individual titration to optimal dose, 4 weeks maintenance of optimal dose) resulted in a statistically significant and clinically meaningful improvement in 6MWD as compared to placebo in patients with symptomatic PAH.

In addition, consistent with the effects observed for the 6MWD, riociguat had superior effects over placebo on the predefined secondary efficacy variables PVR, NT-proBNP, WHO functional class, time to clinical worsening, and Borg CR 10 score that are statistically significant and clinically relevant.

5.2.2 Phase III Study PATENT-2

PATENT-2 is an ongoing phase III, open-label, multicenter, multinational, extension study of the long-term safety and efficacy of oral riociguat in patients with symptomatic PAH. The study included patients who had completed 12 weeks of treatment in the double-blind study PATENT-1. All patients received riociguat TID, as in PATENT-1. The respective single daily doses were to be taken 6 to 8 hours apart.

In order to maintain the blind of study PATENT-1, PATENT-2 included an 8-week titration phase for each patient, in which riociguat study medication was blinded with respect to dose (see Section 5.1.2 for details on the interactive response system with regard to blinding).

Patients from the riociguat IDT group and the riociguat CT group of PATENT-1 entered the extension trial on the same dose level as they received on the last day of PATENT-1. Patients from the placebo group of the PATENT-1 trial started at Visit 1 with a riociguat dose of 1.0 mg TID. Prior to amendment 5, patients of this former PATENT-1 treatment group were to start the titration phase of PATENT-2 at a dose level exceeding the last PATENT-1 dose by 0.5 mg TID, if blood pressure allowed. This briefing document describes the modified titration approach.

Titration in patients from the PATENT-1 riociguat CT group: Patients from the PATENT-1 riociguat CT group entered the extension trial on the same dose level as they received on the last day of PATENT-1 (Visit 6). For patients with a starting dose of 1.5 mg riociguat TID in PATENT-2, the individual optimal riociguat dose was to be determined every 2 weeks according to the peripheral systolic blood pressure measured at trough before intake of the next morning dose. At the end of the titration phase (Visit 5), patients reached riociguat doses between 0.5 mg TID and 2.5 mg TID, inclusive.

Titration in subjects from the PATENT-1 riociguat IDT group: Patients from the riociguat IDT group of PATENT-1 entered the extension trial on the same dose as they received on the last day of PATENT-1 (Visit 6). Although the investigator applied the same titration rules as for PATENT-1 placebo patients, the individual dose was not increased above the dose received on the last day of PATENT-1. If the investigator requested a dose increase above that level via the interactive response system, the patient received a sham titration. However, if the investigator requested a dose decrease (e.g., for safety reasons), dose modifications were possible.

The titration phase ended at day 56 (Visit 5). At this visit, the actual dose of the patients was unblinded by the interactive voice response system while preserving the blind treatment assignment in PATENT-1.

During the subsequent main study phase, investigators openly modified the riociguat dose in a range between 0.5 mg TID and 2.5 mg TID according to the patient's need. For all patients stopping study treatment at any time, a safety follow-up visit was to be performed 30 days after the last dose of riociguat.

Concomitant ERAs and prostanoids could be administered (treatment-naïve patients) or modified (pre-treated patients) starting after day 56 (Visit 5).

As the aim of the long-term extension study was primarily the assessment of safety and tolerability, no single primary efficacy variable was identified. The following were pre-specified as efficacy variables:

- Change from baseline in 6MWD test
- Change from baseline in NT-proBNP
- Change from baseline in WHO functional class
- Time to clinical worsening
- Change from baseline in Borg CR 10 score (measured at the end of the 6MWD test)
- Change from baseline in EQ-5D questionnaire
- Change from baseline in LPH questionnaire

All efficacy analyses reported in the study report were pre-specified in the statistical analysis plan for the study. The analyses were performed for patients entering and treated in the long-term extension study (long-term safety population). A patient was valid for the long-term efficacy analysis if at least 1 dose of study medication was administered in the extension period.

All statistical analyses were exploratory descriptive analyses. Baseline was defined as week 0 of PATENT-1 except for time to clinical worsening for which events in PATENT-2 are summarized. The summary tables were presented for the overall group of patients, and also separately by former treatment groups in PATENT-1.

5.2.2.1 Disposition of Patients in Study PATENT-2

This study is currently ongoing. Of 405 patients who completed PATENT-1, 396 entered PATENT-2. The interim analysis (data cut-off date 16 Apr 2012) included 363 patients (long-term safety population): 215 patients from the former riociguat IDT group, 96 from the former placebo group, and 52 from the former riociguat CT group. There were 55 patients who had prematurely discontinued study medication at the time of the cut-off for the interim analysis. Primary reasons for premature discontinuation of study medication are summarized in Table 24.

Table 24: Disposition for Study PATENT-2 (Long-term Safety Population)

	Number (%) of Patients			
	Former Placebo (N=96)	Former Riociguat IDT (N=215)	Former Riociguat CT (N=52)	Total (N=363)
Prematurely discontinued	19 (19.8)	32 (14.9)	4 (7.7)	55 (15.2)
Adverse event	8 (8.3)	17 (7.9)	1 (1.9)	26 (7.2)
Death	6 (6.3)	6 (2.8)	2 (3.8)	14 (3.9)
Lack of efficacy	1 (1.0)	1 (0.5)	1 (1.9)	3 (0.8)
Non-compliance with study medication	2 (2.1)	0	0	2 (0.6)
Protocol violation	0	2 (0.9)	0	2 (0.6)
Withdrawal by patient	2 (2.1)	5 (2.3)	0	7 (1.9)
Other	0	1 (0.5)	0	1 (0.3)

Definition of abbreviations: CT = capped titration; IDT = individual dose titration.

5.2.2.2 Demographic and Baseline Characteristics in Study PATENT-2

Almost 80% of the 363 patients were female, 62.8% were white, and 32.0% were classified as Asian (Table 25). Very few patients were classified as black (<1%). Mean age was 49.4 years and 22.6% were ≥65 years of age. Mean body mass index was 25.93 kg/m^2. The majority of patients (63.9%) had never smoked, and the majority of patients (62.5%) reported no alcohol consumption. There were no notable differences among the former treatment groups.

Table 25: Demographic and Baseline characteristics in Study PATENT-2 (Long-term Safety Population)

Characteristic	Former Placebo (N=96)	Former Riociguat IDT (N=215)	Former Riociguat CT (N=52)	Total (N=363)
Female, n (%)	76 (79.2)	171 (79.5)	41 (78.8)	288 (79.3)
Race / Ethnicity, n (%)				
White	62 (64.6)	140 (65.1)	26 (50.0)	228 (62.8)
Black or African American	0	2 (0.9)	1 (1.9)	3 (0.8)
Asian	29 (30.2)	68 (31.6)	19 (36.5)	116 (32.0)
Multiple races	1 (1.0)	0	0	1 (0.3)
Hispanic or Latino	4 (4.2)	5 (2.3)	6 (11.5)	15 (4.1)
Age (years)				
Mean (standard deviation)	48.6 (15.8)	50.1 (16.3)	48.0 (16.4)	49.4 (16.2)
Age ≥65 years, n (%)	19 (19.8)	53 (24.7)	10 (19.2)	82 (22.6)
Never smoked, n (%)	58 (60.4)	141 (65.6)	33 (63.5)	232 (63.9)
Alcohol abstinent, n (%)	55 (57.3)	139 (64.7)	33 (63.5)	227 (62.5)
Body mass index (kg/m^2) at baseline				
Mean (standard deviation)	26.17 (5.74)	25.83 (5.54)	25.91 (4.53)	25.93 (5.45)

Definition of abbreviations: CT = capped titration; IDT = individual dose titration.

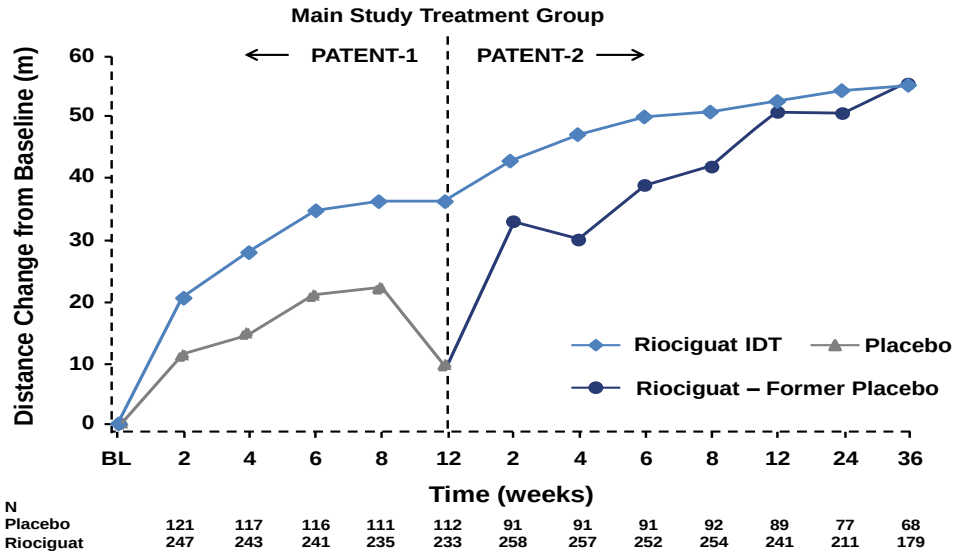
Most patients had a primary diagnosis of idiopathic PAH (62.8%) or PAH due to connective tissue disease (23.7%). More than 95% of patients had a WHO functional class of II or III. About half of the patients were treatment-naïve (48.5%) and half were pre-treated for PAH (51.5%) when they entered the double-blind PATENT-1. Overall, 45.2% of patients were pre-treated with an ERA and 7% with a prostacyclin analogue (oral, inhaled, or subcutaneous).

5.2.2.3 Efficacy Results in Study PATENT-2

Mean changes in 6MWD from baseline for patients in PATENT-2 are displayed over time in Figure 20. The cohort of patients treated with riociguat in PATENT-1 maintained for at least 18 months the mean improvement in 6MWD achieved in PATENT-1. The cohort of patients treated with placebo in PATENT-1 had a small mean change in 6MWD in PATENT-1 and were observed to have improvements in 6MWD following 12 weeks of riociguat treatment in PATENT-2. Differences between these 2 cohorts need to be interpreted with caution due to the different sizes of the cohorts of former riociguat and former placebo subjects; that is, the unbalanced randomization in PATENT-1, discontinuations over time in PATENT-2, and ongoing patients not yet reaching later time points result in few patients in the former placebo cohort after 6 months in PATENT-2.

Mean change from baseline in PATENT-2 was 51.2 meters at 6 months, 53.7 meters at 9 months (n=247), 48.4 meters at 12 months (n=214), and 47.3 meters at 18 months (n=151).

Figure 20: Mean Change From Baseline in 6MWD by Visit in Studies PATENT-1 and PATENT-2 (Long-term Safety Population, Observed Cases)



Definition of abbreviations: 6MWD = 6-minute walking distance; BL = baseline; IDT = individual dose titration; m = meters.

Analyses of Other Efficacy Variables

The findings for NT-proBNP, WHO functional class, Borg CR 10 score, and EQ-5D were consistent with the key findings for 6MWD, namely that clinically relevant improvements seen in PATENT-1 were maintained in PATENT-2, with an indication of long-term maintenance of the riociguat treatment effect and improvement in those patients treated with placebo in PATENT-1.

5.2.2.4 Efficacy Conclusion in Study PATENT-2

Overall, the exploratory analyses of efficacy in PATENT-2 indicate long-term maintenance of the riociguat treatment effect and improvement in those patients treated with placebo in PATENT-1.

5.3 Phase II Study 12166 with Long-term Extension

Study 12166 was multicenter, non-randomized, non-blinded, and non-controlled. It was intended to show the feasibility and safety of an IDT scheme of riociguat based on systolic blood pressure. Inclusion and exclusion criteria as well as study endpoints were similar to study CHEST-1 but included patients diagnosed with CTEPH as well as PAH. Patients were analyzed after a 12-week non-blinded and non-controlled treatment phase. Thereafter the patients could continue treatment with riociguat and enter a long-term extension phase. The treatment period for individual patients was up to 4.5 years at the time of this interim analysis.

Patients received riociguat starting with 1.0 mg TID, and depending on the patient's systolic blood pressure measured every 2 weeks, the riociguat dose was up- or down-titrated for the first 8 weeks by 0.5 mg TID or maintained. The lower and upper limits of daily dosing were 0.5 mg TID and 2.5 mg TID, respectively. The following IDT scheme was based on systolic blood pressure at trough:

- If trough systolic blood pressure was >100 mmHg, dose was increased 0.5 mg TID.
- If trough systolic blood pressure was 90 to 100 mmHg, dose was maintained.
- If trough systolic blood pressure was <90 mmHg without symptoms of hypotension, dose was reduced by 0.5 mg TID.
- If systolic blood pressure was <90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, the study treatment had to be stopped; study treatment was restarted with a dose reduction of 0.5 mg TID after 24 hours.

During long-term extension, down- or titration of the study treatment dose was in the range of 0.5 mg TID to 2.5 mg TID.

For the 6MWD, clinically relevant improvements were observed after 14 days of treatment with riociguat. The mean increase was 61 meters until the end of titration on Day 56 and 68 meters until Day 84. The improvements in 6MWD were sustained during the long-term extended treatment phase up to 4.5 years for the total population comprising 68 patients entering the extended treatment phase, as well as for patients with CTEPH and PAH.

Consistent improvements throughout both phases of the study were seen for other efficacy variables such as Borg CR 10 score, WHO functional class, and NT-proBNP.

5.4 Comparative Efficacy

5.4.1 Primary Efficacy Endpoint (6MWD)

Each individual phase III study (CHEST-1 and PATENT-1) demonstrated clinically meaningful and statistically significantly superior efficacy of riociguat compared with placebo for the primary endpoint of 6MWD (Table 26). Similar results were observed in both studies for the pre-specified, clinically most relevant subgroups of patients: inoperable CTEPH, treatment naïve patients, patients pre-treated with ERA, and patients with familial/idiopathic PAH. When the CIs crossed the zero value, it was mainly due to the low number of patients. Additional benefit can be gained by longer treatment periods as demonstrated during the initial double-blind treatment phase of the long-term extension phases of both studies, where a further increase of 6MWD in patients of the former riociguat IDT group was observed in CTEPH patients as well as in PAH patients. In addition, the extent of improvement of 6MWD seen in the former placebo-treated patients during that initial treatment phase shows the robustness of the 6MWD response to riociguat (Section 5.1.2.3 and Section 5.2.2.3).

The results were directionally consistent across all major subgroups examined, including those for sex, age, race, body weight, WHO functional, baseline 6MWD, and renal function. However, some subgroups (e.g., black race) had few patients, making it difficult to draw conclusions.

Table 26: Change in 6MWD From Baseline to Last Visit for Studies CHEST-1 and PATENT-1 (Safety/ITT Population)

STUDY	Difference of LS-means[a]	95% CI	Stratified Wilcoxon Test p-value	Subgroup	n/N (%)	Difference of LS means	95% CI
CHEST-1 (CTEPH)							
16-week treatment	45.7	24.7 to 66.6	<0.0001	Inoperable CTEPH	189/261 (72%)	53.9	28.5 to 79.3
				Postoperative CTEPH	72/261 (28%)	26.7	-9.7 to 63.1
PATENT-1 (PAH)							
12-week treatment	35.8	20.1 to 51.5	<0.0001	Therapy naïve	221/443 (50%)	38.4	14.5 to 62.3
				Pre-treatment with ERA	194/443 (44%)	25.9	5.3 to 46.5
				IPAH/FPAH	281/443 (63%)	42.8	23.4 to 62.2
				CTD	111/443 (25%)	28.1	-4.4 to 60.6

Definition of abbreviations: CI = confidence interval; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; ERA = endothelin receptor antagonist; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; LS = least squares, PAH = pulmonary arterial hypertension.

a Difference of LS means is riociguat IDT minus placebo.

5.4.2 Secondary Endpoints

The robustness of the study results of the primary endpoint is corroborated by the consistent results of the pre-defined secondary endpoints in both studies. Both studies applied the same approach of a sequential testing procedure for the same secondary efficacy variables. In the hierarchical test procedure the variables PVR, NT-proBNP, and WHO functional class were significant in both indications, whereas the next variable in the hierarchy (time to clinical worsening) was positive for riociguat in PAH only. In CTEPH (Section 5.1.1.4) there was a trend in favor of riociguat consistent with the results of PAH (Section 5.2.1.4), but due to the low number of events in a short observation period it was to be expected that the results would not be significant in favor of riociguat.

For the secondary efficacy variables of PVR and NT-pro BNP, which were based on objective measurements, the gain for riociguat IDT treatment over placebo was similar in CTEPH and PAH (Table 27). Other secondary efficacy variables are summarized following the table.

Table 27: Change in Secondary Endpoints of PVR and NT-proBNP From Baseline to Last Visit in Study CHEST-1 and PATENT-1 (Safety/ITT Population)

	CHEST-1		PATENT-1	
Statistic	**Placebo (N=88)**	**Riociguat IDT (N=173)**	**Placebo (N=126)**	**Riociguat IDT (N=254)**
PVR (dyne*second*cm^{-5})				
Change from baseline to last visit[a]				
Mean (standard deviation)	23 (274)	–226 (248)	–9 (317)	–223 (260)
Treatment comparison	**Riociguat IDT – placebo**		**Riociguat IDT – placebo**	
LS mean difference[b]	–246		–226	
95% confidence interval	–303 to –190		–281 to –170	
p-value (stratified Wilcoxon test)[c]	<0.0001		<0.0001	
NT-proBNP (pg/mL)				
Change from baseline to last visit[a]				
Mean (standard deviation)	76 (1447)	–291 (1717)	232 (1011)	–198 (1721)
Treatment comparison	**Riociguat IDT – placebo**		**Riociguat IDT – placebo**	
LS mean difference[b]	–444		–432	
95% confidence interval	–843 to –45		–782 to –82	
p-value (stratified Wilcoxon test)[c]	<0.0001		<0.0001	

Abbreviations: IDT = individual dose titration; ITT = intent-to-treat; LS = least squares; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; PVR = pulmonary vascular resistance.

a Last visit defined as last observed value post-baseline (not including follow-up).

b For CHEST-1, ANCOVA model with baseline value, treatment group, and region as fixed effects. For PATENT-1, ANCOVA model with baseline value, treatment group, region, and stratification group as fixed effects.

c Stratified by region for CHEST-1 and stratified by region and stratification group for PATENT-1.

The treatment difference for time to clinical worsening was statistically significant in patients with PAH (stratified log-rank test p=0.0046 in PATENT-1) and not significant for patients with CTEPH (p=0.1724 in CHEST-1). Both studies showed a lower proportion of patients with clinical worsening in the riociguat IDT group compared to placebo group in CHEST-1 (2.3% versus 5.7%) and PATENT-1 (1.2% versus 6.3%) as well as death as a component of clinical worsening (1.2% versus 3.4% in CHEST-1 and 0.8% versus 2.4% in PATENT-1). Thus, the 2 studies demonstrate a robust benefit for patients in the riociguat IDT treatment group.

The improvements of 6MWD, a measure of exercise capacity in daily life, are accompanied by:

- Improvement of WHO functional class: the treatment difference in percent of patients who experienced an improvement of at least 1 functional class was 18 points in CHEST-1 and 7 points in PATENT-1.

- Improvement of Borg CR 10 score (difference of mean values), which characterizes the perceived exertion at the end of the test for 6MWD: mean change to last visit for the riociguat IDT and placebo groups was -0.83 and 0.17, respectively, in CHEST-1 and -0.44 and 0.09, respectively, in PATENT-1.

- Improvement of EQ-5D utility score: the treatment group difference for LS means was 0.13 in CHEST-1 and 0.06 in PATENT-1.

- Improvement of LPH questionnaire score: the treatment group difference for LS means was -5.76 in CHEST-1 and -6.17 in PATENT-1.

5.4.3 Efficacy Across the Long-term Extension Studies

Patients from both double-blind, placebo-controlled, phase III studies (CHEST-1 and PATENT-1) were allowed to enter a respective non-controlled long-term extension study (CHEST-2 and PATENT-2, respectively). Both studies demonstrated the benefit of extended treatment. Patients of the former placebo group in the double-blind studies who thereafter received riociguat starting with the same titration scheme that was applied in the double-blind phase had a benefit in improving their 6MWD. Patients maintained on their assigned riociguat dose showed a further improvement of their 6MWD at the end of the first 12 weeks after being switched to the long-term extended treatment. The improvements of their 6MWD were maintained up to 18 months to a clinically relevant degree.

Across the 3 studies with extended treatment (CHEST-2, PATENT-2, and Study 12166), the results of the 6MWD were supported by the data for NT-proBNP, WHO functional class, and Borg CR 10 score.

6. Overview of Clinical Safety

The data which provide the primary basis for the safety assessment of riociguat originate from patients who participated in the phase III controlled clinical studies (the CHEST-1 study for CTEPH and the PATENT-1 study for PAH). Riociguat IDT and CT groups were combined for the safety analyses. The results of the pooled CHEST-1 and PATENT-1 studies are presented because the study protocols were similar, patient characteristics were similar, and similar incidence rates were observed for AEs in the individual studies. Pooling of data was performed mainly to improve signal detection in 2 small patient populations. Safety during long-term exposure is based on patients from both studies who were allowed to be included in the extension studies (CHEST-2 and PATENT-2, respectively).

The safety database from the double-blind pivotal studies comprises 490 riociguat-treated patients and 214 placebo-treated patients who were treated for 12 weeks in PATENT-1 and 16 weeks in CHEST-1. There were 557 of these patients who had entered the respective long-term extension studies as of the cutoff date for the NDA submission.

Safety data are presented as AEs unless otherwise stated. Treatment-emergent AEs occurred during the period after the first dose of study medication up to 2 days after the last dose of study medication.

6.1 Exposure to Study medication

In the phase III studies CHEST-1 and PATENT-1, the majority of patients received either riociguat IDT (up to 2.5 mg TID) or placebo. The safety population in placebo-controlled phase III studies comprises:

- 173 patients treated with riociguat IDT, and 88 patients with placebo in CHEST-1 with a treatment duration of 16 weeks
- 254 patients treated with riociguat IDT, 63 patients with riociguat CT (up to 1.5 mg TID) and 126 patients with placebo in PATENT-1 with a treatment duration of 12 weeks
- 427 patients treated with riociguat IDT, 63 patients with riociguat CT, and 214 patients with placebo from both phase III studies

Treatment duration in studies CHEST-1, PATENT-1, CHEST-2, and PATENT-2 is summarized in Table 28.

Table 28: Treatment Duration in Studies CHEST-1, PATENT-1, CHEST-2 and PATENT-2 (Main and Extension Phases, Safety Population)

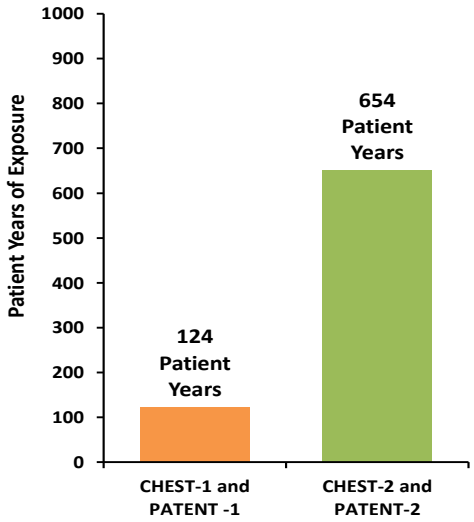
Study	CHEST-1 and PATENT-1		CHEST-2 and PATENT-2
Duration of treatment	**Placebo (N=214)**	**Riociguat (N=490)**	**Riociguat (N=557)**
0–7 days	5 (2.3)	7 (1.4)	1 (0.2)
8–21 days	2 (0.9)	8 (1.6)	2 (0.4)
22–35 days	3 (1.4)	6 (1.2)	4 (0.7)
36–49 days	3 (1.4)	6 (1.2)	1 (0.2)
50–63 days	5 (2.3)	6 (1.2)	26 (4.7)
64–91 days	110 (51.4)	286 (58.4)	52 (9.3)
92–180 days	86 (40.2)	171 (34.9)	69 (12.4)
181–270 days	0	0	65 (11.7)
271–360 days	0	0	49 (8.8)
361–450 days	0	0	48 (8.6)
451–540 days	0	0	48 (8.6)
541–630 days	0	0	55 (9.9)
631–720 days	0	0	43 (7.7)
721–810 days	0	0	40 (7.2)
811–900 days	0	0	38 (6.8)
901–990 days	0	0	13 (2.3)
991–1080 days	0	0	3 (0.5)
Duration of treatment (days)			
Mean (standard deviation)	91.4 (24.1)	90.7 (22.3)	422.8 (272.5)
Median	86.5	86.0	369.0

Note: Sample size for the pooled riociguat group includes the capped dose treatment group in PATENT-1.

Total exposure for combined riociguat treatment in the controlled studies (CHEST-1 and PATENT-1) and corresponding extension studies (CHEST-2 and PATENT-2) is summarized in Figure 21.

Figure 21: Total Exposure for CTEPH (CHEST-1 and CHEST-2) and PAH (PATENT-1 and PATENT-2)

- 443 patients treated for ≥24 weeks
- **319 patients treated for ≥48 weeks**
- 121 patients treated for ≥96 weeks



Definition of abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension.

6.2 Demographic and Baseline Characteristics of Patients in CHEST-1 and PATENT-1

The Safety/ITT population of CHEST-1 and PATENT-1 included a large number of elderly patients (>30% were older than 65 years), and more women than men. The largest ethnic group was white (approximately 65%), followed by Asian (>25%), and black (2%). Patients had a mean age of 54 years (Table 29).

Table 29: Demographic and Baseline Characteristics in Studies CHEST-1 and PATENT-1 (Main Phase, Safety/ITT Population)

Characteristics	Placebo (N=214)	Riociguat (N=490)
Female, n (%)	152 (71.0)	370 (75.5)
Age (years)		
Mean (standard deviation)	54.2 (15.6)	53.7 (16.1)
≥65 to <75, n (%)	58 (27.1)	110 (22.4)
≥75, n (%)	10 (4.7)	44 (9.0)
Race / Ethnicity, n (%)		
White	143 (66.8)	314 (64.1)
Black or African American	2 (0.9)	12 (2.4)
Asian	58 (27.1)	138 (28.2)
Other	11 (5.1)	26 (5.3)
Hispanic or Latino	10 (4.7)	24 (4.9)
Baseline body mass index (kg/m^2)		
Mean (standard deviation)	26.87 (5.71)	26.46 (5.58)
Never Smoked, n (%)	125 (58.4)	324 (66.1)
Abstinent from alcohol, n (%)	118 (55.1)	299 (61.0)
Geographic region, n (%)		
Asia/Pacific	27 (12.6)	75 (15.3)
China	35 (16.4)	74 (15.1)
Europe	112 (52.3)	252 (51.4)
North America	20 (9.3)	44 (9.0)
Latin America[a]	20 (9.3)	45 (9.2)

Note: Sample size for the pooled riociguat group includes the capped dose treatment group in PATENT-1.
a Referred to as South America in the source.

6.3 Adverse Events

6.3.1 Overview of Adverse Events

Pooled Controlled Phase III Studies

In the pooled controlled studies CHEST-1 and PATENT-1, AEs were reported in 90.6% of patients in the riociguat group and 86.0% of patients in the placebo group (Table 30). The incidence of SAEs was 15.1% in the riociguat group and 17.3% in the placebo group. The incidence of AEs leading to discontinuation of study medication was lower in the riociguat group (2.9%) than in the placebo group (5.1%). The incidence of AEs leading to death was also lower in the riociguat group (1.0%) than in the placebo group (2.8% after excluding a patient who had died after 134 days in the extension study PATENT-2 from an AE beginning in PATENT-1).

The overall incidence of AEs was similar between the riociguat and placebo treatment groups in both studies when analyzed individually, and was comparable between the 2 studies. Selected by-study summaries of AEs are provided in Appendix 11.8 (page 213).

Table 30: Overall Summary Adverse Events in Pooled Studies CHEST-1 and PATENT-1 (Main Phase, Safety/ITT Population)

	Number (%) of Patients					
	CHEST-1		PATENT-1		CHEST-1 and PATENT-1	
AEs	Placebo (N=88)	Riociguat (N=173)	Placebo (N=126)	Riociguat (N=254)	Placebo (N=214)	Riociguat (N=490)
Any	76 (86.4)	159 (91.9)	108 (85.7)	227 (89.4)	184 (86.0)	444 (90.6)
Any serious	14 (15.9)	34 (19.7)	23 (18.3)	29 (11.4)	37 (17.3)	74 (15.1)
Any leading to discontinuation of study medication	2 (2.3)	5 (2.9)	9 (7.1)	8 (3.1)	11 (5.1)	14 (2.9)
Any leading to death	3 (3.4)	2 (1.2)	4[a] (3.2)	2 (0.8)	7[a] (3.3)	5 (1.0)

Definition of abbreviations: AE = treatment-emergent adverse event.
Note: Sample size for the pooled riociguat group includes the capped dose treatment group in PATENT-1, but N for the riociguat group in PATENT-1 reflects only the individual dose titration group.
a One AE leading to death, included here, was included in the source tables of the study report of PATENT-1, although the patient had died after 134 days in the extension study PATENT-2. This patient died from metastatic malignant melanoma; the case was assessed as a post-treatment death.

Pooled Non-controlled Extension Studies

In the pooled long-term extension studies (CHEST-2 and PATENT-2), AEs were reported in 91.0% of patients, SAEs in 35.7% of patients, AEs leading to discontinuation in 5.6% of patients, and AEs leading to death in 4.1%. After adjusting for duration of exposure, the number of SAEs

per 100 patient-years of exposure was lower in the pooled long-term extension studies (65.29) than in the pooled controlled studies (92 and 102 for the riociguat and placebo groups, respectively).

6.3.2 Common Adverse Events

Pooled Controlled Phase III Studies

The most common AEs by MedDRA preferred term for each treatment group in the pooled controlled studies are summarized in Table 31. Adverse events reported by a larger proportion of riociguat-treated than placebo-treated patients (≥5% difference) included headache, dizziness, dyspepsia, and hypotension. Adverse events reported by a smaller proportion of riociguat-treated than placebo-treated patients (≥5% difference) included cough and dyspnea.

Table 31: Frequent Treatment-Emergent Adverse Events in Pooled Studies CHEST-1 and PATENT-1 (Main Phase, Safety/ITT Population)

	Number (%) of Patients	
Preferred Term	**Placebo (N=214)**	**Riociguat (N=490)**
Any event	184 (86.0)	444 (90.6)
Headache	37 (17.3)	132 (26.9)
Dizziness	26 (12.1)	94 (19.2)
Dyspepsia	17 (7.9)	87 (17.8)
Edema peripheral	32 (15.0)	85 (17.3)
Nausea	23 (10.7)	69 (14.1)
Nasopharyngitis	22 (10.3)	58 (11.8)
Diarrhea	17 (7.9)	58 (11.8)
Vomiting	14 (6.5)	50 (10.2)
Hypotension	6 (2.8)	43 (8.8)
Palpitations	10 (4.7)	31 (6.3)
Dyspnea	26 (12.1)	28 (5.7)
Cough	29 (13.6)	24 (4.9)

Note: Sample size for the pooled riociguat group includes the capped dose treatment group in PATENT-1.

Pooled Non-controlled Extension Studies

Table 32 presents the most common (≥10 events per 100 patient-years) AEs by MedDRA preferred term per 100 patient-years for the pooled CHEST-2 and PATENT-2 studies. Using this

incidence rate adjusts for differences in exposure among patients in these ongoing studies. The total population includes those patients treated with placebo in the main controlled study who began riociguat treatment in the long-term extension study. The long-term extension studies were not controlled.

The overall rate of AEs in this population was 668 events per 100 patient-years. This rate is lower than those observed for the pooled controlled phase III studies: 1944 events per 100 patient-years for the riociguat group and 1771 events per 100 patient-years for the placebo group.

Table 32: Common Treatment-emergent Adverse Events in Pooled Studies CHEST-2 and PATENT-2 (Extension Phase, Long-term Safety Population)

Preferred Term	Number of events (per 100 patient-years) (N=557)
Any Event	4306 (667.79)
Nasopharyngitis	173 (26.83)
Dizziness	140 (21.71)
Edema peripheral	128 (19.85)
Headache	114 (17.68)
Diarrhea	101 (15.66)
Cough	90 (13.96)
Nausea	80 (12.41)
Dyspepsia	74 (11.48)
Upper respiratory tract infection	74 (11.48)
Respiratory tract infection	73 (11.32)

Note: Common events defined as ≥10 events per 100 patient-years.

6.3.3 Serious Adverse Events

6.3.3.1 Adverse Events Resulting in Death

Studies CHEST-1 and CHEST-2

The most frequent cause for death was due to AEs in the system organ class of cardiac disorders, in particular the preferred term cardiac arrest, as would be expected for the study population (Table 33).

In the Safety/ITT population of CHEST-1, 5 patients died within the study period. The incidence rate of deaths was lower in the riociguat IDT group (1.2% [2/173]) than in the placebo group (3.4% [3/88]).

In the riociguat treatment group, reported primary causes for deaths were cardiac failure (for 1 patient), anemia, catheter side hemorrhage, and acute renal failure (0.6% [1/173] for the other patient). In the placebo group, primary causes were cardiac arrest (2.3% [2/88]) and cardiopulmonary failure (1.1% [1/88]).

In the long-term safety population of CHEST-2, 5 patients died within the study period (Table 33). The incidence rate of deaths was numerically lower in the former riociguat IDT treatment group (2.3% [3/129]) than in the former placebo treatment group (3.1% [2/65]).

In the former riociguat treatment group, reported primary causes for deaths were cardiac arrest (1.6% [2/129]) and acute right ventricular failure (0.8% [1/129]). In the former placebo group, primary causes for deaths were cardiac arrest, gastrointestinal hemorrhage, pneumonia, acute renal failure, asthma, pulmonary hemorrhage, and pulmonary hypertension (1.5% [1/65] each).

Table 33: Listing of Patients Who Died During Studies CHEST-1 and CHEST-2 (Main and Extension Phases, Safety Population)

Patient	Treatment[a]	Age/Sex	Preferred Term	Related to Study Medication[b]
Study CHEST-1				
380018020	Riociguat IDT	74/Female	Cardiac failure	No
470028004	Riociguat IDT	46/ Female	Anemia	No
			Catheter site hemorrhage	No
			Renal failure acute	Yes
100068003	Placebo	73/ Female	Cardiopulmonary failure	No
220018005	Placebo	66/ Female	Cardiac arrest	No
540028032	Placebo	45/ Female	Cardiac arrest	No
Study CHEST-2				
380018004	Riociguat IDT	68/Male	Acute right ventricular failure	No
380018013	Riociguat IDT	65/ Male	Cardiac arrest	No
380018017	Riociguat IDT	60/ Male	Cardiac arrest	No
220018014	Placebo[c]	42/ Male	Cardiac arrest	No
470038003	Placebo[c]	73/ Female	Gastrointestinal hemorrhage	No
			Pneumonia	No
			Renal failure acute	No
			Asthma	No
			Pulmonary hemorrhage	No
			Pulmonary hypertension	No

Definition of abbreviations: IDT = individual dose titration.
a Treatment assignment in CHEST-1 is shown for both studies.
b Relationship was per investigator's judgment.
c Placebo was received in CHEST-1 and riociguat in CHEST-2.

Studies PATENT-1 and PATENT-2

The most frequent cause for death in PATENT-1 and PATENT-2 was due to AEs in the system organ class of respiratory, thoracic and mediastinal disorders, in particular the preferred term pulmonary arterial hypertension, as would be expected of the study population.

In the Safety/ITT population of PATENT-1, 6 patients died within the study period (Table 34). The incidence rate of deaths was lowest in the riociguat IDT group (0.8% [2/254 patients]), followed by the riociguat CT group (1.6% [1/63 patients]) and placebo group (2.4% [3/126 patients]). An additional placebo-treated patient was diagnosed with metastatic malignant melanoma on day 76 of PATENT-1, received riociguat during the long-term extension, and subsequently died on day 134 of PATENT-2. The patient was considered to have died post-treatment in the long-term extension study.

In the riociguat groups, death was caused by sepsis, hemoptysis, right ventricular failure and pulmonary arterial hypertension (the latter 2 in 1 patient). In the placebo group, death was caused by pulmonary arterial hypertension, anxiety, respiratory failure and circulatory collapse (the latter 2 in 1 patient).

In the long-term safety population of PATENT-2, 18 patients died within the study period (Table 34) and 4 patients died post-treatment (Table 35). The incidence rate of deaths was lower in both the former riociguat IDT group (4.2% [9/215 patients]) and the former riociguat CT group (3.8% [2/52 patients]) than in the former placebo group (7.3% [7/96 patients]).

In the former riociguat treatment groups, death was caused by pulmonary arterial hypertension (3/215 patients), pulmonary hemorrhage (2/215 patients), and sepsis (2/215 patients), and other events that occurred in 1 patient per event (renal failure, cardiac failure chronic, pneumonia, cholelithiasis, cardiogenic shock, pulmonary hypertension, shock, abdominal pain, acidosis, non-small cell lung cancer, right ventricular failure and bronchopneumonia). In the former placebo group, death was caused by pulmonary arterial hypertension (2/96 patients) and events that occurred in 1 patient per event (pulmonary hypertension, right ventricular failure, sudden cardiac death, pulmonary embolism, cardiac failure, and septic shock).

Table 34: Listing of Patients Who Died During Studies PATENT-1 and PATENT-2 (Main and Extension Phases, Safety Population)

Patient No.	Treatment[a]	Age/Sex	Preferred Term	Related to Study Medication[b]
Study PATENT-1				
220024001	Riociguat IDT	61/Female	Sepsis	No
540044008	Riociguat IDT	26/Male	Hemoptysis	No
140054001	Placebo	73/Female	Pulmonary arterial hypertension	No
400084010	Placebo	66/Male	Anxiety[c]	No
540024005	Placebo	59/Female	Respiratory failure	No
			Circulatory collapse	No
440034006	Riociguat CT	65/Male	Right ventricular failure	No
			Pulmonary arterial hypertension	No
Study PATENT-2				
100044001	Riociguat IDT	23/Female	Pulmonary hemorrhage	No
			Sepsis	No
			Renal failure	No
100044003	Riociguat IDT	77/Male	Pulmonary arterial hypertension	No
100054003	Riociguat IDT	80/Male	Cardiac failure chronic	No
100094001	Riociguat IDT	61/Female	Pulmonary hemorrhage	Yes
			Pneumonia	Yes
500014005	Riociguat IDT	22/Female	Pulmonary arterial hypertension	Yes
500014009	Riociguat IDT	34/Female	Cholelithiasis	No
			Sepsis	No
500044003	Riociguat IDT	57/Female	Pulmonary arterial hypertension	No
540014003	Riociguat IDT	35/Male	Cardiogenic shock	No
			Pulmonary hypertension	No
610044002	Riociguat IDT	44/Female	Shock	No
			Abdominal pain	No
			Acidosis	No
180014007	Placebo[d]	51/Female	Right ventricular failure	No
200064002	Placebo[d]	18/Male	Sudden cardiac death	No
510024001	Placebo[d]	28/Female	Pulmonary arterial hypertension	No
			Pulmonary embolism	No
540014002	Placebo[d]	33/Female	Death	No
540014010	Placebo[d]	47/Female	Pulmonary hypertension	No
540054009	Placebo[d]	62/Male	Cardiac failure	No
610014003	Placebo[d]	30/Female	Pulmonary arterial hypertension	No
			Septic shock	No
260054001	Riociguat CT	74/Female	Non-small cell lung cancer	No
380024001	Riociguat CT	77/Female	Right ventricular failure	No
			Bronchopneumonia	No

Definition of abbreviations: CT = capped titration; IDT = individual dose titration.

a Treatment assignment in PATENT-1 is shown for both studies.

b Relationship was per investigator's judgment.

c Patient experienced acute respiratory failure and preparation for colonoscopy with this event.

d Placebo was received in CHEST-1 and riociguat in CHEST-2.

Table 35: Listing of Patients Who Died Post-treatment in Study PATENT-2 (Long-term Safety Population)

Patient	Treatment in PATENT-1	Age/Sex	Preferred Term	Day of AE Onset	Day of Death	Day of Study Medication Stopped	Related to Study Medication[a]
470034004	Riociguat IDT	71/Male	Cardio-respiratory arrest	114	114	106	Yes
			Hypoxic-ischemic encephalopathy	114	114	106	Yes
100054005	Placebo[b]	72/Female	Pulmonary embolism	534	534	530	No
140014003[c]	Placebo[b]	55/Female	Metastatic malignant melanoma	76	134	125	No
680014003	Riociguat CT	33/Female	Multi-organ failure	149	151	142	No
			Pulmonary arterial hypertension	148	151	142	No

Abbreviations: CT = capped titration; IDT = individual dose titration.
a Relationship was per investigator's judgment.
b Placebo was received in PATENT-1 and riociguat was received in PATENT-2.
c Event started during PATENT-1.

Study 12166

Seven deaths were reported during the long-term extension phase. Six patients died during treatment with study medication due to cardiac decompensation, worsening of pulmonary arterial hypertension, hepatocellular carcinoma, sudden death after 4.5 months continuous treatment, progressive right heart failure, or decompensated cor pulmonale. One patient died from fatal decompensation of cor pulmonale about 2 months after last intake of study medication. The investigator judged all these events as progression of the underlying diseases and considered them as not related to the study medication.

One patient died due to progressive right heart failure 50 days after stopping study medication. The event was considered unrelated to study medication.

6.3.3.2 Other Serious Adverse Events

Pooled Controlled Phase III Studies

Table 36 summarizes the most common (reported by >2 patients in either treatment group) SAEs in the pooled controlled studies by MedDRA preferred term.

The most common SAEs by preferred term for each treatment group were as follows:

- Riociguat treatment group: right ventricular failure (2.2%), syncope (1.4%), hemoptysis (1.0%), gastritis (0.8%), pneumonia (0.8%), chest pain (0.6%), gastroenteritis (0.6%), renal failure acute (0.6%), and pulmonary hypertension (0.6%)

- Placebo treatment group: syncope (3.7%), right ventricular failure (1.9%), pulmonary arterial hypertension (0.9%), dyspnea (0.9%), and cardiac arrest (0.9%)

Note: Since syncope was an AE of special interest, it was reported as serious.

Table 36: Common Serious Treatment-emergent Adverse Events in Pooled Studies CHEST-1 and PATENT-1 (Main Phase, Safety/ITT Population)

	Number (%) of Patients	
Preferred Term	**Placebo (N=214)**	**Riociguat (N=490)**
Any Event	37 (17.3)	74 (15.1)
Syncope	8 (3.7)	7 (1.4)
Right ventricular failure	4 (1.9)	11 (2.2)
Hemoptysis	0	5 (1.0)
Pulmonary arterial hypertension	2 (0.9)	2 (0.4)
Dyspnea	2 (0.9)	1 (0.2)
Cardiac arrest	2 (0.9)	0
Gastritis	0	4 (0.8)
Pneumonia	0	4 (0.8)
Chest pain	1 (0.5)	3 (0.6)
Gastroenteritis	0	3 (0.6)
Renal failure acute	0	3 (0.6)
Pulmonary hypertension	0	3 (0.6)

Notes: Sample size for the pooled riociguat group includes the capped dose treatment group in PATENT-1. Common events were defined as reported by more than 0.5% of patients in either treatment group.

Pooled Non-controlled Extension Studies

The most common SAEs (reported by >1% of patients) by preferred term in the pooled long-term extension studies were syncope (5.4%), pulmonary arterial hypertension (4.5%), right ventricular failure (4.1%), pulmonary hypertension (2.9%), catheterization cardiac (2.7%), pneumonia (2.0%), hemoptysis (1.3%), bronchitis (1.1%), and dyspnea (1.1%). These are generally consistent with the most common SAEs for the controlled phase III studies.

Of note, the incidence of hemoptysis as an SAE was 1.3% (7/557 patients) in the pooled long-term extension studies, compared with 1.0% (5/490 patients) in the pooled riociguat treatment group in the controlled studies; no hemoptysis events were reported as SAEs in the pooled placebo group. Adjusting for differences in exposure, the rate of hemoptysis as an SAE in 100 patient-years was 1.24 events in the pooled long-term extension studies, compared with 4.93

events in the pooled riociguat group and no events in the pooled placebo group in the controlled studies. The incidence of serious hemoptysis during long-term treatment with riociguat was thus lower than in the riociguat treatment group during the controlled studies. Further details on bleeding events (serious or non-serious) in phase III studies are provided in Section 6.6.3.2.3 (page 161).

Study 12166

A total of 11 of 75 patients reported 17 SAEs (e.g., upper abdominal pain, hematemesis, gastro-intestinal hemorrhage, pulmonary hemorrhage, and pulmonary edema). One case of pulmonary edema was the only SAE considered drug-related by the investigator.

In the long-term extension, 47 of 68 (69.1%) patients reported SAEs. The most frequent SAEs were syncope (n=12 [17.6%]), right ventricular failure (n=8 [11.8%]), pulmonary arterial hypertension (n=7 [10.3%]), cardiac failure (n=6 [8.8%]), pulmonary hypertension (n=5 [7.4%]), atrial flutter (n=4 [5.9%]), and pneumonia (n=4 [5.9%]).

6.3.4 Adverse Events Resulting in Discontinuation

Pooled Controlled Phase III Studies

In the pooled controlled studies, AEs leading to discontinuations were reported in 14 patients (2.9%) in the riociguat group and 11 patients (5.1%) in the placebo group. The most frequent AEs leading to discontinuations in the riociguat group across both studies were in the system organ classes of cardiac disorders (3 patients), gastrointestinal disorders (2 patients), general disorders and administration site conditions (2 patients), and nervous system disorders (2 patients). The most frequent AEs leading to discontinuations in the placebo group across both studies were in the system organ classes of cardiac disorders (2 patients) and respiratory, thoracic and mediastinal disorders (5 patients).

Pooled Non-controlled Extension Studies

In the pooled long-term extension studies, AEs leading to discontinuations were reported in 31 patients (5.6%). The most frequent AEs leading to discontinuations by preferred term were:

- CHEST-2: pulmonary hypertension (2 patients [1.0%])
- PATENT-2: pulmonary arterial hypertension (4 patients [1.1%]), pulmonary hypertension (3 patients [0.8%])

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Three patients discontinued study participation due to an AE (pulmonary edema [unmasking of pulmonary veno-occlusive disease], exanthema, and progression of right heart failure). Pulmonary edema resolved and the exanthema improved but both events were classified as a drug-related AE. The patient with exanthema had been included in the study before it was known that the subject was allergic to multiple substances including therapeutics.

In the long-term extension, 8 of the 68 patients reported AEs as the primary reason for discontinuation of study participation. One subject with an outcome of death had severe cardiac failure and severe malignant hepatic neoplasm as AEs, which were assessed by the investigator as not related to study medication. Treatment-emergent AEs which led to discontinuation and were drug-related per investigator judgment were pulmonary arterial hypertension, pulmonary hypertension, flushing, dizziness, and headache.

6.4 Clinical Laboratory Results

Laboratory comparisons for the pooled controlled phase III studies (CHEST-1 and PATENT-1) were made at Week 12 because it is the latest common evaluation for the 2 studies.

6.4.1 Hematology

Baseline values for hematology and coagulation parameters were comparable between the riociguat and placebo groups in the pooled controlled phase III studies. Mean changes from baseline to Week 12 were small in both treatment groups for most of the hematology and coagulation parameters. Imbalances in the mean changes from baseline to Week 12 were observed for:

- Hemoglobin: riociguat group: –0.58 g/dL, placebo group: 0.13 g/dL
- Hematocrit: riociguat group: –1.66%, placebo group: 0.45%

The number and percent of patients with treatment-emergent low hemoglobin or hematocrit values (<1 times lower limit of normal) were:

- Hemoglobin (g/dL): riociguat group: 87/361 subjects (24.1%),
  placebo group: 15/164 subjects (9.1%)
- Hematocrit (%): riociguat group: 54/407 subjects (13.3%),
  placebo group: 9/182 subjects (4.9%)

For the pooled long-term extension studies, mean changes from baseline were small for most of the hematology and coagulation parameters. For hemoglobin, mean change from baseline was

-0.24 g/dL at Month 9 (n=254) and –0.28 g/dL at Month 21–23 (n=207). For hematocrit, mean change from baseline was –0.62% at Month 9 (n=253) and –0.78% at Month 21–23 (n=207).

6.4.2 Clinical Chemistry

Baseline values for clinical chemistry parameters were comparable between the riociguat and placebo groups in the pooled controlled phase III studies. Mean changes from baseline to Week 12 were small in both treatment groups for most of the clinical chemistry parameters. Imbalances in the mean changes from baseline to Week 12 were observed for:

- Creatinine clearance: riociguat group: 1.96 mL/min, placebo group: -2.29 mL/min
- Estimated GFR: riociguat group: 2.58 mL/minute/1.73m^2, placebo group: -2.72 mL/minute/1.73m^2
- Potassium: riociguat group: –0.131 mmol/L, placebo group: -0.014 mmol/L
- Urate: riociguat group: –0.39 mg/dL, placebo group: 0.24 mg/dL
- Urea: riociguat group: -0.80 mg/dL, placebo group: 0.74 mg/dL

For the pooled long-term extension studies, mean changes from baseline were small for most of the clinical chemistry parameters. For potassium, mean change from baseline was -0.063 mmol/L at Month 9 (n=263), and –0.041 mmol/L at Month 21-23 (n=211). For urate, mean change from baseline was -0.384 mg/dL at Month 9 (n=268), and -0.533 mg/dL at Month 21-23 (n=214).

6.4.3 Urinalysis

Formal urinalysis was not performed in the studies.

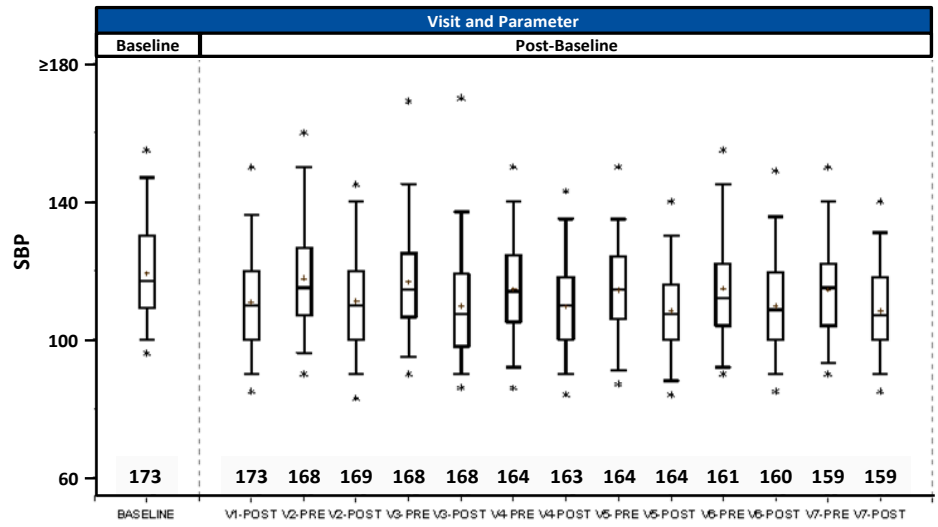
6.5 Vital Signs

6.5.1 Systolic Blood Pressure

In the pooled controlled phase III studies, mean baseline values for systolic blood pressure were comparable between the riociguat group (116.05 mmHg) and the placebo group (118.05 mmHg). Mean systolic blood pressure decreased in the riociguat group and in the placebo group. The mean change at Week 12 was –6.83 mmHg in the riociguat group, and -1.80 mmHg in the placebo group.

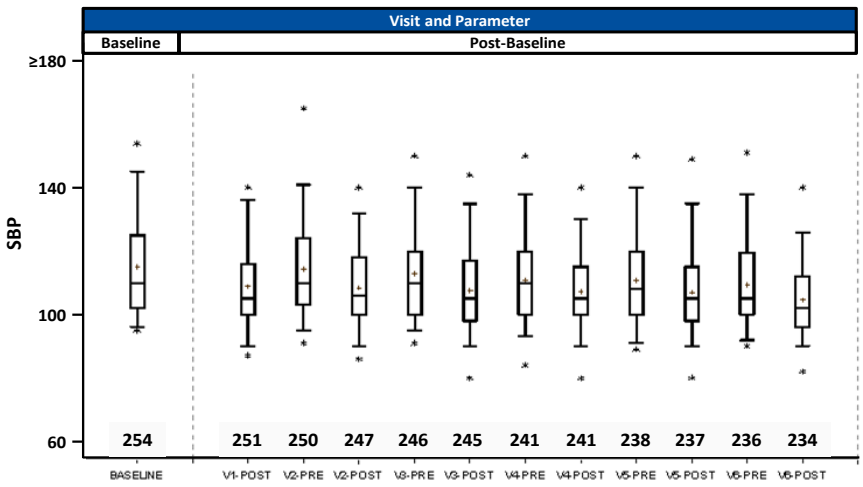
Box plots of systolic blood pressure before and 2 to 3 hours after riociguat dosing are shown for visits 2 through 7 of CHEST-1 and PATENT-1 in Figure 22 and Figure 23, respectively. As expected from the pharmacokinetic profile of riociguat, systolic blood pressure values were generally lower 2 to 3 hours after riociguat dosing as compared to before dosing.

Figure 22: Box Plot of Systolic Blood Pressure Before Dosing and 2 to 3 Hours After Dosing in CHEST-1 (Safety/ITT Population)



ithmetic mean is denoted by +
w (1st percentile) and high extremes (99th percentile) are denoted by *
E is measure 1-0 hours before 1st dose received at visit.
OST is measured 2-3 hours after 1st dose received at visit.

Figure 23: Box Plot of Systolic Blood Pressure Before Dosing and 2 to 3 Hours After Dosing in PATENT-1 (Safety/ITT Population)



Arithmetic mean is denoted by +
Low (1st percentile) and high extremes (99th percentile) are denoted by *
PRE is measure 1-0 hours before 1st dose received at visit.
POST is measured 2-3 hours after 1st dose received at visit.

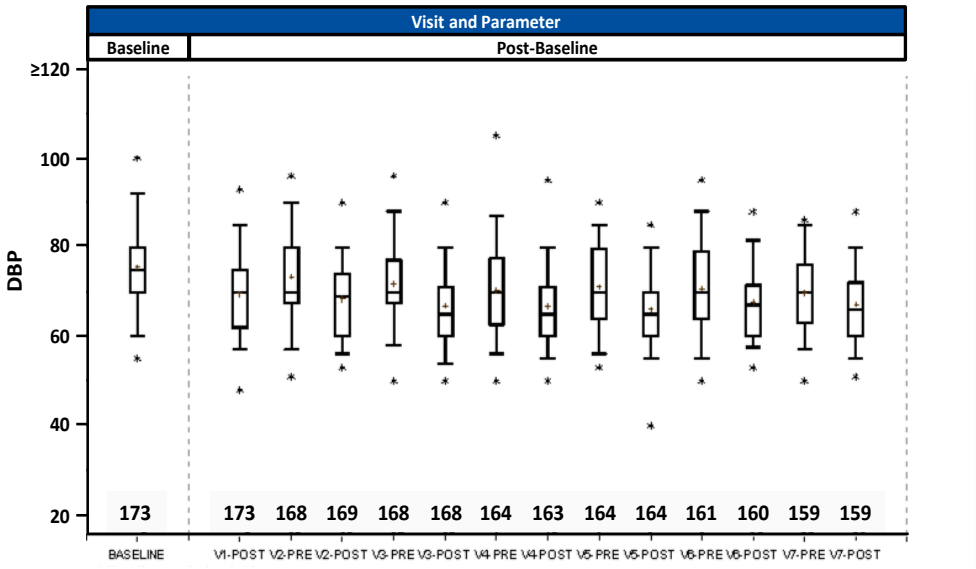
For the pooled non-controlled extension studies, the mean change in systolic blood pressure was –4.39 mmHg at Month 9 (n=280), and –3.93 mmHg at Month 21-23 (n=221).

6.5.2 Diastolic Blood Pressure

In the pooled controlled phase III studies, mean baseline values for diastolic blood pressure were comparable between the riociguat group (72.92 mmHg) and the placebo group (74.57 mmHg). The mean change from baseline to Week 12 was –5.91 mmHg in the riociguat group and -0.26 mmHg in the placebo group.

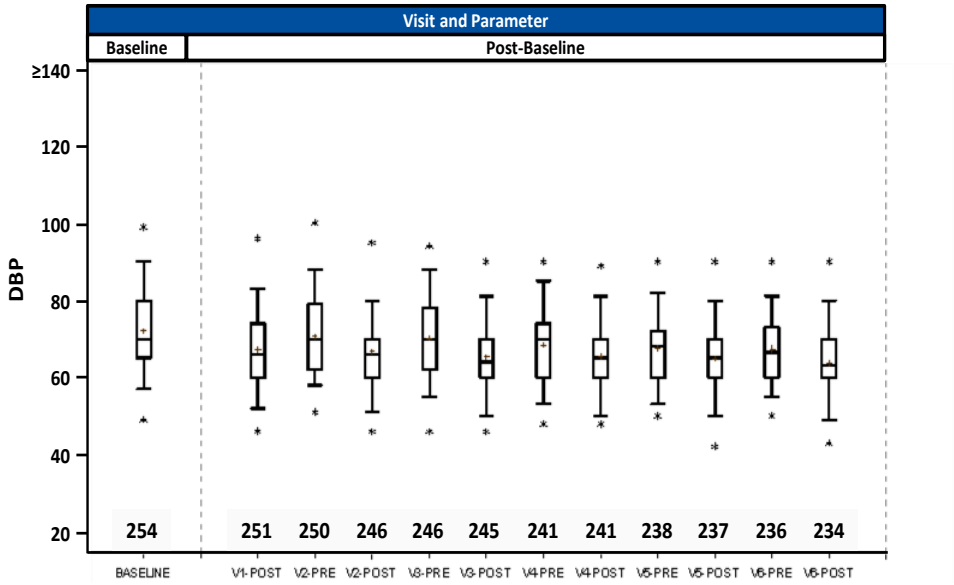
Box plots of diastolic blood pressure before and 2 to 3 hours after riociguat dosing are shown for visits 2 through 7 of CHEST-1 and PATENT-1 in Figure 24, and Figure 25, respectively. As expected from the pharmacokinetic profile of riociguat, diastolic blood pressure values were generally lower 2 to 3 hours after riociguat dosing as compared to before dosing.

Figure 24: Box Plot of Diastolic Blood Pressure Before and 2 to 3 Hours After Dosing of Riociguat in CHEST-1 (Safety/ITT Population)



Arithmetic mean is denoted by +
Low (1st percentile) and high extremes (99th percentile) are denoted by *
PRE is measure 1-0 hours before 1st dose received at visit.
POST is measured 2-3 hours after 1st dose received at visit.

Figure 25: Box Plot of Diastolic Blood Pressure Before Dosing and 2 to 3 Hours After Dosing in PATENT-1 (Safety/ITT Population)



Arithmetic mean is denoted by +
Low (1st percentile) and high extremes (99th percentile) are denoted by *
PRE is measure 1-0 hours before 1st dose received at visit.
POST is measured 2-3 hours after 1st dose received at visit.

In the pooled long-term extension studies, the mean change in diastolic blood pressure from baseline to Month 9 (n=280) was –4.90 mmHg, and –5.24 mmHg at Month 21-23 (n=221).

6.5.3 Heart Rate

In the pooled controlled phase III studies, mean baseline values for heart rate were comparable between the riociguat group (76.79 beats/minute) and the placebo group (77.29 beats/minute). The mean change from baseline to Week 12 was 0.22 beats/minute in the riociguat group and 0.93 beats/minute in the placebo group.

In the pooled long-term extension studies, the mean change in heart rate from baseline to Month 9 (n=280) was 1.33 beats/minute and 0.02 beats/minute at Month 21-23 (n=220).

6.5.4 Weight

In the pooled controlled phase III studies, mean baseline values for weight were comparable between the riociguat group (70.77 kg) and the placebo group (72.33 kg). The mean change in

weight from baseline to Week 12 was -0.30 kg in the riociguat group, and 0.26 kg in the placebo group.

In the pooled long-term extension studies, the mean change in weight from baseline to Month 9 (n=277) was -0.57 kg, and -0.55 kg at Month 21-23 (n=221).

6.6 Safety Topics of Special Interest

6.6.1 Pre-defined Safety Topics of Special Interest

Based on observations made in the phase II proof-of-concept study, and given the mechanism of action of riociguat, syncope and hypotension were pre-defined as safety topics of special interest for phase III. Syncope is part of the symptoms with which patients with pulmonary hypertension present. Syncope is often associated with worsening disease state. Riociguat's positive impact on the overall cardiovascular system, including increased cardiac output in response to therapy, could impact this event. Hypotension could also be affected by riociguat's vasodilatory mechanism of action.

6.6.1.1 Syncope

Syncope is part of the symptoms with which patients with pulmonary hypertension present. As recently published (40), in newly diagnosed PAH patients 12% already had a history of syncope, and presyncope was found to be an independent and strong predictor of a poor prognosis. For CHEST-1 and PATENT-1, syncope was defined as a safety-related event of special interest. Thus, by definition any syncope had to be reported as an "important medical event" and therefore as a SAE within 24 hours of the investigator becoming aware of the event after the respective amendment came into force for CHEST-1 and PATENT-1.

Table 37 presents an overview of the AEs of syncope in the pooled controlled studies. Overall, treatment-emergent syncope events were reported in 16 patients (3.3%) in the pooled riociguat group and 10 patients (4.7%) in the pooled placebo group.

All cases reported as treatment-emergent syncope were assessed as mild or moderate by the investigator except 5 severe cases (2 cases with riociguat and 3 cases with placebo). Treatment-emergent syncope events were assessed as serious in 8 patients (1.6%) in the pooled riociguat group and 10 patients (4.7%) in the pooled placebo group. Two patients discontinued study medication because of syncope AEs (1 with riociguat and 1 with placebo).

Table 37: Number of Patients with Treatment-emergent Adverse Events of Syncope in Pooled Controlled Studies (CHEST-1 and PATENT-1) and Pooled Long-term Extension Studies (CHEST-2 and PATENT-2)

	Number (%) of Patients		
Preferred Term	**Placebo (N=214)**	**Riociguat (N=490)**	**Long-term Extension (N=557)**
Any Event	10 (4.7)	16 (3.3)	38 (6.8)
Syncope	8 (3.7)	7 (1.4)	30 (5.4)
Presyncope	1 (0.5)	9 (1.8)	10 (1.8)
Loss of consciousness	1 (0.5)	0	0

Note: Sample size for the pooled riociguat group includes the capped dose treatment group in PATENT-1.

The overall rate of treatment-emergent syncope in the pooled long-term extension studies was 8.06 events per 100 patient-years. This rate was lower than in the pooled controlled studies (14.79 events per 100 patient-years for riociguat, 20.55 for placebo). The AEs related to syncope were syncope (6.20 per 100 patient-years) and presyncope (1.86 per 100 patient-years).

The majority of cases reported as treatment-emergent syncope were assessed as mild or moderate by the investigator, but 11 cases were assessed as severe. Treatment-emergent syncope events were assessed as serious in 31 patients (5.6%) in the pooled long-term extension studies.

Most patients with syncope had a single syncope event. Syncope events were not related to drug exposure or a change of riociguat dose during the titration phase, and thus not directly connected to the intake of riociguat. Many of the syncope events occurred as exertional syncope, which is typically observed in patients with pulmonary hypertension. Syncope was the reason for discontinuation of study medication for 1 patient of each treatment group. Analyses across various subgroups did not identify a subgroup at increased risk for syncope when receiving riociguat.

The data from the placebo-controlled clinical studies in the applied indications did not indicate an increased rate of syncope events for riociguat treated patients. The evidence of the data from the riociguat studies suggest that the occurrence of syncope is rather to be seen as a symptom of the underlying disease (40, 41) which has been shown to be directly related to the prognosis of affected patients (27).

6.6.1.2 Hypotension

The evaluation of hypotension as a AE of special interest was performed for associated MedDRA preferred terms (blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure orthostatic decreased, blood pressure systolic decreased, blood pressure systolic inspiratory decreased, hypotension, orthostatic hypotension, and diastolic hypotension). An overview of the hypotension AEs of special interest in the pooled controlled

studies and pooled extension studies is presented in Table 38. Overall, treatment-emergent hypotension events were reported in 49 patients (10.0%) in the pooled riociguat group and 8 patients (3.7%) in the pooled placebo group.

Table 38: Number of Patients with Treatment-emergent Adverse Events of Hypotension in Pooled Controlled Studies (CHEST-1 and PATENT-1) and Pooled Long-term Extension Studies (CHEST-2 and PATENT-2)

	Number (%) of Patients		
Type of Adverse Event	**Placebo (N=214)**	**Riociguat (N=490)**	**Long-term Extension (N=557)**
Any	8 (3.7)	49 (10.0)	41 (7.4)
Any serious	0	2 (0.4)	4 (0.7)
Any resulting in discontinuation of study medication	0	1 (0.2)	0
Any with outcome of death	0	0	0

Note: Sample size for the pooled riociguat group includes the capped dose treatment group in PATENT-1.

The overall rate of treatment-emergent hypotension in the pooled long-term extension studies was 7.13 events of hypotension recorded as an AE per 100 patient-years and 49.47 events of recorded systolic blood pressure <90 mmHg per 100 patient-years. These rates were lower than those in the placebo group in the controlled studies (hypotension recorded as AE: 14.94 events per 100 patient-years; recorded systolic blood pressure <90 mmHg: 70.98 events per 100 patient-years). However, the higher rates in controlled studies compared to long-term extension studies may reflect the larger number of protocol-specified blood pressure measurements in the controlled studies.

Most hypotension events occurred during the titration phase in both treatment groups. Treatment-emergent hypotension events were assessed as serious in 2 patients (0.4%) in the pooled riociguat group and no patients in the pooled placebo group. One patient in the riociguat group discontinued study medication because of hypotension.

Overall, treatment-emergent hypotension (defined as systolic blood pressure <90 mmHg) events were reported in 17.8% of patients in the pooled riociguat group and 9.8% in the pooled placebo group. Treatment-emergent hypotension events (documented as AE or recorded systolic blood pressure <90 mmHg) were reported in 23.3% of patients in the pooled riociguat group and 12.1% in the pooled placebo group).

Whilst in PATENT-1 the incidence of hypotension was reported in a larger proportion of patients in the riociguat IDT group (10% of patients) than the riociguat CT and placebo groups (3% and 2%, respectively), there was no clear relationship to dose. Of the 25 patients with a report of hypotension in the riociguat IDT group, 8 of the events occurred once the patient had received

2.5 mg TID. Eight patients experienced hypotension after receiving their first dose of 1.0 mg TID (at Visit 1), 4 patients after receiving 1.5 mg TID, and 5 patients after receiving 2.0 mg TID.

In the riociguat CT group (approximately one-fourth the size of the IDT group), 1 patient experienced hypotension after receiving the first dose of 1.0 mg TID and 1 patient experienced hypotension after receiving 1.5 mg TID.

Additionally, at Visit 2, 11 patients had a systolic blood pressure <90 mmHg: 2 of them occurring 1 hour before the first dose and the others occurring 2 to 3 hours after the first dose. Five of these patients were taking placebo; 4 of them had taken 1.5 mg for the first time, and even though they had systolic blood pressure <90 mmHg, the dose was not modified. Two of these patients did not have their dose increased when the investigator decided to maintain the dose at 1.0 mg. It is noteworthy that placebo-treated patients experienced the lowest systolic blood pressures.

The incidence of treatment-emergent hypotension (reported as AEs) by dose level and time interval in pooled CHEST-1 and PATENT-1 illustrates that most hypotensive events occurred during the first riociguat dose titration; once the appropriate dose had been identified for each patient, fewer events occurred during the rest of the study (Table 39).

Table 39: Number (Percent) of Patients with Treatment-emergent Hypotension (Reported as Adverse Events) by Dose Level and Time Interval in Pooled CHEST-1 and PATENT-1 (Main Phase, Safety/ITT Population)

Visit Interval Dose	Titration				Maintenance	
	Week 0-2	Week 2-4	Week 4-6	Week 6-8	Week 8-12	Week 12-16
2.5 mg				4/323 (1.2%)	10/307 (3.3%)	1/123 (0.8%)
2.0 mg			7/349 (2.0%)	1/44 (2.3%)	-	-
1.5 mg		9/428 (2.1%)	2/95 (2.1%)	-	-	-
1.0 mg	17/490 (3.5%)	-	-	-	1/16 (6.3%)	-
0.5 mg		-	-	-	-	-
Placebo	2/214 (0.9%)	1/208 (0.5%)	1/204 (0.5%)	1/201 (0.5%)	0/200 (0.0%)	3/84 (3.6%)

Interestingly, from the pooled analysis of the placebo-controlled Phase 3 studies and the non-controlled Phase 3 extension studies (Table 40), AEs in patients with systolic blood pressure

<90 mmHg were similar in the placebo-treated and riociguat-treated groups. Indeed, the proportion of patients who discontinued due to AEs was higher in the placebo-treated group.

Table 40: Overall Summary of AEs in Riociguat-treated Patients by Treatment-emergent Systolic Blood Pressure <90 mmHg in Pooled Studies CHEST-1 and PATENT-1 (Main Phase, Safety/ITT Population)

	Placebo N=214		Riociguat N=490	
	Systolic Blood Pressure		Systolic Blood Pressure	
AE	<90 mm Hg N=19	≥90 mmHg N=195	<90 mm Hg N=86	≥90 mmHg N=404
Number of patients (%) with				
Any	16 (84.2%)	168 (86.2%)	81 (94.2%)	363 (89.9%)
Any severe	3 (15.8%)	26 (13.3%)	11 (12.8%)	42 (10.4%)
Any adverse event with an outcome of death	1 (5.3%)	6 (3.1%)	3 (3.5%)	2 (0.5%)
Any hypotension adverse event with an outcome of death	0	0	0	0
Any serious	4 (21.1%)	33 (16.9%)	16 (18.6%)	58 (14.4%)
Discontinuation of study medication due to AE	1 (5.3%)	10 (5.1%)	2 (2.3%)	12 (3.0%)
Discontinuation of study medication due to SAE	1 (5.3%)	8 (4.1%)	2 (2.3%)	7 (1.7%)

Definition of abbreviations: AE = treatment-emergent adverse event.

Based on the tight dosing window, the reporting of systemic blood pressure drops and hypotension were more common in the riociguat-treated patients. Importantly, every time a systolic blood pressure <90 mmHg was reported during the titration phase, the site was asked whether this drop in blood pressure was clinically significant. Some investigators only reported the AE of hypotension after this query was raised.

Riociguat reduces systolic blood pressure, which might be associated with the incidence of hypotension. However hypotension AEs in PATENT-1 do not appear to be profoundly dose related. Hypotension, reductions in systolic blood pressure, and the incidence of AEs occur across the spectrum of individual doses.

In summary, where hypotension was reported, this was frequently when the patient had their first contact with riociguat, or during early titration, in the majority of patients. Indeed, adding up all the events of hypotension, the majority of these occurred when patients were taking less than 2.5 mg TID.

Taken together, titration of riociguat to a maximum dose of 2.5 mg TID ensures safety, tolerability, and optimal efficacy for each patient with good tolerability shown in the long-term extension studies.

6.6.2 Safety Topics of Special Interest Based on Riociguat's Mechanism of Action

The following additional safety topics were based on riociguat's mechanism of action.

- Gastrointestinal motility disturbances: The gastrointestinal system is sensitive to stimulation of the sGC and subsequent increase of intracellular cGMP levels.
- Bone metabolism: Effects on bone metabolism were observed in growing rats.
- Fetal Toxicity: In rats, an increase of cardiac malformations was seen

6.6.2.1 Gastrointestinal Motility Disturbances

Overall, treatment-emergent gastrointestinal disorders were reported in 255 (52.0%) patients in the pooled riociguat group and 72 (33.6%) patients in the pooled placebo group. Most of these events were non-serious: gastrointestinal disorders were reported as SAEs in 1.6% of patients in the pooled riociguat group and 0.9% of patients in the pooled placebo group. Gastrointestinal AEs leading to discontinuation were reported in 2 patients (0.4%) in the pooled riociguat group and 1 patient (0.5%) in the pooled placebo group. Most of the events were located in the upper gastrointestinal tract. Notably, use of concomitant gastric pH-increasing medications was more frequent in the pooled riociguat group than in the pooled placebo group (56.1% versus 35.0%).

The most frequent treatment-emergent gastrointestinal disorders (as defined by SMQ) by preferred term for each treatment group in the pooled controlled studies were:

- **Riociguat**: dyspepsia (17.8%), nausea (14.1%), diarrhea (11.8%), vomiting (10.2%), chest pain (5.9%), gastro-esophageal reflux disease (5.1%), constipation (4.5%), abdominal pain upper (3.3%), abdominal pain (2.9%), and gastritis (2.9%).
- **Placebo**: nausea (10.7%), diarrhea (7.9%), dyspepsia (7.9%), chest pain (7.0%), vomiting (6.5%), abdominal pain upper (3.7%), gastro-esophageal reflux disease (1.9%), abdominal discomfort (1.4%), abdominal pain (1.4%), and constipation (1.4%).

The observed gastrointestinal events are principally related to the mechanism of action of riociguat (relaxation of smooth muscle).

The overall rate of treatment-emergent gastrointestinal disorders in the pooled long-term extension studies was 89.79 events per 100 patient-years.

The most frequently reported preferred terms (rates per 100 patient-years) were: diarrhea (15.66), nausea (12.41), dyspepsia (11.48), chest pain (8.99), vomiting (8.84), abdominal pain (4.65), constipation (4.65), abdominal pain upper (4.34), gastro-esophageal reflux disease (4.19), and gastritis (2.79).

Long-term exposure to riociguat did not increase the incidence of these AEs: lower incidences per 100 patient-years were observed in the pooled long-term extension studies than in the pooled riociguat group in the controlled studies. However, over the course of the pooled long-term extension studies the cumulative event rate in patients who had received placebo during the controlled studies came closer to that for patients who had received riociguat.

The incidence of discontinuations due to gastrointestinal AEs remained low (2 patients [0.4%] in the pooled long-term extension studies), indicating that gastrointestinal disorders did not limit treatment with riociguat for the majority of patients.

6.6.2.2 Bone Metabolism

Riociguat has shown morphological changes on long bones in juvenile and adolescent (growing) rats, but not in adult rats and dogs.

In adolescent rats, widening of the growth plates of long bones was seen after short-term treatment with riociguat. After longer term treatment, the growth plate changes disappeared and remodeling processes in the areas involved in bone growth (metaphysis, diaphyseal funnel, subperiostal diphysis) resulting in an overall increase in bone mass were observed. Treatment of full-grown rats at comparable exposure levels did not result in morphological changes of the skeleton, in any biologically relevant effects on bone mineral density, or in any changes on markers for bone formation or resorption. Furthermore, no changes in bone morphology were observed in dogs.

The morphology of these effects does not correspond to lesions observed in various osteoporosis models in rats, which primarily show bone mass and bone mineral density reduction in cancellous (metaphyseal) bone, whereas in juvenile and adolescent rats after treatment with riociguat an overall increase of bone mass was observed.

It is generally accepted that the NO-sGC-cGMP and the pGC-cGMP pathway play a role in regulation of bone and cartilage homeostasis and the stimulation of these pathways results in activation of bone formation rather than in bone resorption. This provides evidence that the observed effects are related to the pharmacological mechanism of action of riociguat

Based on the absence of morphological effects on bone in riociguat-treated adult rats and dogs, the findings in juvenile and adolescent rats are considered to be of no relevance for adult patients with CTEPH and PAH. The exploratory biomarker type CTX evaluated in clinical Studies CHEST-1 and PATENT-1 provides additional evidence for this conclusion.

The International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine Working Group on Bone Marker Standards recommended serum CTX be used as a reference analyte because it is well characterized, is specific to collagen type I which is found predominantly in bone, has performed well in clinical trials, is widely available, has well defined biological and analytical variability, is relatively easy to handle samples, is stable, is a serum assay (instead of urine) marker, is easy to analyze, and has potential to be standardized (23). In addition, patients on agents that stimulate bone resorption, such as glucocorticoids, have increased CTX levels and bone loss, even with a short course of a few months of therapy (24, 25). In summary, CTX is a sensitive marker to assess an agent's potential for increasing or decreasing bone resorption.

Baseline CTX values were within the expected range for the study population in both studies. In CHEST-1, the baseline measurements of CTX showed mean values of 0.397 mcg/L for the riociguat group and 0.388 mcg/L for the placebo group. In PATENT-1, the baseline measurements of CTX showed mean values of 0.379 mcg/L for the riociguat IDT group, 0.365 mcg/L for the placebo group, and 0.392 mcg/L for the riociguat CT group.

Treatment differences in the change from baseline were too small to be of clinical significance. In CHEST-1, CTX increased from baseline to week 16 (last observation until week 16) by 0.069 mcg/L (mean) in the riociguat group and by <0.001 mcg/L (mean) in the placebo group. In PATENT-1, values at the end of the study were increased from baseline in all treatment groups. The mean change from baseline to week 12 (last observation until week 12) were 0.017 mcg/L for the riociguat IDT group, 0.048 mcg/L for the placebo group, and 0.015 mcg/L for the riociguat CT group. Thus, the analyses gave no indication of an impact of riociguat on bone metabolism.

Rates of fractures in all completed phase II and phase III clinical studies were similar in the all riociguat group (5/754 [0.7%]) and in the placebo group (1/289 [0.3%]) and also showed no increased event rate during long term treatment (event rate per 100 person years: 3.6 all riociguat versus 1.4 placebo during the initial treatment phase and 3.1 during long-term extension).

6.6.2.3 Fetal Toxicity

Maternal tolerability and embryo-fetal, as well as pre- and early postnatal, development was mainly influenced by the pharmacological properties of riociguat. In rats, an increase of cardiac malformations was seen to be most likely a consequence of the hemodynamic effects of riociguat

and potential anti-proliferative effects on undifferentiated mesenchymal cells during cardiac development.

During the clinical trials program, patients were counseled to use contraception, and regular pregnancy testing was performed. Three patients had a positive pregnancy test during the long-term extension studies. The outcomes of these pregnancies resulted in 1 spontaneous abortion, 1 elective abortion, and 1 ectopic pregnancy.

6.6.3 Safety Topic of Special Interest Based on Observations in Phase III

The following additional safety topics were based on observations in phase III.

- Hemoglobin and hematocrit decrease: Mean decreases from baseline were observed in phase III studies. Incidences and cases in PATENT-1 and CHEST-1 are critically reviewed.

- Bleeding: Anticoagulants are often used as supportive therapy in patients with CTEPH or PAH. Incidences and cases in PATENT-1 and CHEST-1 are critically reviewed.

- Renal function: Hypotension followed by reduced renal perfusion may worsen renal function. Otherwise, restoration of the NO-cGMP pathway may be beneficial for renal function, since NO and cGMP deficiency is involved in the pathogenesis of chronic kidney disease.

6.6.3.1 Hemoglobin and Hematocrit Decreases

Baseline values for hematology and coagulation parameters were comparable between the riociguat and placebo groups in the pooled, controlled phase III studies. Mean changes from baseline to Week 12 were small in both treatment groups for most of the hematology and coagulation parameters. Imbalances in the mean changes from baseline to Week 12 were observed for:

- Hemoglobin: –0.58 g/dL for riociguat group; 0.13 g/dL for placebo group:

- Hematocrit: –1.66% for riociguat group; 0.45% placebo group

To further describe and evaluate changes in hemoglobin observed in CHEST-1 and PATENT-1, a repeated measurement model analysis was performed for change from baseline in hemoglobin and hematocrit. This analysis showed that there was an average decrease in hemoglobin of -0.56 g/dL in the riociguat group compared to no change in the placebo group (0.08 g/dL). The average difference between riociguat and placebo ranged from -0.54 g/dL to -0.73 g/dL. The magnitude of the baseline value influenced the magnitude of the change from baseline

(p<0.0001). There was no difference observed between PATENT-1 and CHEST-1. Comparable results were observed for hematocrit.

In the group treated with riociguat, a decrease in hemoglobin was visible at week 2 to 3 and remained stable during the following visits. In patients with a low baseline hemoglobin (<12 g/dL), the previously described trend was not observed; whereas in the group of patients with a baseline hemoglobin between 14 g/dL to 16 g/dL, a change to baseline was visible at week 2 to 3. The effect was described for more than 75% of patients with baseline hemoglobin 14-16 g/dL in the riociguat group at week 4 to 5.

To evaluate further if the observed decrease in hemoglobin was related to bleeding, patients with or without bleeding were analyzed in pooled CHEST-1 and PATENT-1. In patients without a bleeding event (413 riociguat, 183 placebo), a mean change of -0.36 g/dL was visible in the riociguat treated groups at week 2 to 3, compared to no change (mean 0.09 g/dL) in the placebo group. In patients with a bleeding event (77 riociguat, 31 placebo), a mean decrease of -0.52 g/dL in the riociguat group was visible at week 2 to 3, compared to +0.20 g/dL in the placebo group.

Of further note, the effect is visible after a short treatment time (2 weeks), whereas the Kaplan-Meier plot for time to first bleeding event (Figure 26, page 162) demonstrates that bleeding events occurred during the whole study period, as would be expected in a population with a high proportion of anticoagulated patients.

These results show that the observed decrease in mean hemoglobin in the riociguat group appears to be independent from the occurrence of bleeding events. A similar observation was made for the decrease in hematocrit.

Pooled data analysis from CHEST-1 and PATENT-1 showed that anemia-related events reported as an AE had a higher rate in the all riociguat group (6.7% [33/490]) compared to placebo (2.3% [5/214]). However, the numbers of treatment-emergent SAEs of anemia were low and balanced for both groups (riociguat group 0.4% [2/490] versus placebo group 0.5% [1/214]).

The incidence of blood transfusions was comparable between riociguat and placebo. Transfusions were reported in 9 patients; 4 of those were placebo-treated patients. Three of the identified blood transfusions occurred in patients with a bleeding event reported as serious. Causes of transfusions were diverse and included co-morbidities such as multiple myeloma, prophylaxis (transfusion before procedure), bleeding, and anemia.

Overall, the analyses do not indicate an increased risk for clinical relevant anemia for pulmonary hypertension patients treated with riociguat.

6.6.3.2 Bleeding

6.6.3.2.1 Non-clinical Findings

As the sGC is expressed in platelets and may thus play a role in platelet aggregation via increase of cGMP concentration in thrombocytes, riociguat was investigated on its potential to influence platelet function *in vitro* and *in vivo* and on potential interaction with drugs inhibiting platelet aggregation and coagulation. Riociguat is a weak platelet aggregation inhibitor *in vitro* at concentrations about 50-fold above maximum concentrations in patients.

In vivo, administration of riociguat at pharmacologically active doses resulted in blood pressure reduction and moderate prolongation of bleeding time. Combination with rivaroxaban, iloprost, and clopidogrel did not affect rat tail transection bleeding time in a biologically relevant manner.

Co-administration of riociguat and acetylsalicylic acid resulted in a statistically prolonged rat tail transection bleeding time. Based on the metabolism of acetylsalicylic acid, a pharmacokinetic drug-drug interaction can be excluded. The mechanism of interaction remains open.

No interaction of riociguat and acetylsalicylic acid was observed in humans; thus, the slight effects seen in rats are not considered clinically relevant.

Additional non-clinical information is found in Section 3 (page 62).

6.6.3.2.2 Clinical Pharmacology

A possible interaction of riociguat and Aspirin® was tested in an interaction study in healthy young male subjects. No relevant pharmacodynamic or pharmacokinetic interactions between aspirin and riociguat were observed.

A possible interaction of riociguat and warfarin (Coumadin®) was tested in a formal interaction study in healthy young male subjects. No relevant pharmacodynamic or pharmacokinetic interactions between riociguat and the oral anticoagulant warfarin were observed.

The effect of riociguat was also tested in a dose range of 0.25 to 5 mg in a single-dose escalation study and no effect on platelet aggregation was demonstrated.

Additional clinical pharmacology information is found in Section 4 (page 66).

6.6.3.2.3 Clinical Data From Phase III Clinical Studies

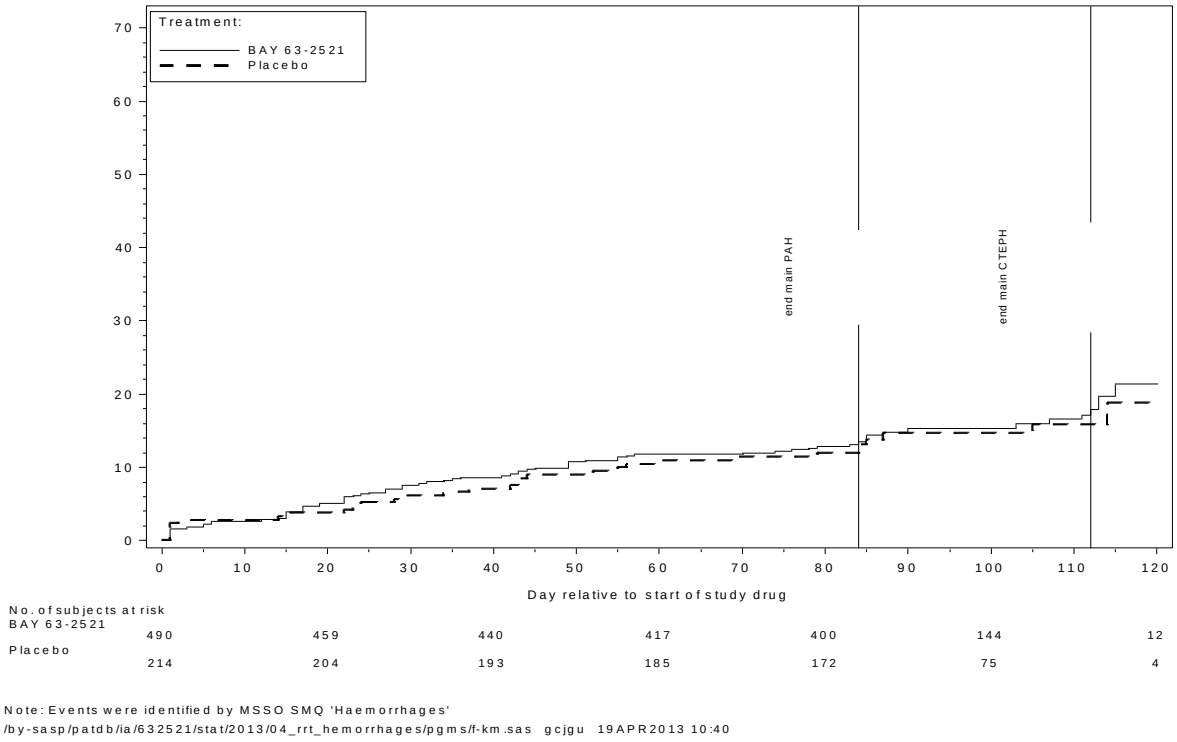
Anticoagulation is recommended as basic supportive therapy for CTEPH and PAH to protect against the increased risk of thrombosis and its sequelae (17, 27), which is reflected by the high

rate of concomitant administration of anticoagulants in both studies CHEST-1 and PATENT-1. More than 90% of the patients in the CHEST-1 trial, and more than 50% of the patients in the PATENT-1 trial were anticoagulated.

Any Treatment-emergent Bleeding Events

The incidence rate of treatment-emergent bleeding events (identified by SMQ "haemorrhage") was 15.7% (77/490) in all riociguat-treated patients versus 14.5% (31/214) in placebo-treated patients in the pooled main and extension phases of phase III studies. A Kaplan-Meier plot showed no difference regarding time to first event occurrence between the riociguat and placebo groups.

Figure 26: Kaplan-Meier Plot for Time to First Treatment-emergent Hemorrhage After Start of Study Medication in CHEST-1 and PATENT-1 (Safety/ITT Population)



Note: BAY 63-2521 is riociguat.

Overall, bleeding rates in CHEST-1 and PATENT-1 occurred in a comparable range between the riociguat and placebo treatment groups, but an increased rate in respiratory tract bleeding events was observed in the riociguat group compared to placebo. Respiratory bleeding events with a higher rate in the riociguat group were epistaxis (2.9% riociguat versus 1.4% placebo) and hemoptysis (2.0% riociguat versus 0.9% placebo). After adjusting for duration of exposure, the numbers of epistaxis events per 100 patient-years of exposure in pooled controlled studies were

14.8 and 5.6 for the riociguat and placebo groups respectively. The number of serious events per 100 patient-years of exposure in the pooled extension studies was 8.7.

The incidence of hemoptysis as an AE (serious or non-serious) was 4.96 events per 100 patient-years in the pooled long-term extension studies, compared with 9.04 events in the pooled riociguat group and 5.60 events in the pooled placebo group in the controlled studies. The incidence of hemoptysis during long-term treatment with riociguat was thus comparable to the incidence in the placebo group during the controlled studies, suggesting that the incidence of this event reflects its underlying occurrence in this population.

Twelve patients reported 14 events of hemoptysis in CHEST-1 or PATENT-1. Characteristics of the 14 events are summarized in Table 41. No temporal or dose-related pattern was identified.

Table 41: Characteristics of Hemoptysis Events Reported in CHEST-1 or PATENT-1

Characteristic of Hemoptysis Event	Number of Events[a]
Any event	11 riociguat, 3 placebo
Serious	5
Mild / moderate / severe intensity	6 / 6 / 2
Related to study medication	1 (placebo group)
Action taken	
None	8
Remedial drug therapy	5
Observation at hospital	1
Outcome	
Resolved	13
Outcome of death	1

a Two events each were reported by 2 patients in PATENT-1.

Serious AEs of respiratory tract bleeding in pooled controlled studies consisted of 5 patients (1.0%) reporting hemoptysis in the riociguat group. After adjusting for duration of exposure, the numbers of hemoptysis events per 100 patient-years of riociguat exposure was 4.93 in pooled controlled studies and 1.24 in pooled long-term extension studies. In CHEST-1, 3 patients experienced 1 instance each of serious hemoptysis. Onset was between day 22 and day 78 of the study, severity was mild or moderate, and none was related to study medication in the investigator's judgment. All events resolved spontaneously without treatment or intervention after 1 to 2 days duration. One of the 3 patients reported a history of hemoptysis prior to study enrollment. In PATENT-1, 2 patients experienced hemoptysis. One patient was hospitalized for hemoptysis due to coughing on day 84; the event was of moderate severity. The other patient was

hospitalized twice (days 3 and 55) for hemoptysis and died as a result of the second episode of hemoptysis. The patient with a fatal outcome had a medical history of hemoptysis, with the most recent episode occurring 2 weeks prior to randomization in PATENT-1.

6.6.3.2.4 Summary

Overall, bleeding rates in CHEST-1 and PATENT-1 occurred in a comparable range between the riociguat and placebo treatment groups, but a trend for increased rate in respiratory tract bleedings was observed. Additionally, published literature indicates that, in some patients with pulmonary hypertension, hemoptysis may be regarded as complication of the underlying disease (21, 22). More than 90% of the patients in the CHEST-1 trial, and more than 50% of the patients in the PATENT-1 trial were anticoagulated.

A recent publication focused on anticoagulation treatment in pulmonary hypertension (21). It was noted that the bleedings occurred independent from vitamin K antagonist INR target. Notably, hemoptysis was described by the authors to be well known for patients with pulmonary hypertension, but hardly reported in patients using vitamin K antagonists for atrial fibrillation or venous thromboembolism.

There were more serious bleeding events observed in riociguat-treated patients versus placebo; this was mainly driven by the event of hemoptysis. Importantly, no further pattern or bleeding site was identified from the pooled CHEST-1 and PATENT-1 studies. From the reviewed cases, no excess serious bleeding risk on other sites prone to bleeding (typically the gastrointestinal tract in an anticoagulated population) was identified, with plausible alternative explanations in all cases. However, hemoptysis is regarded as a potential risk, especially in patients with a history of lung bleeding, and will be addressed in labeling.

6.6.3.3 Renal Function

6.6.3.3.1 Non-clinical Data

Riociguat has shown renal protection in various models of chronic kidney disease supporting the consensus reached over the last decade that NO and cGMP deficiency is critically involved in the pathogenesis of chronic kidney disease by increasing pathological matrix production and accumulation in the kidney.

Based on clinical pathology and histopathology data, riociguat did not reveal any evidence of renal toxicity. The main metabolite M-1 has shown clear signs of renal toxicity at high exposure levels starting about 60-fold of human exposure and borderline effects at exposure levels about 40-fold of human exposure, both in terms of AUC for unbound drug. The no observed adverse effect level after chronic dosing corresponded to safety margins of 13 in terms of AUC for unbound drug.

In dogs, neither riociguat nor metabolite M-1 revealed evidence for renal toxicity up the highest dose tested.

Overall, considering that in rat and dog studies riociguat at high exposure levels with M-1 levels covering or exceeding human exposure has been devoid of renal toxicity and the renal toxicity of M-1 was restricted to very high exposure levels in rats, a clinical relevance for M-1-related renal toxicity is not assumed.

Non-clinical pharmacology data

Research over the last decade has shown that deficiencies in NO and cGMP are critically involved in the pathogenesis of chronic kidney disease by increasing pathological matrix production and accumulation in the kidney. Nitric oxide deficiency has been documented in numerous experimental and human renal diseases, such as diabetic and hypertensive nephropathy, chronic glomerulosclerosis, obstructive nephropathy, and chronic interstitial nephritis. Nitric oxide and cGMP deficiency contributes to the progression of chronic renal disease through both hemodynamic and direct pro-fibrotic effects. In order to investigate whether restoring the NO-cGMP pathway by sGC stimulation prevents deterioration of renal function, riociguat was investigated in various models for chronic kidney disease. In summary, riociguat has shown clear evidence of renal protection in a low NO model (induced by L-NAME) in hypertensive transgenic high renin rat. Furthermore, riociguat was effective with regard to fibrotic tissue remodeling and survival in salt-sensitive Dahl rats. Finally, renal protection was seen in a long-term low-renin model in 5/6 nephrectomized rats and in diabetic eNOS knockout mice on top of angiotensin II receptor blockade.

Non-clinical safety data

Riociguat was tested in repeat-dose studies in rats and dogs up to 26 weeks and 52 weeks, respectively. Additionally in rats and mice, riociguat was administered in a life-long treatment in the carcinogenicity studies.

Metabolite M-1 was also tested in a standard program of repeat-dose systemic toxicity studies.

In rats, systemic exposure up to 26-fold of human exposure in terms of AUC of unbound drug was achieved. Systemic exposure of M-1 was up to 3.5-fold higher than in humans.

In the carcinogenicity study in rats and mice, margins of exposure were up to 9-fold for riociguat.

In the repeat-dose toxicity studies in dogs with treatment duration up to 1 year, systemic exposure up to 4-fold of human exposure in terms of AUC for unbound drug was achieved. Systemic exposure of the metabolite M-1 was up to 9-fold higher when compared to M-1 exposure in humans.

Neither in rats and mice nor in dogs, there was morphological evidence or clinical pathology indicative for adverse effects of riociguat on the kidneys.

Metabolite M-1 was tested in systemic repeat-dose toxicity studies up to 26-week treatment duration. In repeat-dose toxicity studies up to 13 week treatment duration, at exposure levels of about 60-fold of human exposure (AUC for unbound drug) at 2.5 mg TID and higher, clear evidence of degeneration and regeneration followed by tubular hyperplasia was seen.

With prolongation of treatment duration, the no observed adverse effect level slightly decreased. After chronic treatment, systemic exposure of 38-fold (males) to 47-fold (females) of the human exposure of the M-1 at 2.5 mg riociguat TID was correlated with borderline effects with respect to the collecting duct changes and safety margins of 13 were established.

More severe lesions were accompanied by increases in plasma urea levels, whereas creatinine levels remained unchanged.

In dogs, M-1 was administered in repeat-dose systemic toxicity studies up to treatment duration of 39 weeks. At exposure levels of M-1 up to 23-fold of human exposure at 2.5 mg riociguat TID in terms of AUC for unbound drug, neither clinical pathology nor histopathology provided evidence of renal toxicity induced by M-1.

6.6.3.3.2 Clinical Data

Creatinine (mL/minute) – Phase III Controlled Studies (Safety/ITT Population)

The baseline values for creatinine were balanced between the treatment groups and also the changes until end of study were rather small.

Based on a repeated measurement model of change from baseline for creatinine, the change of the LS mean until visit at week 12 (the last common visit for both studies CHEST-1 and PATENT-1) was -0.01 mg/dL for the riociguat group compared to +0.04 mg/dL for the placebo group. The LS mean change from baseline was lower for the other study visits. The trend as expressed in the pairwise comparison shows a decrease of creatinine in the riociguat group over the course of the double-blind treatment phase and an increase for the placebo group.

Creatinine Clearance (mg/dL) - Phase III Controlled Studies (Safety/ITT Population)

A mean increase from baseline to Week 12 was observed for creatinine clearance for the riociguat group compared to a mean decrease in the placebo group (riociguat group: 1.96 mL/min, placebo group: -2.29 mL/min).

Based on a repeated measurement model of change from baseline for creatinine clearance (Cockroft Gault), the change of the LS mean until visit at week 12 (the last common visit for both

studies CHEST-1 and PATENT-1) was +1.96 mL/min for the riociguat group compared to -2.20 mL/min for the placebo group. The LS mean change from baseline was trend-wise similar for the other study visits. The trend as expressed in the pairwise comparison shows an increase of the creatinine clearance in the riociguat group over the course of the double-blind treatment phase and a decrease for the placebo group.

Serum Urea – Phase III Controlled Studies (Safety/ITT Population)

Based on a repeated measurement model of change from baseline for urea, the change of the LS mean until visit at week 12 (the last common visit for both studies CHEST-1 and PATENT-1) was -0.78 mg/dL for the riociguat group compared to +0.77 mg/dL for the placebo group. The LS mean change from baseline was trend-wise similar for the other study visits. The trend as expressed in the pairwise comparison shows a decrease of urea in the riociguat group over the course of the double-blind treatment phase and an increase for the placebo group.

Mean changes in cystatin from baseline to week 12/13 in pooled CHEST-1 and PATENT1 were 8.0 ng/mL and 43.3 ng/mL in the riociguat and placebo groups, respectively.

In summary, the laboratory parameters of creatinine, creatinine clearance and urea were rather stable over the course of 3 to 4 months of treatment in riociguat- and placebo-treated patients, but a trend was observed toward a slight improvement of renal function in the riociguat group when compared with placebo.

Renal Adverse Events

A broad SMQ can be used to identify potential cases of renal failure, but events may not be specific to renal failure. When using the broad search for the SMQ of acute renal failure, 24 patients had an event during the double-blind treatment phase of CHEST-1 and PATENT-1. Fifteen events occurred in the riociguat treatment group (15/490 [3.1%]) and 9 events in the placebo group (9/214 [4.2%]).

During double-blind treatment in CHEST-1 and PATENT-1, SAEs labeled as renal and urinary disorders were reported for 6 (1.2%) patients in the riociguat group and 1 (0.5%) patient in the placebo group. The patient in the placebo group experienced renal impairment. Events classified as renal failure included acute renal failure (3 patients in riociguat group), chronic renal failure (2 patients in riociguat group), and renal failure (1 patient in riociguat group). After adjusting for duration of exposure, the number of serious renal events per 100 patient-years of exposure was lower in the pooled long-term extension studies (0.93) than in the pooled controlled studies (5.75 and 1.87 for the riociguat and placebo groups, respectively).

Upon medical review, the majority of patients with a renal event had no temporal relationship to a hypotensive event. Overall, events of renal impairment were very often associated with other medical conditions including pre-existing medical history of renal impairment which needs

consideration. In all cases concomitant events are reported which need to be considered in the context of the serious renal event. A specific signal for a potential negative impact of riociguat on renal function could not be identified.

With respect to investigations, more laboratory abnormalities indicating a worsening of renal function were seen in the placebo group, whereas renal failure was more frequently reported in riociguat-treated patients. From all patients with renal events (broad SMQ), 1 patient had an event leading to discontinuation and the same patient also had an outcome of death.

6.6.3.3.3 Summary

Based on histopathology and clinical pathology data, riociguat did not reveal any evidence of renal toxicity in non-clinical studies. In additional animal studies with the direct application of the main metabolite M-1, a clear cut renal toxicity was shown at high exposure levels (~60-fold of human exposure) and borderline effects at exposure levels about 40-fold of human exposure in terms. An unequivocal no observed adverse effect level was established at 10 mg/kg after chronic dosing resulting in safety margins of 13. Considering that in rat and dog studies riociguat at high exposure levels with M-1 levels covering or exceeding human exposure has been devoid of renal toxicity and the renal toxicity of M-1 was restricted to very high exposure levels in rats, a clinical relevance is not assumed.

The laboratory parameters of creatinine, creatinine clearance and urea were rather stable over the course of 3 to 4 months of treatment in riociguat- and placebo-treated patients, but a trend was observed toward a slight improvement of renal function in the riociguat group when compared with placebo.

Medical analysis of renal events occurring in CHEST-1 and PATENT-1 identified 7 SAEs (1 placebo and 6 riociguat). In all cases, concomitant events are reported which need to be considered in the context of the serious renal event. These confounding factors indicated that the event was not related to riociguat. Two of the 7 events were chronic renal failure, both not indicating a riociguat-related effect as due to renal impairment at baseline.

The majority of patients with a renal event had no temporal relationship to a hypotensive event. Overall, in patients in CHEST and PATENT, events of renal impairment were very often associated with other medical conditions including pre-existing medical history of renal impairment which needs consideration. A specific signal for a potential negative impact of riociguat on renal function could not be identified.

6.6.4 Other Safety Topic of Special Interest

Other topics of special interest include:

- Co-administration with PDE5 inhibitor medications: Both riociguat and PDE5 inhibitor medications have vasodilatory mechanism of action and could have more than additive effects.

- Liver function: The potential for liver toxicity was assessed.

- Electrocardiogram: The potential for changes of the QT interval was assessed.

6.6.4.1 Co-administration with PDE5 Inhibitor Medications

Riociguat should not be co-administered with PDE5 inhibitor medications.

Background

Riociguat is the first member of a novel class of compounds, the sGC stimulators. Soluble guanylate cyclase catalyzes the generation of cGMP, which plays a pivotal role in regulating cellular processes such as vascular tone, proliferation, fibrosis, and inflammation. Riociguat has a dual mechanism of action. It sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. Riociguat also directly stimulates sGC via a different binding site, independently of NO. Riociguat restores the NO-sGC-cGMP pathway and leads to increased generation of cGMP.

Phosphodiesterase type-5 is responsible for degradation of cGMP. Sildenafil and tadalafil are inhibitors of PDE5 and also work by increasing cGMP. Both drugs are approved for PAH in the United States.

Riociguat and PDE5 inhibitors are both modulators of intracellular cGMP through different modes of action. When intracellular cGMP is elevated by combining both principles, an additive effect might be anticipated.

Non-clinical data

Non-clinical studies in animal models showed an additive systemic blood pressure lowering effect when riociguat was combined with either sildenafil or vardenafil. With increased doses, more than additive effects on systemic blood pressure were observed in some cases.

Clinical Data

In exploratory interaction Study 11917, 7 patients with PAH on stable sildenafil treatment (20 mg TID) received single doses of riociguat (0.5 mg and 1 mg sequentially). Results showed additive hemodynamic effects. Doses above 1 mg riociguat were not investigated in this study.

PATENT-Plus (Study 15096) was designed as an interaction study to evaluate changes in blood pressure following 1, 1.5, 2, and 2.5 mg riociguat TID (i.e., the IDT regimen) compared to

placebo treatment on the background of stable sildenafil pre-treatment in patients with symptomatic PAH. Patients receiving stable (≥90 days) sildenafil therapy (approved dose: 20 mg TID) were included and randomized to placebo or riociguat administered according to a titration regimen (up to 2.5 mg TID) for 12 weeks. The primary outcome was the maximum change in supine systolic blood pressure from baseline within 4 hours of dosing. Secondary objectives of this study were to investigate the safety of the riociguat/sildenafil combination, pharmacodynamic changes and analysis of exploratory efficacy variables after 12 weeks of study treatment in the 6MWD test, WHO functional class, NT-proBNP, and right heart catheterization variables and the pharmacokinetics of riociguat and sildenafil.

Patients could enter a long-term extension following the main study, where all patients received riociguat plus stable sildenafil. No primary or secondary objectives were specifically defined for the optional extension phase. The goal of the long-term extension was to collect data on the safety and tolerability of the long-term administration of the combination of sildenafil and riociguat.

Twenty-four patients were enrolled at 11 study centers in 5 European countries: Czech Republic (2 patients), Germany (15), Italy (5), Spain (1), and the United Kingdom (1). Eighteen of the 24 patients were randomized and received study medication: 12 patients received riociguat at an individually titrated dose, and 6 patients received placebo. Seventeen of the 18 patients continued onto the long-term extension phase of the trial. At baseline, most patients were reported having WHO functional class II (10 patients) or III (6 patients); class I and IV were reported for 1 patient each (both assigned to receive riociguat treatment). Baseline 6MWD tests were ≥320 meters for 13 patients and <320 meters for the remaining 5 patients. Idiopathic PAH (5/12 in the riociguat group and 4/6 in the placebo group) and connective tissue disease (5/12 in the riociguat group and 1/6 in the placebo group) were the most frequent classes of PAH in the study population.

At 12 weeks, the mean ± standard deviation of maximum change in supine systolic blood pressure was -20.2 ± 12.9 mmHg in the placebo group (n=5) versus -20.7 ± 18.0 mmHg in the riociguat group (n=10); maximum change in standing systolic blood pressure was -16.8 ± 10.6 and -18.0 ± 16.5 mmHg, respectively. Similarly, maximum change in supine diastolic blood pressure was -13.8 ± 12.9 mmHg at Week 12 in the placebo group and -13.7 ± 11.7 mmHg in the riociguat group, while maximum change in standing diastolic blood pressure was -14.2 ± 10.0 and -14.4 ± 10.6 mmHg, respectively. In an analysis of potential outliers, there were 32 low systolic blood pressure (<85 mmHg) and/or diastolic blood pressure (<45 mmHg) events in the riociguat group (n=12) versus 24 in the placebo group (n=6). One patient in the riociguat group withdrew from the main study due to blurred vision (drug-related). No deaths were reported during the main study period.

Combination therapy did not show favorable effects in exploratory clinical parameters including pulmonary hemodynamics, 6MWD, biomarkers, and functional class.

Combination of riociguat and sildenafil led to 5 discontinuations during the long-term extension: hypotension (n=4) and upper abdominal pain (n=1). During the long-term extension phase up

until 13 December 2012, 3 deaths had been reported. In one case a 67-year old female patient experienced fatal 'cardiac arrest' which was assessed by the investigator and Bayer as not related to riociguat. In the second case, a 46-year old female died following acute 'decompensation of chronic right heart failure.' The investigator and Bayer assessed the event as not related to riociguat. In the third case, a 53-year old white female experienced 'fall' and 'subdural hematoma' leading to death. As a causal involvement of riociguat in the fall via a decrease in blood pressure could not be excluded with certainty, the causal relationship was assessed as related to riociguat.

Summary

On the basis of the safety, tolerability and efficacy data available, and in particular the apparent high rate of discontinuations due to hypotension and a lack of overall clinical benefit in the patient population studied, the benefit/risk balance for combination treatment of patients still participating in the long-term extension part of Patent-Plus with sildenafil and riociguat could no longer be viewed as positive. After a review of the above data, the long-term extension phase of Patent-Plus was discontinued.

Finally, given the above data, clinicians will be advised that concomitant administration of riociguat with PDE5 inhibitors (such as sildenafil, tadalafil, and vardenafil) should be avoided.

6.6.4.2 Liver Function

Treatment-emergent abnormal liver function test results in phase III studies are summarized in Table 42. One patient (placebo group) had concurrent elevations of ALT (>3× ULN) and bilirubin (2×ULN). There is no evidence that riociguat affects liver function.

Table 42: Treatment-emergent Abnormal Liver Function Test Results (Main and Extension Phase, Safety Population)

	Number of Patients Meeting Criteria / Number of Patients Assessed (%)			
	CHEST-1 and PATENT-1		CHEST-2 and PATENT-2	
Criteria	Placebo N=214	Riociguat N=490	Placebo in Main N=161	Riociguat in Main N=396
ALT >3×ULN and not above ULN at baseline	3/185 (1.6)	1/418 (0.2)	1/141 (0.7)	2/337 (0.6)
AST >3×ULN and not above ULN at baseline	2/186 (1.1)	0/422	0/140	0/341
Total bilirubin >2×ULN and not above ULN at baseline	2/170 (1.2)	2/396 (0.5)	1/133 (0.8)	3/322 (0.9)
ALT >3×ULN and total bilirubin >2×ULN (same blood sample)	1/185 (0.5)	0/418	0/141	0/337
ALT >3×ULN and total bilirubin >2×ULN (within 30 days after ALT increase)	1/185 (0.5)	0/418	0/141	0/337

Definition of abbreviation: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of laboratory reference range.

6.6.4.3 Evaluation of QT/QTc

A thorough QT/QTc study in healthy volunteers is usually part of a clinical study program for any new investigational drug. In such a study a threshold pharmacologic effect on cardiac repolarization is intended to be evaluated by administration of the investigational drug with doses that achieve higher plasma concentrations than would be anticipated with the intended therapeutic doses.

In accordance with the respective International Conference on Harmonisation guideline E14, riociguat is not a suitable drug for the conduct of such a study in healthy volunteers due to safety reasons. The justification to obtain the QT assessment of riociguat from a pulmonary hypertension study population as part of the phase III clinical study program, together with details of the QT assessment are reviewed for preclinical pharmacology in Section 6.6.4.3.1 and clinical investigations in Section 6.6.4.3.2.

6.6.4.3.1 Preclinical Pharmacology

Riociguat and its main metabolite were investigated *in vitro* for its potential on the current of hERG potassium channel and the duration and shape of the action potential of rabbit Purkinje fibers. Effects of both compounds on the QT interval were investigated in anesthetized and conscious, telemeterized dogs.

It is unlikely that riociguat and M-1 possess a biologically relevant arrhythmogenic potential, given the following findings:

Minor *in vitro* effects of riociguat and its main metabolite (10% to 20% hERG current inhibition and 10% prolongation of action potential duration at 10 μM) at concentrations of at least 400-fold higher than unbound plasma concentrations in patients; and

Absence of QTc prolongation with riociguat up to hemodynamically active doses.

6.6.4.3.2 Clinical Investigation

In studies with healthy volunteers, there were no clinically relevant effects on the parameters of the ECG like PR, QRS, and QTcF. As the heart rate in healthy subjects increased with dose, the QT interval was reduced and therefore only QTcF or QTcB can be used for evaluation. There was no signal for an arrhythmogenic potential of riociguat in healthy subjects.

During the riociguat development program, the administered maximum dose to patients enrolled in clinical studies was 2.5 mg TID. In healthy subjects, the maximum tested dose was 5 mg. A dose of 2.5 mg was well tolerated by healthy subjects while 5 mg riociguat given as a single dose in healthy subjects generated pronounced hemodynamic effects. Therefore dose escalation was stopped at this level and doses higher than 2.5 mg could not be justified in healthy subjects. In addition, exposure data from patients enrolled in phase II studies showed that exposure in patients with pulmonary hypertension was 2-fold higher in maximum concentration and up to 3-fold higher in AUC compared to healthy subjects**.** Thus, the ECG data with riociguat were obtained from a patient population within the phase III clinical study program.

The assessment of QT/QTc prolongation is based on the following approach:

- Thorough QT/QTc analysis: An extended ECG monitoring program integrated in the placebo-controlled PATENT-1 study with central independent and blinded assessment of the ECGs for validity for QT/QTc assessment as replacement of the thorough QT/QTc study in healthy subjects.

- Validation study: A randomized, double blind, placebo-controlled study in healthy volunteers, which investigated the effects of a single dose of moxifloxacin versus placebo on QT/QTc. This study was conducted in centers participating in the PATENT-1 study using the same methodology of ECG recording and assessment that was used in all of the PATENT-1 study centers. This study was designed as a validation study to test the ECG assay sensitivity of PATENT-1.

- In addition, routine ECG monitoring for all patients in the placebo-controlled clinical studies PATENT-1 and CHEST-1. The respective ECGs were assessed independently and their validity criteria for QT/QTc assessment was essentially the same as for the thorough QT/QTc analysis but obtained from routine ECG monitoring according to the study protocol.

6.6.4.3.3 Results of Thorough QT Analysis in PATENT-1

Triplicate ECG readings about 1 minute apart were recorded at the time points defined in the protocol. The means of adequate readings at each time point were calculated and used as baseline and post-baseline analysis values. The validity for the QT/QTc analysis was assessed by an independent contract research organization. All ECGs were assessed centrally by an independent contract research organization. Changes from baseline to the following time points were summarized:

- Visit 1: 2 to 3 hours after the first study medication administration; prior to second dose administration, and 2 to 3 hours after the second administration
- Visit 2: Prior to study medication administration, and 2 to 3 hours after administration
- Visit 6: prior to study medication administration, and 2 to 3 hours after administration
- Last visit

There were 133 subjects valid for the thorough QT/QTc analysis (35 placebo, 76 riociguat IDT, 22 riociguat CT). The majority of subjects were female (84%). Most of the subjects were either white (55%) or Asian (41%). The mean age was 49 years and 20% were of age 65 or above. The majority of subjects had never smoked (70%) and reported no alcohol consumption (66%). The mean body mass index was 26 kg/m^2. There were no obvious imbalances between the treatment groups.

The most common type of pulmonary hypertension in each treatment group was idiopathic PAH (64%), followed by PAH due to connective tissue disease (23%). More than 90% of subjects had a WHO functional class of II (42%) or III (56%). The 6MWD was <320 meters for 22% of the subjects.

The mean treatment duration was 85 days and few subjects had treatment durations of less than 50 days (2%).

The mean changes of the QTc duration at the regular visits were numerically different between the 2 treatment groups but, importantly, not clinically different for QTcB (mean change of +2 msec from baseline to last visit in the riociguat IDT group compared to +4 msec in the placebo group) and QTcF (mean change of 0 msec from baseline to last visit in the riociguat IDT group compared to +4 msec in the placebo group). Taken together, the ECG data did not indicate a QT prolongation for riociguat-treated patients when compared to placebo. The QT prolongations observed in PAH patients (riociguat as well as placebo) were lower than the ones observed in moxifloxacin-treated healthy volunteers in the validation study. The differences of QT changes between riociguat and placebo did not reach values seen in the validation study when comparing moxifloxacin against placebo.

The analyses of QTcB and QTcF for absolute increase showed no increase of QT >60 msec in any of the riociguat treated patients and increases to a value of >500 msec were seen in few patients with no obvious difference between riociguat and placebo treated patients.

Mean changes in heart rate from baseline did not exceed 5 beats/minute, mean changes in PR interval from baseline did not exceed 5 msec, and mean changes in QRS from baseline did not exceed 2 msec. No strong trend was observed during treatment in any direction. There was no clinically relevant change in PR or QRS duration nor was there a difference between the riociguat treatment groups and placebo.

The analyses of AEs for arrhythmias also did not indicate a difference between riociguat and placebo treated patients. In the population selected for the thorough QT analysis, there were no reports of torsades de pointes arrhythmias, ventricular fibrillation, ventricular flutter, or sudden death.

Collectively, the data from the thorough QT analysis demonstrate that there is no QT prolongation with riociguat.

6.6.4.3.4 Validation of QT Measurement in PATENT-1

The sensitivity of ECG measurements was tested in a subset of PATENT-1 centers in healthy volunteers. The ECG assay sensitivity was tested by investigating the influence of a single dose of 400 mg moxifloxacin on the QTc interval relative to placebo in a subset of PATENT-1 centers. The selected centers used the same ECG methodology for recording and assessment which thereafter was applied to patients with PAH. It was shown that the setting of the study was sensitive to detect a mean difference of 15 msec for QTcF and of 16 msec for QTcB between moxifloxacin and placebo 3 hours after dosing. Thus, it was demonstrated that the methodology had the potential to detect a clinically relevant QTc prolongation after administration of riociguat.

6.6.4.3.5 Analysis of the Placebo-controlled PATENT-1 and CHEST-1

Data from PATENT-1 and CHEST-1 confirm that riociguat does not have an effect on QT prolongation or arrhythmia in patients with PAH or CTEPH. Differences of QT changes between riociguat and placebo treated patients were lower than those observed between moxifloxacin and placebo in the validation study

The sample comprised 283 riociguat-treated patients and 100 placebo-treated patients and assessed the treatment difference for change from baseline week 12-13, which was appropriate due to the different durations of double blind treatment (12 weeks in PATENT-1 and 16 weeks in CHEST-1). Mean changes from baseline did not indicate prolongation of QTcB (e.g., mean change of 0 msec from baseline to week 12-13 in the riociguat group compared to +2 msec in the placebo group) and QTcF (e.g., mean change of +1 msec in the riociguat group compared to +1 msec in the placebo group).

6.6.4.3.6 Summary of QT Analyses

Taken together, the collective data set obtained from the PATENT-1 patients selected for the thorough QT/QTc analysis, from analysis of routine ECGs obtained from patients with PAH (PATENT-1) and patients with CTEPH (CHEST-1) demonstrate that riociguat does not have any clinically relevant effects on QT prolongation.

7. Evaluation of Dosing in Phase III

The goal in developing riociguat was to safely maximize the benefit for each patient with PAH or CTEPH by individualizing the patient's dose. High between-patient variability in riociguat exposure for a given dose and a steep concentration-response curve with respect to hemodynamics (reason for 0.5 mg increments) did not support traditional dose-ranging studies with riociguat, but instead suggested a dose-ranging approach based on a minimal effective dose. A traditional fixed-dose, parallel group, dose-ranging study would have had considerable overlap in serum concentrations for fixed, tolerable doses. Given the close and direct relationship between riociguat plasma concentrations and hemodynamic effects, differentiation between oral doses would have been difficult in the presence of overlapping serum concentrations.

Several factors (identified in clinical pharmacology, proof-of-concept, and pharmacokinetic/pharmacodynamic studies) suggested that an individualized dose titration approach would be superior to a fixed dose regimen (Section 2.4, page 60). The use of titration to safely increase dose to efficacious levels is an accepted and common practice in many therapeutic areas and is analogous to the treatment of PAH with parenteral prostanoids and of systemic hypertension (e.g., captopril which is initiated at 25 mg twice daily or TID and increased to 50 mg twice daily or TID).

Thus, gradual dose titration (from 1 mg TID up to 2.5 mg TID) based upon monitoring of blood pressure and signs/symptoms of hypotension, was developed in phase II to provide safe escalation in dosage for each patient to safely maximize benefit for long-term treatment. As a consequence of phase II results the individual dose titration was chosen for the phase III program as the treatment to be compared to placebo.

PATENT-1 included a second riociguat dosing group in addition to the primary IDT regimen. The primary IDT regimen had a maximum dose of 2.5 mg TID and the exploratory CT regimen had a maximum dose of 1.5 mg TID. A riociguat CT group was not included in CHEST-1. Taking into consideration that PAH is a rare disease and that the patient numbers needed for a statistical comparison of the CT arm against placebo would likely be too large, the sample size of 63 patients for the riociguat group was chosen on the basis of clinical judgment rather than statistical power. The riociguat CT group was part of the Statistical Analysis Plan, but only descriptive analyses were planned. No inferential testing (formal or exploratory) was proposed in the Statistical Analysis Plan for the CT group. Additionally, given that it was anticipated that patients in the riociguat CT group would not have the same magnitude of effect at patients

randomized to the riociguat IDT group, it was reasonable to randomize fewer patients to the CT arm.

Assuming that the riociguat regimen would get individual patients to their maximum tolerated dose in order to gain the maximum benefit and based on the dose response observed for the improvement in hemodynamic parameters, it was expected that the riociguat CT group would confirm the rationale for the IDT regimen and that the riociguat IDT group would out-perform the riociguat CT group across all endpoints evaluated. In CHEST-1 and PATENT-1 phase III studies, riociguat IDT was shown to be a safe and effective therapy in the patient populations studied. In addition, the long-term extension studies showed a sustainability of clinical relevant parameters and the tolerability in the long-term use of the drug.

Although the number of patients included in the exploratory arm of the CT group is small and the results must be treated with caution, it is noteworthy that the mean change from baseline in 6MWD patients randomized to the riociguat CT group of PATENT-1 was similar to the mean change in baseline of riociguat IDT group (mean change to final visit of 31.1 meters versus 29.6 meters). This result prompted a post-hoc comparison of riociguat CT versus placebo. Nominally statistically significant differences favoring riociguat CT versus placebo included 6MWD ($p<0.0001$), PVR ($p<0.0001$), NT-proBNP ($p<0.0001$), and LPH ($p<0.0001$). However, nominal statistical significance was not observed for WHO functional class ($p=0.0674$), time to clinical worsening ($p=0.3939$), Borg CR 10 ($p=0.1068$), and EQ-5D ($p=0.0914$).

However, the mean change from baseline to last visit was numerically superior in the riociguat IDT group compared to the riociguat CT group for 2 clinically important cardiovascular measures:

- PVR: Mean change from baseline to last visit of -8.9, 223.3, and -167.8 dyne*second*cm^{-5} in the placebo, riociguat IDT, and riociguat CT groups, respectively.
- Cardiac output: Mean change from baseline to last visit of -0.01, 0.93, and 0.42 L/min in the placebo, riociguat IDT, and riociguat CT groups, respectively.

The hemodynamic measurements of PVR and cardiac output are objective markers of disease severity and are used by clinicians to monitor the clinical progress and response to therapy of patients with pulmonary hypertension.

The mean of 6MWD for baseline and change from baseline is summarized in Table 43 for subgroups of patients based on their riociguat dose at day 56 of PATENT-1. At the final visit of PATENT-1, the mean change from baseline for 6MWD was 17.9 meters and 38.9 meters for patients in the 1.5 mg TID and 2.5 mg TID subgroups, respectively.

Table 43: Mean (Standard Deviation) 6MWD for Baseline and Change From Baseline in Study PATENT-1 (Safety/ITT Population)

	Riociguat IDT (Dose on Day 56 in PATENT-1)				
Study Visit	1.0 mg TID (N=7)	1.5 mg TID (N=14)	2.0 mg TID (N=37)	2.5 mg TID (N=177)	Riociguat CT (N=54)
Baseline	349.7 (67.1)	339.8 (69.6)	362.8 (71.0)	365.6 (66.2)	358.2 (68.5)
Change to					
Day 14	37.0 (53.5)	9.8 (27.8)	6.1 (36.0)	22.8 (37.8)	19.6 (50.0)
Day 28	18.9 (98.0)	14.9 (29.7)	14.4 (42.9)	30.9 (43.7)	25.7 (51.8)
Day 42	35.9 (77.9)	10.2 (35.0)	24.6 (48.6)	37.1 (46.5)	33.1 (44.0)
Day 56	36.7 (68.5)	28.2 (25.3)	25.1 (62.0)	37.4 (54.3)	38.7 (50.8)
Day 84	23.4 (97.8)	14.2 (32.0)	33.2 (52.2)	38.9 (51.0)	45.3 (53.2)
Last Visit	23.4 (97.8)	17.9 (33.6)	31.2 (51.4)	38.9 (51.0)	45.3 (53.2)

Definition of abbreviations: 6MWD = 6-minute walking distance, CT = capped titration; IDT = individual dose titration; ITT = intent to treat; TID = three times daily.

The safety database in PATENT-1 comparing IDT to CT is relatively small, making it difficult to discern a clear dose-related difference in the AE profile between the 2 randomized groups. However, a larger proportion of patients in the riociguat CT group than the riociguat IDT group reported at least 1 AE and at least 1 SAE (Table 44). Thus, it appears that titration to a maximum dose of 2.5 mg TID is not associated with an increase AE or SAE reporting.

Table 44: Overall Adverse Event Profile for PATENT-1 (Safety/ITT Population)

Type of AE, (% of patients)	Placebo (N=126)	Riociguat IDT (N=254)	Riociguat CT (N=63)
Any	88.1	90.6	93.7
Any serious	18.3	11.4	17.5
Any leading to discontinuation	7.1	3.1	1.6
Any leading to death	2.4	0.8	1.6

Definition of abbreviations: CT = capped titration; IDT = individual dose titration; ITT = intent-to-treat; AE = treatment-emergent adverse event.

The incidence of AEs by dose level and time interval in pooled CHEST-1 and PATENT-1 illustrates that most events occurred during the first riociguat dose titration; once the appropriate dose had been identified for each patient, fewer events occurred during the rest of the study (Table 45).

Table 45: Number and Percent of Patients AE by Dose at Time of Event in CHEST-1 and PATENT-1 (Safety/ITT Population)

Dose at time of event	Number (%) of Patients with AE During Visit Interval					
	Visit 1 to 2	Visit 2 to 3	Visit 3 to 4	Visit 4 to 5	Visit 5 to 6	Visit 6 to 7
0.5 mg		1/9 (11.1)	2/7 (28.6)	2/4 (50.0)	2/4 (50.0)	0/1
1.0 mg	314/490 (64.1)	25/41 (61.0)	10/22 (45.5)	4/15 (26.7)	6/16 (37.5)	2/6 (33.3)
1.5 mg		196/428 (45.8)	44/95 (46.3)	28/80 (35.0)	30/78 (38.5)	3/11 (27.3)
2.0 mg			157/349 (45.0)	16/44 (36.4)	28/55 (50.9)	9/20 (45.0)
2.5 mg				113/323 (35.0)	146/307 (47.6)	51/123 (41.5)
Placebo	98/214 (45.8)	78/208 (37.5)	80/204 (39.2)	74/210 (36.8)	102/200 (51.0)	42/84 (50.0)
Total Riociguat	314/490 (64.1)	222/478 (46.4)	213/473 (45.0)	163/467 (34.9)	212/460 (46.1)	65/161 (40.4)

Definition of abbreviations: ITT = intent to treat; AE = treatment-emergent adverse event.

The incidence of serious AEs by dose level and time interval in pooled CHEST-1 and PATENT-1 was similar across the titration intervals (Table 46).

Table 46: Overall Summary of Number (Percent) of Patients with Serious AEs by Dose of Riociguat in CHEST-1 and PATENT-1 (Safety/ITT Population)

Dose at	n/N (%) of Patients with AE During Visit Interval					
	Titration				Maintenance	
time of event	Week 0 to 2	Week 2 to 4	Week 4 to 6	Week 6 to 8	Week 8 to 12	Week 12 to 16
0.5 mg		0/9	0/7	0/4	0/4	0/1
1.0 mg	16/490 (3.3)	1/41 (2.4)	1/22 (4.5)	0/15	0/16	0/6
1.5 mg		13/428 (3.0)	4/95 (4.2)	5/80 (6.3)	1/78 (1.3)	1/11 (9.1)
2.0 mg			10/349 (2.9)	0/44	1/55 (1.8)	1/20 (5.0)
2.5 mg				9/323 (2.8)	19/307 (6.2)	4/123 (3.3)
Placebo	7/214 (3.3)	7/208 (3.4)	5/204 (2.5)	8/201 (4.0)	13/200 (6.5)	3/84 (3.6)
Riociguat	16/490 (3.3)	14/478 (2.9)	15/473 (3.2)	14/467 (3.0)	21/460 (4.6)	6/161 (3.7)

Definition of abbreviations: ITT = intent to treat; n = number of patients with event; N = number of patients at risk for the interval and dose; AE = treatment-emergent adverse event; TID = three times daily.
Note: In case of time information was available to decide that an event occurred before or after dose medication, the event was assigned to the higher dose.

The data clearly support that the riociguat CT with a maximum dose of 1.5 mg TID can be an effective and safe dose in patients with PAH. However, patients who can tolerate higher doses of riociguat may have additional clinical benefit. Further, the gradual dose escalation from 1.5 mg to 2.5 mg is well tolerated and does not appear to be associated with incremental safety concerns.

Based on the totality of data, the IDT regimen for riociguat (from 1 mg TID up to 2.5 mg TID) offers the best treatment approach for patients with CTEPH and PAH. This conclusion is based on the consistency of results for riociguat IDT across multiple endpoints in the CHEST-1 and PATENT-1 studies, together with the positive benefit-risk assessment of riociguat IDT to placebo. In both PATENT-1 and CHEST-1, the majority of patients tolerated doses of 2.5 mg. In

the long-term extension studies PATENT-2 and CHEST-2, the great majority received 2.5 mg as their chronic dose. This finding is in line with what was observed during phase II in the main phase of Study 12166, and in its ongoing long-term extension in which the majority of patients continue to receive 2.5 mg TID following 4.5 years of treatment. Based on the data from the exploratory arm in PATENT-1, it appears that 1.5 mg TID of riociguat is an effective and safe dose of riociguat, and data from this exploratory arm provide important clinical information on the use of 1.5 mg as a first target dose in the titration scheme of riociguat for patients with PAH.

The worsening of cardiopulmonary parameters in the progression of pulmonary hypertension requires flexible management to improve these parameters. The data of both PATENT-1 and CHEST-1 confirmed the usefulness of the 2.5 mg TID maximum dose when individualizing dose in the management of pulmonary hypertension. Many patients may benefit from a dose of 1.5 mg, but some will require further dose escalation in order to achieve maximum benefit. Further, the gradual dose escalation from 1.5 mg to 2.5 mg is well tolerated and does not appear to be associated with incremental safety concerns.

In summary, the PATENT-1 and CHEST-1 studies established that IDT dosing of riociguat (beginning at 1 mg TID and titrating to 2.5 mg TID, based on symptoms and systemic blood pressure) is safe and effective in both CTEPH and PAH, and should be the recommended dosing approach. The exploratory CT treatment group from the PATENT-1 study provides additional important information for prescribers. Although these data suggest that many patients with PAH may derive benefit from riociguat at a dose of 1.5 mg TID, dose escalation may be needed for these patients following disease progression and worsening hemodynamic status. Due to a variety of factors (e.g., variability in pharmacokinetics or in pharmacodynamic sensitivity to the vasodilating effects of riociguat), there are patients who will derive additional benefit from doses up to 2.5 mg TID. In both PATENT-1 and CHEST-1, the preponderance of patients were safely and successfully titrated to 2.5 mg TID and have continued on this dose for an extended period in the long-term extension studies.

8. Risk Evaluation and Mitigation Strategy

Bayer is proposing REMS to ensure that the benefits of riociguat outweigh the potential risk of embryo-fetal toxicity in females of reproductive potential. This proposal is based on discussions with the FDA, precedents in the United States marketplace regarding products with embryo-fetal toxicity, and data from non-clinical studies suggesting a potential risk of fetal harm associated with riociguat.

The goal of the riociguat REMS is to minimize the risk of fetal exposure and adverse fetal outcomes in females of reproductive potential prescribed riociguat. Specifically, women who are pregnant should not be prescribed riociguat, and women taking riociguat should not become pregnant.

The proposed riociguat REMS consists of an ETASU, an Implementation System, and a Timetable for REMS Assessments.

Medication Guide

All patients treated with riociguat will receive a Medication Guide with each dispensing. The Medication Guide provides educational information to patients about the safe use of riociguat and the risks associated with product use. It instructs females of reproductive potential about the risk of embryo-fetal toxicity and the importance of effective contraception while using riociguat.

Elements to Assure Safe Use

The REMS will include the following elements to assure safe use:

- Healthcare professionals must be educated, certified and enrolled in the REMS in order to prescribe riociguat

  To become certified, prescribers are required to review the Prescribing Information, Medication Guide, and the Prescriber's Guide and to complete the Prescriber Enrollment and Acknowledgement Form. The REMS educational tools provide guidance to prescribers on identifying and counseling female patients of reproductive potential about the risk of embryo-fetal toxicity associated with the use of riociguat and the need for highly effective contraception and monthly pregnancy laboratory tests.

- Pharmacies, practitioners, or health care settings that dispense the drug will be certified and enrolled in the REMS Program

  A limited number of specialty pharmacies will be certified through contracts with Bayer and must agree to follow the REMS requirements. The pharmacy must verify that, prior to dispensing a prescription for a patient, his/her prescriber is enrolled in the REMS Program. If the patient is a female of reproductive potential, both the prescriber and the patient must be enrolled in the REMS Program. Hospital pharmacies will also be enrolled in order for hospitals to stock riociguat.

- The drug will be dispensed only to female patients of reproductive potential who are enrolled in the REMS and have evidence of monthly laboratory pregnancy tests

  Females of reproductive potential must be counseled by their prescriber and together complete an Enrollment and Consent Form. The patient must agree to follow the REMS requirements including monthly pregnancy tests and use of effective contraception. Patients must have a negative pregnancy test prior to starting treatment, every month to continue treatment, and 30 days after discontinuation

Implementation System

Bayer will develop a validated database including information on all enrolled and certified prescribers, specialty pharmacies, and hospitals and enrolled patients. Bayer will monitor and evaluate the implementation of the ETASU and take reasonable steps to work to improve implementation of these elements if needed.

Timetable for Submission of Assessments

Bayer will evaluate the success of the REMS in meeting its goal and submit assessment reports to FDA at 6 and 12 months after REMS approval and annually thereafter. Assessments will include operational metrics of certification and enrollment; knowledge, attitude and behavior surveys of prescribers and enrolled patients; and root cause analysis of any pregnancies.

9. Benefit-Risk Assessment

The aim of the clinical study program was to demonstrate that riociguat, administered at an individually selected dose after a dose titration, is a therapy suitable for treatment of patients with either CTEPH or PAH. The study program demonstrated that riociguat is effective in treating patients with inoperable and postoperative CTEPH, as well as patients with PAH, either when administered alone or in combination with ERAs or prostanoids. The observed AE profile was within the range expected in these chronically ill patient groups. In these severely ill patients, the overall rates of SAEs, AEs resulting in discontinuation of study medication, and death were lower in riociguat treated patients than in patients receiving placebo. Overall, riociguat was safe and well-tolerated and did not present untoward side effects not already identified in the patient populations studied. In summary, the benefit-risk assessment is positive.

9.1 Unmet Medical Need

Two groups of CTEPH patients are appropriate candidates for medical therapy: patients with inoperable CTEPH and patients with persistent pulmonary hypertension after surgical treatment. Currently, no medical therapy has demonstrated benefit in either of these 2 distinct groups. Further substantiating the unmet need for medical treatment is the finding that a high proportion of CTEPH patients are currently receiving PAH-specific therapies that have not been approved for this indication and thus are unproven in CTEPH (41, 42). A series of small, uncontrolled studies with drugs indicated for PAH have suggested some potential benefit in this patient population (43). However, no randomized, controlled studies has yet demonstrated clinical efficacy of targeted PAH drugs in patients with CTEPH (29, 30). The BENEFIT trial (11) which evaluated the ERA bosentan in patients with CTEPH demonstrated a hemodynamic improvement, but failed to show any improvement in exercise capacity. The unmet medical need in patients with inoperable CTEPH and patients with persistent pulmonary hypertension after surgical treatment is high.

Despite advances in the diagnosis and treatment of PAH (with several disease-specific medicines being approved), most patients with PAH will experience progression of their disease, with high morbidity and early mortality being reported in the majority of patients. Even with increased awareness of the disease over the last decade or more, data on incidence and prevalence of the disease (based on regional registries) indicate that PAH still is often mis-diagnosed or under-diagnosed.

Increasingly, physicians are using a combination approach to treat patients with PAH (combination of PAH-specific medicines). While this has mechanistic plausibility, there remains a paucity of data to support this emerging practice. Despite this, data are emerging suggesting that this practice is gaining ground in the setting of PAH. The most commonly used combination of PAH-specific drugs is that of ERAs with PDE5 inhibitors (12). However, no randomized, placebo-controlled studies have been completed to support this treatment paradigm. In fact several studies have failed to show the benefit of dual oral therapy (13, 14, 15). Importantly, there is a known pharmacokinetic interaction between the ERA bosentan and PDE5 inhibitors sildenafil and tadalafil, although the precise clinical relevance of this remains to be established.

Significant unmet medical need exists in PAH. The PAH community is actively seeking to find new effective therapies that will bring benefit to patients with this uniformly fatal condition. In acknowledgement of this fact, several new agents are currently under investigation in phase II and III trials. These are being evaluated either as monotherapy or, more frequently, as part of a combination approach.

9.2 How Riociguat Addresses Unmet Needs in CTEPH and PAH

Riociguat is the first member of a novel class of compounds, the sGC stimulators. This new class of compound is not only structurally different from currently approved pharmacotherapies for PAH, but exhibits a different mechanism of action. *In vitro* and *in vivo* riociguat stimulates sGC and increases production of the second messenger cGMP. It does this independently of NO and, importantly, in the presence of NO, it enhances the effects of NO. Stimulation of sGC and production of cGMP has been associated with antifibrotic, antiproliferative, vasodilatory, and anti-inflammatory effects in pre-clinical models. The NO-sGC-cGMP signal-transduction pathway likely plays an important role in the regulation of pulmonary vascular tone and resistance in pulmonary hypertension. Reduced bioavailability of NO leads to decreased cGMP production and pulmonary hypertension. Based on the unique mechanism of action, riociguat may offer distinct advantages over current therapeutic approaches (such as PDE5 inhibitors and ERAs) through direct NO-independent stimulation of sGC and sensitization of sGC to low levels of endogenous NO. Endothelial cell dysfunction, together with decreased bioavailability of NO, is a common pathological feature in CTEPH and PAH. Indeed, these 2 features are considered by some experts to be strongly linked to disease severity and progression.

It is widely accepted in the expert community that novel drugs targeting new pathways or drugs that optimize targeting of existing pathways, are much needed for patients with CTEPH and those with PAH. It is hoped that new classes of agents may provide additional clinical benefits in addition to those achieved with current therapies.

Based on the preclinical profile in multiple experimental settings of pulmonary hypertension, together with the large body of data suggesting that pulmonary hypertension is associated with impaired NO-sGC-cGMP signaling, riociguat has been studied in patients with CTEPH and PAH. As of today, over 600 patients with CTEPH and PAH have been treated with riociguat. Based on efficacy and safety data obtained from phase I, II and III studies, riociguat has demonstrated the potential to address the unmet medical need in patients with both CTEPH and PAH.

To-date, no randomized, controlled studies have demonstrated clinical efficacy in patients with CTEPH (29, 30). Consequently, there are still no approved pharmacotherapies for CTEPH to address the unmet needs in patients with inoperable CTEPH or CTEPH patients with persistent pulmonary hypertension after surgical treatment. As described above, there is a paucity of data that demonstrate the benefit of combination therapy in patients with PAH despite the increasing use of PAH agents in combination.

The CHEST and PATENT studies represent the first time that a compound has demonstrated effectiveness in patients with either CTEPH of PAH. In both studies, both primary endpoints were reached with high statistical significance. Additionally, the subgroups of patients with greatest need (e.g., those with more advanced disease at baseline as measured by lower 6MWD or WHO functional class strata), showed the most profound effects of riociguat versus placebo, which was largely driven by the poor response in the placebo groups. The CHEST-1 study should be considered a landmark study in the field of CTEPH: as this is the first randomized, placebo-controlled study to demonstrate significant benefit in this population. The PATENT-1 trial demonstrated statistically significant improvement in both treatment naïve patients and is also the first controlled study in patients pre-treated with PAH-specific therapies across a wide range of clinically-relevant endpoint in PAH.

9.3 Limitations of Alternative Treatment Options

For CTEPH, surgical pulmonary endarterectomy is the treatment of choice for patients with symptomatic, operable CTEPH. In some patients this is curative. There are no approved pharmacotherapies for patients with inoperable CTEPH or for patients with residual pulmonary hypertension following pulmonary endarterectomy. With no disease-specific drug therapies approved for CTEPH, it is virtually impossible to state what the limitations are of alternative treatment options. That said, data from the European CTEPH Registry (41) indicate that PAH-specific therapies (including ERAs and PDE5 inhibitors) are frequently used in patients with CTEPH despite there being no positive, placebo-controlled clinical data to support their use. As discussed below, PAH-specific medicines have a well-characterized safety profile in patients with

PAH; however, in patients with CTEPH, this profile remains unknown. Anticoagulation is frequently needed to prevent further embolism and *in situ* thrombosis in patients with CTEPH, and the safety profile of this class of drugs is also well-characterized.

Until the early 1980s, conventional therapy for PAH consisted of anticoagulation, diuretics, digitalis extracts and supplemental oxygen, with a poor median survival of 2.8 years, and an estimated 5-year survival of 34%. The introduction of the intravenous prostacyclin poprostenol in 1995 was a therapeutic breakthrough in the treatment of PAH with survival figures for PAH patients markedly improving after its introduction. Since 1995, and with significant advances in the understanding of the pathophysiology of the condition, several disease-specific therapies have been approved for patients with PAH. Generally, speaking, there are 3 classes of medicines: PDE5 inhibitors, ERAs, and prostanoids. These drugs are typically defined as vasodilators and, as such, have a fairly well characterized safety profile. However, each of these classes of drugs comes with a different safety profile:

Prostanoids: Prostanoids are complex and difficult to administer. For example, epoprostenol has a short serum half-life (approximately 6 minutes) and needs to be administered by continuous infusion via an indwelling central venous catheter. This delivery system is associated with considerable inconvenience and a number of risks related to the delivery system, including infection and potentially life-threatening interruption of dosing due to pump failure. A number of prostanoids have been developed that attempt to overcome some of these limitations, including subcutaneous treprostinil, inhaled iloprost and inhaled treprostinil. However, despite improving a number of clinical and hemodynamic parameters, neither analogue has demonstrated an impact on survival and each is associated with a range of disadvantages, including injection site reactions (treprostinil) and the need for frequent administration (iloprost).

Endothelin receptor antagonists: The ERAs are orally administered, but bosentan is associated with increased incidence of liver toxicity (requiring monthly monitoring of liver function). In some cases, ERAs are associated with peripheral edema. The ERAs have been studied as add-on therapy to prostacyclins and failed to show any benefit of combination use (44, 45). Additionally, significant drug-drug interactions are possible due to the ERAs (especially bosentan) being substrates and inducers of CYP3A4.

Phosphodiesterase-5 inhibitors: The PDE5-inhibitors are the most recent class of compounds approved for PAH therapy. The PDE5-inhibitors are also administered orally and are generally safe and well tolerated in patients with PAH. This class of compounds has shown short- and long-term benefit in PAH, but treatment effects using PDE5-inhibitors alone are often unsatisfactory. In addition, the benefits of combination therapy using PDE5-inhibitors with other oral PAH therapies has not been established in randomized controlled clinical trials so far (46).

9.4 Beneficial Effects of Riociguat

Riociguat's benefit to patients with CTEPH and PAH has been demonstrated in 2 comprehensive, phase III, randomized, placebo-controlled studies. Both CHEST-1 and PATENT-1 met their primary endpoints with highly statistical significance. Additionally, benefit to patients was shown across multiple secondary endpoints and in virtually all subgroups analyzed.

6MWD (primary endpoint)

In CHEST-1 and PATENT-1, individual dose titration of riociguat to 2.5 mg TID showed superiority versus placebo in terms of improving exercise capacity, as measured by increased 6MWD. In study CHEST-1, the placebo-corrected increase in 6MWD was 45.7 meters (95% CI: 24.7 to 66.3; $p<0.0001$). In study PATENT-1, the placebo-corrected increase in 6MWD was 35.8 meters (95% CI: 20.1 to 51.5; $p<0.0001$).

It is widely acknowledged in the expert community that the 6MWD is clinically meaningful as it reflects ability of patients with PAH to perform usual activities of living; it is routinely used in clinical practice to assess response to therapy and clinical status of the patient. Importantly, the 6MWD has served as the main outcome variable in every trial that has led to approval of available pharmacotherapies for PAH.

Importantly, the benefits of riociguat therapy were observed in 4 distinct populations: (i) patients with inoperable CTEPH; (ii) patients with persistent or recurrent CTEPH following pulmonary endarterectomy; (iii) PAH patients as a monotherapy; (iv) PAH patients as a combination therapy (on top of PAH-specific therapies). This is the first time that a compound has demonstrated effectiveness in 2 etiologies within the Dana Point Classification scheme (1) and in 4 distinct patient populations.

Two open-label extension studies provide further evidence for benefit with riociguat in CTEPH and PAH patients. During the long-term extension studies (CHEST-2 and PATENT-2), the clinical benefit and safety profile observed in the respective preceding double-blind studies (CHEST-1 and PATENT-1) were maintained and patients previously treated with placebo improved to a clinically relevant extent after the switch from placebo to riociguat IDT and then was also maintained during the further observation with extended treatment.

The pattern of benefit shown with riociguat in terms of improvements in 6MWD across all subgroups analyzed is clinically relevant. The increase from baseline seen in both CTEPH and PAH was >20 meters which Benza and colleagues (47) presented as the threshold for short term studies to demonstrate results with the prospect of being of prognostic importance, and also >33 meters which Mathai and colleagues (48) found as the minimally important difference in a study investigating tadalafil composed of patients who were treatment naïve or on background therapy with bosentan.

Secondary Endpoints

The robustness of benefit shown in both studies in terms of walk distance was confirmed with statistically significant and clinically relevant improvements demonstrated across multiple, pre-defined clinically-relevant, secondary endpoints, such as PVR, NT-pro-BNP, WHO functional class, and time to clinical worsening (PATENT-1 only). Time to clinical worsening was not significantly different versus placebo in study CHEST-1, but there was a trend in favor of riociguat-treated patients.

The clinical importance of the secondary endpoints is to be seen in the context, that the positive results for 6MWD as a parameter of managing exertions of daily life is corroborated by an objective invasive measurement (PVR) and by an easily measured laboratory parameter, which is routinely used to assess the severity of heart failure (NT-pro-BNP).

For patients with CTEPH, the clinical benefits observed in study CHEST-1 are unique, as no previous randomized, placebo-controlled studies (using PAH specific drugs) have shown clinical benefit, as the benefits are shown not only for the primary endpoint but also consistently for important secondary endpoints.

The primary endpoint data from study PATENT-1 (in patients with PAH) are comparable to that previously shown in the clinical trials of compounds that were approved for patients with PAH. For the first time the benefits have been shown consistently over a broad range of secondary endpoints. However, the unique feature of the PATENT-1 data is the consistency of benefit in both treatment naïve and pre-treated patients. The latter finding is important based on the fact that there is increased use of combination therapy in PAH without much evidence-based medicine to support this concept.

Consistent with the primary and secondary efficacy endpoints, no negative impact on all-cause mortality was seen, but a numerically lower rate of death for riociguat-treated patients compared to placebo-treated patients was observed in the pooled placebo-controlled studies. Also, the death rate was low during the extended non-controlled studies (4% over a mean duration of 14 months).

The improvements observed in multiple pre-specified secondary endpoints demonstrate a consistent benefit of riociguat in patients with both CTEPH and PAH.

Limitations and Uncertainties

The major limitation of the efficacy considerations is due to the rarity of disease, which prohibits enrollment of large numbers of patients. Thus, a clinical development program was chosen to investigate important disease characteristics (PAH: treatment naïve and pretreated patients; CTEPH: inoperable patients and patients with post-operative pulmonary hypertension) within a single study each for CTEPH and PAH. With this approach patient numbers in many of the analyzed subgroups are rather low and impacted by outliers, missing values and temporary increases reflecting instability of the disease. In the overall context the robustness is demonstrated by the consistency of the efficacy endpoints across the 2 studies for CTEPH and PAH.

In addition, the database on black race is very small. Based on pharmacokinetic investigations the characteristics are comparable to the ones obtained from white patients. From pathophysiology, a differing response is not to be expected. Other studies reported low numbers for this ethnic group and did not find a different response compared to other ethnicities (13, 46, 49, 50).

The most powerful demonstrations of a drug's benefits in pulmonary hypertension are the clinical hard endpoints among the variables of time to clinical worsening, namely hospitalization due to pulmonary hypertension (including surgical interventions), progression of pulmonary hypertension (as persistent worsening of WHO functional class due to pulmonary hypertension combined with deterioration of 6MWD) and all-cause mortality (16). The study period in both studies was too short for a full assessment of these endpoints and thus, the respective event rates were too low to demonstrate this effect. But riociguat did demonstrate superiority on time to clinical worsening in study PATENT-1, and in study CHEST-1 the results for time to clinical worsening were directionally consistent. Also, the rates of all-cause mortality, hospitalization due to pulmonary hypertension, and persistent worsening WHO functional class due to pulmonary hypertension the event rates were consistently lower in both studies in the riociguat IDT group compared to the placebo group.

9.5 Unfavorable Effects

In CHEST-1 and PATENT-1, riociguat proved to be safe and well-tolerated using an IDT regimen. In both studies, the majority of AEs were consistent with the mechanism of action of the compound on smooth muscle cells (direct stimulation of sGC).

Although increased rates were seen for some AEs in riociguat-treated patients, they did not translate into an overall increased rate for death (1% riociguat versus 3% placebo), SAEs (15% versus 17%) and discontinuations due to AEs (3% versus 5%) which were numerically lower in riociguat-treated patients compared to placebo, demonstrating the favorable safety profile of riociguat in these severely affected patients.

For riociguat a dose titration scheme was applied which takes into consideration blood pressure measurements as well as symptomatic hypotension. Hypotension was identified as an AE consistent with the mechanism of action and had a higher incidence rate in riociguat-treated patients compared to placebo. The vast majority of events were mild or moderate in severity, had an outcome of resolved, and did not result in discontinuation of riociguat. Hypotension was not linked to syncope and was presumably asymptomatic in the majority of patients. Syncope was observed more frequently in placebo-treated patients and did not seem to be related to riociguat exposure. Thus, the riociguat dose titration scheme applied allows the administration of an appropriate dose. The flexibility to adapt the riociguat dose based on blood pressure and hypotension symptoms also allows patients to be maintained on treatment to gain the benefits of efficacy.

Gastrointestinal motility disorders (such as dyspepsia, nausea and vomiting), especially of the upper gastrointestinal tract were more frequently seen in riociguat-treated patients and were expected from riociguat's mechanism of action. The vast majority of patients could continue treatment irrespective of the outcome of the event, the events were mostly non-serious and treated with respective medication (drugs increasing pH).

The most serious and significant AEs observed under riociguat treatment in patients with CTEPH and PAH were hemoptysis and pulmonary hemorrhage including cases with a fatal outcome. However, the overall incidence of AEs leading to death in CHEST-1 and PATENT-1 was lower in the riociguat group than in the placebo group (1.0% versus 2.8%). This finding should be balanced by the fact that in patients with pulmonary hypertension, there is an increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. However, the risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious hemoptysis including those managed by bronchial arterial embolization. Hemoptysis and pulmonary hemorrhage are regarded as potential risks when patients are treated with riociguat in the light of being already a feature of events occurring in patients diagnosed with pulmonary hypertension as part of their disease. In light of that risk, the treating physician should regularly assess the benefit–risk with each individual patient.

Limitations and Uncertainties

Again a major limitation of the database is related to the rarity of disease, which limited the number of patients that could be enrolled into controlled studies. In part, this can be overcome for the frequent AEs in the consistency between the 2 different classes of pulmonary hypertension, CTEPH and PAH, which makes the results robust and underscores the overall beneficial profile when compared to placebo. Imbalances based on small numbers such as seen for hemoptysis/pulmonary hemorrhage (which rarely but typically occurs in pulmonary hypertension as part of the disease and also in many cases in the presence of concomitant medication for anticoagulation) are therefore assessed as potential risks.

9.6 Benefit-Risk

Benefit-risk was assessed by comparing the patients receiving individual dose titration of riociguat to 2.5 mg TID with patients receiving placebo. In weighing the risks and benefits for riociguat, and based on the data from the clinical development program with this compound, together with the risk factors associated with these life-threatening conditions, the benefit-risk ratio to patients with CTEPH and PAH treated with riociguat is positive.

Riociguat is the first drug to demonstrate consistent efficacy results in 2 classes of pulmonary hypertension, namely CTEPH and PAH over a broad range of efficacy endpoints and for the main patient subgroups of interest (CTEPH: inoperable patients and patients with persistent or recurrent CTEPH after surgical therapy; PAH: for therapy-naïve patients as well as for patients pretreated with ERAs or prostanoids). The flexibility to adapt the riociguat dose based on blood pressure and hypotension symptoms allowed patients to be maintained on treatment to gain the benefits of efficacy. At the same time riociguat has a safety profile which is consistent between CTEPH and PAH, and patients treated with riociguat are expected to present with an AE profile that is familiar to treating physicians as typically seen in patients with CTEPH and PAH as part of their disease or known from treatment with other drugs for pulmonary hypertension. No liver toxicity was seen and ECG analyses did not indicate a proarrhythmic effect for riociguat.

Riociguat has the potential to impact the management of patients with CTEPH, by providing treating physicians with the first specific therapy for this rare, progressive, and life threatening cardiopulmonary condition. CTEPH impacts not only the individual patient's life, but also adds burden to the caregiver and society. Vasodilators investigated so far in CTEPH showed an improvement in hemodynamics not accompanied, however, by an improvement in exercise capacity. As demonstrated in the phase III studies, riociguat is the first drug that not only improves exercise capacity, but also hemodynamics, WHO functional class, and quality of life in this severe and life-threatening disease while being safe and well tolerated.

PAH is a uniformly fatal disease for which there remains no cure. Many treating physicians use combinations of PAH-specific medicines in an attempt to attenuate disease progression. The scientific logic for this approach of targeting multiple different, yet complementary pathophysiological pathways is clear; however, there is a paucity of data to support this concept. The results from PATENT-1 provide treating physicians with the first evidence-based data on the use of dual oral combination therapy in patients with PAH. Riociguat will provide treating physicians with a drug belonging to a new therapeutic class of agents to treat patients with PAH, and is likely to be used as a monotherapy or in combination with other PAH-specific medicines. In terms of safety, riociguat appears to be a safe and well-tolerated medicine in the populations studied, with AEs based on the known mechanism of action of this compound.

9.7 Conclusion

The overall benefit of riociguat in the setting of both CTEPH and PAH outweighs potential risks, and thus, the overall benefit-risk balance is positive.

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11. Appendices

11.1 World Health Organization Functional Class

The patient's functional class was determined according to the WHO classification (1):

Group 1: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Group 2: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Group 3: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Group 4: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

11.2 Borg CR 10 Scale

Bayer HealthCare
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Modified Borg and Borg CR 10©

Borg CR 10 Scale		Modified Borg Dyspnea Scale	
0	"Nothing at all," means that you don't feel any exertion whatsoever, no muscle fatigue, no breathlessness or difficulties breathing.	0	Nothing at all
0.3			
0.5	"Extremely weak," "Just noticeable"	0.5	Just noticeable
0.7			
1	"Very weak" means a very light exertion. As taking a shorter walk at your own pace.	1	Very slight
1.5			
2	"Weak," "Light"	2	Slight
2.5			
3	"Moderate" is somewhat but not especially hard. It feels good and not difficult to go on	3	Moderate
4		4	Somewhat severe
5	"Strong – Heavy." The work is hard and tiring, but continuing isn't terribly difficult. The effort and exertion is about half as intense as 'Maximal."	5	Severe
6		6	Between 5 and 7
7	"Very strong" is quite strenuous. You can still go on, but you really have to push yourself and you are very tired.	7	Very severe
8		8	Between 7 and 9
9		9	Very, very severe (almost maximal)
10	"Extremely strong – Maximal" is an extremely strenuous level. For most people this is the most strenuous exertion they have ever experienced previously in their lives.	10	Maximal
11			
	•Is "Absolute maximum – Highest possible" for example "12" or even more		

SD-28

11.3 EuroQol EQ-5D questionnaire

The EQ-5D-3L questionnaire comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. Additionally, a visual analog scale records the respondent's self-rated health on a vertical, 20 centimeter line, where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.

For the analysis, the answers to the 5 questions (each with 3 categories) were combined to a score which has a range of possible values from –0.594 (worst outcome, all 5 questions answered with 3) to 1.00 (best outcome, all 5 questions answered with 1). An increase in the utility score represents an improvement in quality of life.

11.4 Living with Pulmonary Hypertension Questionnaire

The LPH questionnaire is designed to measure the effects of pulmonary hypertension and treatments specific to pulmonary hypertension on an individual's quality of life.

The LPH is a self-report questionnaire and needs to be completed by the patient (questionnaires will be provided in local language). However, if the patient has problems completing the questionnaire, an attempt should be made to explain the questions in a neutral and unpersuasive manner.

After the patient has filled in the questionnaire, the questionnaire is transferred to the study personnel, who will enter the content into the electronic case report form.

To measure the effects of symptoms, functional limitations, psychological distress on an individual's quality of life, the LPH asks patients to indicate using a 6-point, zero to five, Likert scale how much each of 21 facets prevented them from living as they desired.

LIVING WITH PULMONARY HYPERTENSION

The following questions ask how much your pulmonary hypertension affected your life during the past 7 days. After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your pulmonary hypertension prevent you from living as you wanted during the past 7 days by -	No	Very Little				Very Much
1. causing swelling in your ankles, legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making it difficult to walk about or climb stairs?	0	1	2	3	4	5
4. making it difficult to work around the house or in the garden?	0	1	2	3	4	5
5. making it difficult to go anywhere away from home?	0	1	2	3	4	5
6. making it difficult to sleep well at night?	0	1	2	3	4	5
7. making it difficult to have relationships or do things with your friends or family?	0	1	2	3	4	5
8. making it difficult to work to earn a living?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or lacking in energy?	0	1	2	3	4	5
14. making you stay in hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

11.5 Brief Descriptions of Other Clinical Studies

11.5.1 Descriptions of Phase II Studies

Study 12166

This 12-week, open-label study assessed safety, tolerability, and pharmacodynamics including invasive hemodynamics of riociguat at doses of 1.0 to 2.5 mg TID in 75 evaluable subjects with PAH or CETPH. Seventy-two subjects completed the 12 week treatment period (main study). Subjects were then given the opportunity to enter a long-term extension for up to 12 months. Riociguat exerted significant, strong, and favorable effects on pulmonary hemodynamics and functional capacity in subjects with PAH or CETPH. This was supported by echocardiographic data, NT-proBNP, and WHO functional class assessment.

Study 11874

This single-dose, proof-of-concept study looking at invasive hemodynamics in 19 subjects with PAH, CTEPH, and interstitial lung disease-associated pulmonary hypertension demonstrated that riociguat favorably influenced all main hemodynamic parameters in subjects with pulmonary hypertension without altering gas exchange or inducing a ventilation-perfusion mismatch. The study outcome proves that sGC stimulation as exerted by riociguat has the expected positive hemodynamic effects in this disease.

Study 11917

This study assessed potential interactions between riociguat and sildenafil. Single doses of 0.5 and 1 mg riociguat were administered to 7 subjects with pulmonary hypertension who received treatment with sildenafil at a stable dose of 20 mg TID. The doses of 0.5 and 1 mg were administered 3 and 5 hours, respectively, after the last intake of sildenafil. Effects were assessed by measuring peak post-baseline effects of Swan-Ganz hemodynamic parameters.

Study 12915

This single-dose (1 or 2.5 mg riociguat) proof-of-concept study demonstrated clinically relevant hemodynamic effects in subjects with pulmonary hypertension associated with chronic obstructive pulmonary disease. In the 2.5 mg group, mPAP and PVR were reduced by 4.83 mmHg and 123.8 dyn*s*cm^{-5}, respectively. CO increased by 1.6 L/min. The no-effect level of riociguat was <1.0 mg. The hemodynamic effects in percent compared to baseline are comparable to the results in patients with CTEPH and PAH (Study 11874).

Study 12916

Study 12916 was a multicenter, non-randomized, non-blinded, non-controlled study that investigated the effects of multiple doses of riociguat on safety, tolerability, and efficacy parameters in 22 subjects with pulmonary hypertension due to interstitial lung disease.

Study 14308

Study 14308 was a phase II, randomized, double-blind, placebo-controlled study that evaluated treatment with 3 different doses of riociguat in subjects with symptomatic pulmonary hypertension associated with left ventricular systolic dysfunction.

11.5.2 Phase 1 Studies

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List of all clinical pharmacology studies conducted in healthy and special population subjects and the number of placebo and riociguat (alone) treatment periods included in the pooled analysis

Study Number	Report Number	Study	Placebo	Single dose of riociguat administered alone ≤0.5 mg	1.0 mg	1.5 mg	2.0 mg	2.5 mg	5.0 mg
		Single Dose Studies							
11258	PH-34400	Single-Dose Escalation Study [a, b]	13	11	12	0	0	12	10
11259	PH-34409	Relative Bioavailability Study [a, b]	0	13	0	0	0	40	0
11261	PH-35000	Interaction Study with Ketoconazole [b]	0	16	0	0	0	0	0
11262	PH-35196	Interaction Study with Omeprazole [b]	0	0	0	0	0	12	0
11525	PH-34359	Absorption Site Study [c]	0	8	26	0	0	0	0
11526	PH-34631	Modified-release Tablets [d]	0	0	0	0	0	80	0
11888	PH-35251	Modified-release Tablets [d]	0	0	0	0	0	36	0
11890	PH-35362	Interaction Study with Aluminum Hydroxide / Magnesium Hydroxide (Maalox®) [b]	0	0	0	0	0	12	0
11910	PH-36361	Absolute Bioavailability Study [e]	0	7	49	0	0	0	0
11911	PH-35429	Mass Balance Study [f]	0	0	4	0	0	0	0
11914	PH-35666	Age & Gender Study [b]	11	0	0	0	0	36	0
11915	PH-36285	Renal Impairment Study I [b]	0	8	24	0	0	0	0
11916	PH-36317	Hepatic Impairment Study I [b]	0	0	32	0	0	0	0
12639	MRR-00304	Single-Dose Escalation in Japanese Subjects [b]	9	9	9	0	0	9	0
13009	PH-36258	Dose Proportionality Study [b]	0	26	26	26	26	24	0
13010	PH 36249	Pivotal Food Effect Study [b]	0	0	0	0	0	46	0
13284	PH-36280	Interaction Study with Clarithromycin [b]	0	0	14	0	0	0	0
14204	PH-36360	Interaction Study with Aspirin [b]	0	0	0	0	0	15	0
14769	A51270	0.5 mg Bioequivalence Study Japan [b]	0	47	0	0	0	0	0
14845	A51271	1.0 mg Bioequivalence Study Japan [b]	0	0	48	0	0	0	0
15000	PH-36745	Renal Impairment Study II [b]	0	0	40	0	0	0	0
15001	PH-36744	Hepatic Impairment Study II [b]	0	0	32	0	0	0	0
		Total number of treatment periods	**33**	**145**	**316**	**26**	**26**	**322**	**10**

List of all clinical pharmacology studies conducted in healthy and special population subjects and the number of placebo and riociguat (alone) treatment periods included in the pooled analysis

Study Number	Report Number	Study	Placebo	Daily dose of riociguat administered alone					
				1.5 - 2.0 mg	3.0 mg	4.5 mg	5.0 mg	6.0 mg	7.5 mg
		Special Design Study							
14360	PH-36542	Interaction Study with Nitroglycerin [b, g]	0	0	0	0	0	0	0
		Multiple Dose (bid, tid) Studies							
11260	PH-34881	Multiple-Dose Escalation Study [b]	58	14	10	12	12	0	12
11918	PH-35468	Interaction Study with Warfarin [b, g]	0	0	0	0	0	0	0
12640	A43125	Multiple-Dose Escalation in Japanese Subjects [b]	6	0	9	9	0	0	0
13790	PH-36405	Influence of Riociguat on Bone Metabolism Study [b, g]	0	0	0	0	0	0	0
14361	A57942	Single- and Multiple-Dose Escalation in Chinese Subjects [b]	12	0	12	0	0	12	0
14982	PH-36597	Interaction Study with Midazolam [b, g]	0	0	0	0	0	0	0
		Total number of treatment periods	**76**	**14**	**31**	**21**	**12**	**12**	**12**

Abbreviations: bid = *bis in die*, 2 times per day; tid = *ter in die*, 3 times per day; MRR = medical research report

Note: The following clinical pharmacology studies on riociguat were not included in the pooled analysis:

- Hemodynamic Proof-of-Concept Study in Subjects with Pulmonary Hypertension (Study 11874 [PH-34730]): study was conducted in adult subjects with suspected pulmonary hypertension.
- Interaction Study with Sildenafil (Study 11917 [PH-36136]): study was conducted in adult subjects with pulmonary arterial hypertension.
- Relative bioavailability and food effect study of 2 oral liquid formulations for pediatric use (Study 14986 ([PH-36814]): study for the development in pediatric subjects was completed in 2012.

[a] Studies used oral solution

[b] Studies used IR tablet

[c] 1.0 mg as granules (obtained from a crushed 2.5 mg tablet) administered to the distal small bowel via the Enterion® capsule, 1.0 mg as granules administered to the ascending colon via the Enterion® capsule, 0.25 mg as solution administered to the ascending colon via the Enterion® capsule, and 1.0 mg as solution administered orally

[d] Studies evaluated prototypes of modified-release tablets

[e] 0.25 and 0.5 mg were administered intravenously, 1.0 mg was administered intravenously as well as orally as IR tablet

[f] Only [^{14}C] riociguat (oral solution) was administered

[g] Riociguat or placebo were given only in combination with another drug within the same study period. Therefore, none of the treatment periods were included in the pooled analysis. Only serious adverse events and significant adverse events of these study periods are presented in this document.

11.6 Assay Methodology for Riociguat

High-pressure liquid chromatography with tandem mass spectrometric detection assays with different working ranges were developed for the simultaneous determination of riociguat and its main metabolite M-1 in plasma and urine. Sample processing for plasma and urine involved protein precipitation followed by a reverse-phase chromatographic separation and tandem mass spectrometric detection. The assays were fully validated according to pertinent guidelines, and were found to be appropriate with respect to limit of quantification, accuracy and precision to deliver valid analytical data of riociguat for subsequent pharmacokinetic investigations.

11.7 Statistical Methods for Efficacy in CHEST-1 and PATENT-1

The 6MWD was compared between the riociguat IDT arm and the placebo arm first by the ANCOVA for change from baseline to last visit using treatment group and region (PATENT-1 also included a factor for pre-treatment status [pre-treated or therapy-naïve]) as main effects with baseline 6MWD as a covariate. If the residuals from this ANCOVA model did not pass a Shapiro-Wilk test of normality ($p \leq 0.05$), a stratified (by region for CHEST-1; by region and pre-treatment status for PATENT-1) Wilcoxon test was used to test for treatment differences in change from baseline to last visit in 6MWD. The secondary efficacy variables of PVR, NT-proBNP, EQ-5D and LPH were also analyzed using this strategy. In both studies, there was evidence for non-normality for all these efficacy variables, and thus the treatment comparison from the stratified Wilcoxon test was used.

The secondary efficacy variables of WHO functional class and Borg CR 10 score are categorical with a limited number of possible scores; hence, the stratified Wilcoxon test was applied directly. For time to clinical worsening, the stratified log-rank test was used. The Mantel-Haenszel test on the proportion of patients with an event was also used as a sensitivity analysis.

Imputation in the Case of Withdrawal

The last visit was week 12 in PATENT-1 and week 16 in CHEST-1 for patients who completed the study. The worst value was assigned as the last visit value in the case of death, clinical worsening without a termination visit, or termination visit without the efficacy parameter being measured. The last observed value in the main study phase was assigned as the last visit value for other discontinued patients and completers in the few cases where a 6MWD was not measured at the final visit.. Worst values were 0 meters for 6MWD; WHO functional class IV if still alive or class V in case of death; -0.594 for EQ5D; and 105 for LPH total score. No worst case imputation was made for PVR or NT-proBNP in the pre-specified analysis, as these were used to verify the direct action of the treatments. Baseline was last measurement prior to start of study drug.

Preservation of the Type 1 Error Rate

A sequential testing procedure was applied. The secondary efficacy variables were formally tested for statistical significance of a difference between riociguat and placebo, only if the primary comparison of 6MWD was statistically significant at the two-sided 5% level. A sequential testing procedure was performed for these 7 secondary efficacy variables, strictly in the order: PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg CR 10 score, EQ-5D, and LPH.

Primary Patient Population

A patient was valid for the safety/ITT population if the patient was randomized and at least 1 dose of study medication was administered.

Sample Size Assumptions

The primary efficacy outcome in both studies was change in 6MWD from baseline to last visit.

For CHEST-1, a standard deviation of 70 meters was assumed. In order to detect a placebo-adjusted difference of 30 meters with a power of 90% and a 2-sided significance level of 5%, with a 2:1 randomization, 174 and 87 patients valid for the safety/ITT population were required in the riociguat and placebo groups, respectively. Thus, a total of 261 patients valid for the efficacy analysis were needed.

For PATENT-1, a standard deviation of 70 meters was assumed. In order to detect a placebo-adjusted difference of 25 meters with a power of 90% and a 2-sided significance level of 5%, with a 4:2 randomization, 250 and 125 patients valid for the safety/ITT population were required in the riociguat IDT and placebo groups, respectively. In addition, the exploratory riociguat CT group had a sample size of one-half that of the placebo arm, approximately 63 patients. Thus, a total of 438 patients valid for the efficacy analysis were needed.

Missing Data Sensitivity Analyses for 6MWD

The last observation carried forward strategy leads to unbiased estimates of the treatment effect only if the missing data are missing completely at random (MCAR); that is, the missingness is independent of both observed and unobserved outcomes. In addition, it must be assumed that outcomes will, on average, be constant after dropout. Although these conditions might hold approximately, they are unlikely to hold exactly. In accordance with the European Medicines Agency "Guideline on Missing Data in Confirmatory Clinical Trials" other ways of handling missing data were investigated. The sensitivity analyses were pre-specified prior to unblinding and were based on advice by an external consultant Professor Michael Kenward, University of London.

A termination visit was counted as the next regular visit, whereas unscheduled visits were excluded from the analysis. A worst case value of 0 meters was not imputed.

Missing at random (MAR) analysis: A less restrictive assumption than MCAR is MAR, meaning that missingness does depend on observed outcomes but not on unobserved outcomes. Equivalently, the future statistical behavior of those who drop out, given their past measurements

(or history), will be the same as of those who remain on study with the same history. Under such an assumption, the estimated treatment effect is the same as that would be seen if all subjects completed, which is sensible for a completers or per protocol type analysis. An analysis under the MAR assumption can be constructed using standard maximum likelihood methods, without the need to explicitly model the drop-out process. Given an approximation-to-normality assumption for the primary outcome, the multivariate normal linear model was used, with minimal additional assumptions (i.e., unconstrained time profiles and unstructured covariance matrices). This is termed a Mixed-Effect Model Repeated Measure (MMRM) analysis in the guideline. SAS PROC MIXED was used, with the following generic code using $6WMD_{change}$ (change in 6MWD from baseline) and the dependent variable and independent variables of $6WMD_{base}$ (baseline 6MWD), treat (treatment group), stratgroup (stratification group for PATENT-1 only), region, visit, and patno (subject number):

```
PROC MIXED DATA=mwt;

CLASS treat stratgroup region visit;

MODEL 6WMD_change = 6WMD_base visit stratgroup region treat visit visit*6WMD_base visit*treat /
        DDFM=KR;

REPEATED visit / subject = patno TYPE=UN GROUP=treat;

LSMEANS treat*visit / CL PDIFF;

RUN;
```

The adjusted means (LS means) were calculated at each time point with the standard error of the difference of means used to derive the 95% confidence intervals of treatment difference at each visit. The comparison of main interest was the treatment difference at visit 7 (CHEST-1) or visit 6 (PATENT-1).

Missing not at random (MNAR) analysis: The MNAR analysis assumes that missingness depends both on observed and unobserved outcomes. This requires an explicit model for the patient's statistical behavior after drop-out. Blinded review prior to study unblinding showed that patients who drop out tend to have lower outcomes than completers. Thus, it seemed sensible to assume a fixed or declining decrease below the group average for patients who dropped out, where the pattern and size of the decrease were varied across several sensitivity analyses. This is sometimes called the delta method of sensitivity analysis in a pattern mixture framework (Carpenter and Kenward, 2008, Chapter 6). Various scenarios of fixed penalties or decreasing slopes after drop-out were proposed and investigated, where different values were assigned to the treatment groups.

The sensitivity analyses included one analysis imposing a major penalty on the riociguat treatment group and the other imposing a similar penalty to both treatment groups.

Fixed penalties after drop-out:

- Placebo 0 meters / Riociguat -60 meters (i.e., a value of 60 meters was subtracted from the patient's value at last visit)
- Placebo -60 meters / Riociguat -60 meters

Decreasing slopes after drop-out:

- Placebo 0 meters / Riociguat -20 meters per visit after drop-out
- Placebo -20 meters / Riociguat -20 meters per visit after drop-out

To properly account for the incompleteness of the data, multiple imputation was used to draw sets of completed data that were then modified according to the scenarios given above. Multiple imputation was done using SAS PROC MI using the following generic code, where the stratification group and region are coded as dummy variables using therapy-naïve and Europe as respective reference groups: An example for Study 12934 follows.

PROC MI DATA=trans_mwt SEED=12934 NIMPUTE=50 OUT=mwt_mi;

BY treat;

MCMC NITER=500 NBITER=500;

VAR $6MWD_{change}$_visit2 - $6MWD_{change}$_visit6 $6MWD_{base}$ stratgroup region1 - region4;

RUN;

After modifying the completed data sets according to the preceding scenarios, the ANCOVA of the main analysis were performed at visit 6 in PATENT-1 or visit 7 in CHEST-1 for each completed data set. The results were then combined using SAS PROC MIANALYSE.

For each scenario, a 95%-confidence interval and a p-value were obtained for the treatment difference at visit 6.

Reference

Carpenter, J.R. and Kenward, M.G. (2008): Missing Data in Randomised Controlled Trials – A Practical Guide. Birmingham, UK: National Health Service Coordinating Center for Research Methodology.

11.8 Selected Summary Tables by Study

Treatment duration (in days) – Safety Population of Controlled and Long-term Extension Phase III Studies (CHEST-1 and PATENT-1 Main Phase; CHEST-2 and PATENT-2 Extension Phase)

Study	CHEST-1				PATENT-1				CHEST-1 and PATENT-1				CHEST-2 and PATENT-2	
Duration of treatment	**Riociguat**		**Placebo**		**Riociguat**		**Placebo**		**Riociguat**		**Placebo**			
N	**173**		**88**		**254**		**126**		**490**		**214**		**557**	
Duration of treatment (category)														
0–7 days	4	(2.3%)	0	–	3	(1.2%)	5	(4.0%)	7	(1.4%)	5	(2.3%)	1	(0.2%)
8–21 days	0	–	1	(1.1%)	5	(2.0%)	1	(0.8%)	8	(1.6%)	2	(0.9%)	2	(0.4%)
22–35 days	2	(1.2%)	0	–	3	(1.2%)	3	(2.4%)	6	(1.2%)	3	(1.4%)	4	(0.7%)
36–49 days	1	(0.6%)	0	–	3	(1.2%)	3	(2.4%)	6	(1.2%)	3	(1.4%)	1	(0.2%)
50–63 days	3	(1.7%)	2	(2.3%)	3	(1.2%)	3	(2.4%)	6	(1.2%)	5	(2.3%)	26	(4.7%)
64–91 days	3	(1.7%)	2	(2.3%)	229	(90.2%)	108	(85.7%)	286	(58.4%)	110	(51.4%)	52	(9.3%)
92–180 days	160	(92.5%)	83	(94.3%)	8	(3.1%)	3	(2.4%)	171	(34.9%)	86	(40.2%)	69	(12.4%)
181–270 days	0	–	0	–	0	–	0	–	0	–	0	–	65	(11.7%)
271–360 days	0	–	0	–	0	–	0	–	0	–	0	–	49	(8.8%)
361–450 days	0	–	0	–	0	–	0	–	0	–	0	–	48	(8.6%)
451–540 days	0	–	0	–	0	–	0	–	0	–	0	–	48	(8.6%)
541–630 days	0	–	0	–	0	–	0	–	0	–	0	–	55	(9.9%)
631–720 days	0	–	0	–	0	–	0	–	0	–	0	–	43	(7.7%)
721–810 days	0	–	0	–	0	–	0	–	0	–	0	–	40	(7.2%)
811–900 days	0	–	0	–	0	–	0	–	0	–	0	–	38	(6.8%)
901–990 days	0	–	0	–	0	–	0	–	0	–	0	–	13	(2.3%)
991–1080 days	0	–	0	–	0	–	0	–	0	–	0	–	3	(0.5%)
Duration of treatment (days)														
N with data	173		88		254		126		490		214		557	
Mean (SD)	108.2 (21.2)		110.2 (14.8)		81.4 (15.6)		78.2 (20.5)		90.7 (22.3)		91.4 (24.1)		422.8 (272.5)	
Median	113.0		113.0		85.0		84.		86.0		86.5		369.0	

Note: N for the pooled riociguat group includes the capped dose treatment group in PATENT-1, but N for the riociguat group in PATENT-1 reflects only the individual dose treatment group.

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Demographic characteristics – Safety Population of Controlled Phase III Studies (CHEST-1 and PATENT-1 Main Phase)

Study	CHEST-1		PATENT-1		CHEST-1 and PATENT-1	
Characteristics	**Riociguat**	**Placebo**	**Riociguat**	**Placebo**	**Riociguat**	**Placebo**
N	**173**	**88**	**254**	**126**	**490**	**214**
Sex						
Male	55 (31.8%)	34 (38.6%)	51 (20.1%)	28 (22.2%)	120 (24.5%)	62 (29.0%)
Female	118 (68.2%)	54 (61.4%)	203 (79.9%)	98 (77.8%)	370 (75.5%)	152 (71.0%)
Age (years)						
n	173	88	254	126	490	214
Mean (SD)	59.3 (13.9)	59.2 (12.7)	51.1 (16.6)	50.7 (16.5)	53.7 (16.1)	54.2 (15.6)
Median (Min–Max)	62.0 (19–80)	61.0 (26–77)	52.5 (18–80)	51.0 (18–79)	56.0 (18–80)	55.0 (18–79)
Age group						
<65 years	99 (57.2%)	52 (59.1%)	188 (74.0%)	94 (74.6%)	336 (68.6%)	146 (68.2%)
≥65 years	74 (42.8%)	36 (40.9%)	66 (26.0%)	32 (25.4%)	NA NA	NA NA
≥65 years – <75 years	NA NA	NA NA	NA NA	NA NA	110 (22.4%)	58 (27.1%)
≥75 years	NA NA	NA NA	NA NA	NA NA	44 (9.0%)	10 (4.7%)
Race / Ethnicity						
White	120 (69.4%)	65 (73.9%)	161 (63.4%)	78 (61.9%)	314 (64.1%)	143 (66.8%)
Black or African American	7 (4.0%)	1 (1.1%)	4 (1.6%)	1 (0.8%)	12 (2.4%)	2 (0.9%)
Asian	37 (21.4%)	20 (22.7%)	79 (31.1%)	38 (30.2%)	138 (28.2%)	58 (27.1%)
Multiple races	1 (0.6%)	0 –	1 (0.4%)	1 (0.8%)	NA NA	NA NA
Other	NA NA	NA NA	NA NA	NA NA	26 (5.3%)	11 (5.1%)
Hispanic or Latino	8 (4.6%)	2 (2.3%)	9 (3.5%)	8 (6.3%)	24 (4.9%)	10 (4.7%)
Baseline BMI (kg/m^2)						
n	173	88	254	126	490	214
Mean (SD)	27.13 (5.75)	27.73 (5.30)	25.91 (5.48)	26.26 (5.92)	26.46 (5.58)	26.87 (5.71)
Median (Min–Max)	26.64 (16.9–53.1)	26.52 (17.6–44.0)	25.18 (16.3–49.7)	24.89 (17.1–46.6)	25.54 (16.3–53.1)	25.83 (17.1–46.6)

(continued)

Demographic characteristics – Safety Population of Controlled Phase III Studies (CHEST-1 and PATENT-1 Main Phase)
(continued)

	CHEST-1				PATENT-1				CHEST-1 and PATENT-1			
Characteristics	**Riociguat**		**Placebo**		**Riociguat**		**Placebo**		**Riociguat**		**Placebo**	
N (= 100%)	**173**		**88**		**254**		**126**		**490**		**214**	
Baseline weight (kg)												
n	173		88		254		126		490		214	
Mean (SD)	73.99 (18.47)		76.24 (16.33)		68.62 (18.42)		69.60 (17.63)		70.77 (18.25)		72.33 (17.38)	
Median (Min–Max)	73.60 (36.0–158)		76.50 (44.0–120)		65.00 (37.7–140)		65.85 (38.4–141)		68.00 (36.0–158.3)		69.55 (38.4–141.0)	
Smoking history												
Never	113	(65.3%)	47	(53.4%)	171	(67.3%)	78	(61.9%)	324	(66.1%)	125	(58.4%)
Former	52	(30.1%)	34	(38.6%)	66	(26.0%)	38	(30.2%)	136	(27.8%)	72	(33.6%)
Current	6	(3.5%)	5	(5.7%)	17	(6.7%)	7	(5.6%)	28	(5.7%)	12	(5.6%)
Missing	2	(1.2%)	2	(2.3%)	0	–	3	(2.4%)	2	(0.4%)	5	(2.3%)
Alcohol use												
Abstinent	90	(52.0%)	45	(51.1%)	167	(65.7%)	73	(57.9%)	299	(61.0%)	118	(55.1%)
Light	77	(44.5%)	39	(44.3%)	80	(31.5%)	49	(38.9%)	177	(36.1%)	88	(41.1%)
Moderate	5	(2.9%)	3	(3.4%)	7	(2.8%)	3	(2.4%)	13	(2.7%)	6	(2.8%)
Heavy	0	–	1	(1.1%)	0	–	0	–	0	–	1	(0.5%)
Missing	1	(0.6%)	0	–	0	–	1	(0.8%)	1	(0.2%)	1	(0.5%)
Geographic region												
Asia/Pacific	18	(10.4%)	9	(10.2%)	46	(18.1%)	18	(14.3%)	75	(15.3%)	27	(12.6%)
China	21	(12.1%)	11	(12.5%)	43	(16.9%)	24	(19.0%)	74	(15.1%)	35	(16.4%)
Europe	104	(60.1%)	53	(60.2%)	118	(46.5%)	59	(46.8%)	252	(51.4%)	112	(52.3%)
North America	15	(8.7%)	9	(10.2%)	24	(9.4%)	11	(8.7%)	44	(9.0%)	20	(9.3%)
Latin America [a]	15	(8.7%)	6	(6.8%)	23	(9.1%)	14	(11.1%)	45	(9.2%)	20	(9.3%)

Note: N for the pooled riociguat group includes the capped dose treatment group in PATENT-1, but N for the riociguat group in PATENT-1 reflects only the individual dose treatment group.

Abbreviations: NA=not available

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

Overall summary of number of subjects with adverse events – Safety Population of Controlled Phase III Studies (CHEST-1 and PATENT-1 Main Phase)

Study	CHEST-1		PATENT-1		CHEST-1 and PATENT-1	
Number (%) of subjects with:	Riociguat	Placebo	Riociguat	Placebo	Riociguat	Placebo
N (= 100%)	173	88	254	126	490	214
Any AE	160 (92.5%)	78 (88.6%)	230 (90.6%)	111 (88.1%)	449 (91.6%)	189 (88.3%)
Any AE	159 (91.9%)	76 (86.4%)	227 (89.4%)	108 (85.7%)	444 (90.6%)	184 (86.0%)
Any study medication-related AE	103 (59.5%)	36 (40.9%)	162 (63.8%)	66 (52.4%)	304 (62.0%)	102 (47.7%)
Any severe AE	19 (11.0%)	10 (11.4%)	28 (11.0%)	19 (15.1%)	53 (10.8%)	29 (13.6%)
Any drug-related severe AE	4 (2.3%)	2 (2.3%)	15 (5.9%)	5 (4.0%)	20 (4.1%)	7 (3.3%)
Any SAE	34 (19.7%)	14 (15.9%)	29 (11.4%)	23 (18.3%)	74 (15.1%)	37 (17.3%)
Any study medication-related SAE	6 (3.5%)	1 (1.1%)	8 (3.1%)	5 (4.0%)	16 (3.3%)	6 (2.8%)
Any AE leading to discontinuation of study medication	5 (2.9%)	2 (2.3%)	8 (3.1%)	9 (7.1%)	14 (2.9%)	11 (5.1%)
Any AE leading to death	2 (1.2%)	3 (3.4%)	2 (0.8%)	[a] 4 (3.2%)	5 (1.0%)	[a] 7 (3.3%)

[a] One AE leading to death (subject 140014003, placebo group), included here, was included in the source tables of the study report of PATENT-1, although the subject had died after 134 days in the extension study PATENT-2. This subject died from *metastatic malignant melanoma*; the case was assessed as a post-treatment death .

Note: N for the pooled riociguat group includes the capped dose treatment group in PATENT-1, but N for the riociguat group in PATENT-1 reflects only the individual dose treatment group.
Incidences are based on the number of subjects, not the number of events. Although a subject may have had ≥2 AEs, the subject is counted only once in a category. The same subject may appear in different categories.

AEs: Most frequent MedDRA preferred terms – Safety Population of Controlled Phase III Studies (CHEST-1 and PATENT-1 Main Phase)

CHEST-1			PATENT-1			CHEST-1 and PATENT-1		
MedDRA preferred term	**Riociguat**	**Placebo**	**MedDRA preferred term**	**Riociguat**	**Placebo**	**MedDRA preferred term**	**Riociguat**	**Placebo**
N (= 100%)	**173**	**88**	**N (= 100%)**	**254**	**126**	**N (= 100%)**	**490**	**214**
Most common AEs ranked by incidence irrespective of treatment group								
ANY EVENT	159 (91.9%)	76 (86.4%)	ANY EVENT	227 (89.4%)	108 (85.7%)	ANY EVENT	444 (90.6%)	184 (86.0%)
Headache	43 (24.9%)	12 (13.6%)	Headache	69 (27.2%)	25 (19.8%)	Headache	132 (26.9%)	37 (17.3%)
Dizziness	39 (22.5%)	11 (12.5%)	Dyspepsia	48 (18.9%)	10 (7.9%)	Dizziness	94 (19.2%)	26 (12.1%)
Oedema peripheral	27 (15.6%)	18 (20.5%)	Oedema peripheral	44 (17.3%)	14 (11.1%)	Dyspepsia	87 (17.8%)	17 (7.9%)
Cough	9 (5.2%)	16 (18.2%)	Dizziness	40 (15.7%)	15 (11.9%)	Oedema peripheral	85 (17.3%)	32 (15.0%)
Dyspepsia	31 (17.9%)	7 (8.0%)	Nausea	40 (15.7%)	16 (12.7%)	Nausea	69 (14.1%)	23 (10.7%)
Nasopharyngitis	26 (15.0%)	8 (9.1%)	Diarrhoea	35 (13.8%)	13 (10.3%)	Cough	24 (4.9%)	29 (13.6%)
Dyspnoea	8 (4.6%)	12 (13.6%)	Nasopharyngitis	26 (10.2%)	14 (11.1%)	Dyspnoea	28 (5.7%)	26 (12.1%)
Nausea	19 (11.0%)	7 (8.0%)	Dyspnoea	16 (6.3%)	14 (11.1%)	Diarrhoea	58 (11.8%)	17 (7.9%)
Diarrhoea	17 (9.8%)	4 (4.5%)	Cough	12 (4.7%)	13 (10.3%)	Nasopharyngitis	58 (11.8%)	22 (10.3%)
Vomiting	17 (9.8%)	3 (3.4%)	Vomiting	26 (10.2%)	11 (8.7%)	Vomiting	50 (10.2%)	14 (6.5%)

Note: N for the pooled riociguat group includes the capped dose treatment group in PATENT-1, but N for the riociguat group in PATENT-1 reflects only the individual dose treatment group.
Incidences are based on the number of subjects, not the number of events. Although a subject may have had ≥2 AEs, the subject is counted only once in a category. The same subject may appear in different categories.

Study medication-related AEs: Most frequent MedDRA preferred terms – Safety Population of Controlled Phase III Studies (CHEST-1 and PATENT-1 Main Phase)

CHEST-1			PATENT-1			CHEST-1 and PATENT-1		
MedDRA preferred term	**Riociguat**	**Placebo**	**MedDRA preferred term**	**Riociguat**	**Placebo**	**MedDRA preferred term**	**Riociguat**	**Placebo**
N (= 100%)	**173**	**88**	**N (= 100%)**	**254**	**126**	**N (= 100%)**	**490**	**214**
Most common AEs ranked by incidence irrespective of treatment group								
ANY EVENT	103 (59.5%)	36 (40.9%)	ANY EVENT	162 (63.8%)	66 (52.4%)	ANY EVENT	304 (62.0%)	102 (47.7%)
Headache	27 (15.6%)	7 (8.0%)	Headache	51 (20.1%)	19 (15.1%)	Headache	93 (19.0%)	26 (12.1%)
Dizziness	26 (15.0%)	3 (3.4%)	Dyspepsia	42 (16.5%)	9 (7.1%)	Dyspepsia	70 (14.3%)	15 (7.0%)
Dyspepsia	21 (12.1%)	6 (6.8%)	Dizziness	26 (10.2%)	12 (9.5%)	Dizziness	63 (12.9%)	15 (7.0%)
Oedema peripheral	5 (2.9%)	8 (9.1%)	Hypotension	22 (8.7%)	2 (1.6%)	Nausea	38 (7.8%)	13 (6.1%)
Hypotension	14 (8.1%)	0	Nausea	21 (8.3%)	8 (6.3%)	Hypotension	38 (7.8%)	2 (0.9%)
Nausea	11 (6.4%)	5 (5.7%)	Diarrhoea	10 (3.9%)	8 (6.3%)	Oedema peripheral	20 (4.1%)	12 (5.6%)
Vomiting	8 (4.6%)	2 (2.3%)	Flushing	5 (2.0%)	7 (5.6%)	Diarrhoea	19 (3.9%)	11 (5.1%)
Diarrhoea	7 (4.0%)	3 (3.4%)	Palpitations	13 (5.1%)	3 (2.4%)	Flushing	13 (2.7%)	9 (4.2%)
Flushing	7 (4.0%)	2 (2.3%)	GERD	11 (4.3%)	3 (2.4%)	Vomiting	20 (4.1%)	4 (1.9%)
Abdominal discomfort	6 (3.5%)	1 (1.1%)	Hot flush	1 (0.4%)	5 (4.0%)	Palpitations	19 (3.9%)	5 (2.3%)
						GERD	19 (3.9%)	3 (1.4%)

Note: N for the pooled riociguat group includes the capped dose treatment group in PATENT-1, but N for the riociguat group in PATENT-1 reflects only the individual dose treatment group.
Incidences are based on the number of subjects, not the number of events. Although a subject may have had ≥2 AEs, the subject is counted only once in a category. The same subject may appear in different categories.

Abbreviations: GERD = gastro-oesophageal reflux disease.

SAEs: Most frequent MedDRA preferred terms – Safety Population of Controlled Phase III Studies (CHEST-1 and PATENT-1 Main Phase)

CHEST-1				PATENT-1				CHEST-1 and PATENT-1			
MedDRA preferred term	**Riociguat**		**Placebo**	**MedDRA preferred term**	**Riociguat**		**Placebo**	**MedDRA preferred term**	**Riociguat**		**Placebo**
N (= 100%)	**173**		**88**	**N (= 100%)**	**254**		**126**	**N (= 100%)**	**490**		**214**
Most common AEs ranked by incidence irrespective of treatment group											
ANY EVENT	34	(19.7%)	14 (15.9%)	ANY EVENT	29	(11.4%)	23 (18.3%)	ANY EVENT	74	(15.1%)	37 (17.3%)
Right ventricular failure	6	(3.5%)	3 (3.4%)	Syncope	3	(1.2%)	5 (4.0%)	Syncope	7	(1.4%)	8 (3.7%)
Syncope	4	(2.3%)	3 (3.4%)	Pulmonary arterial hypertension	1	(0.4%)	2 (1.6%)	Right ventricular failure	11	(2.2%)	4 (1.9%)
Cardiac arrest	0	–	2 (2.3%)	Right ventricular failure	2	(0.8%)	1 (0.8%)	Haemoptysis	5	(1.0%)	0 –
Haemoptysis	3	(1.7%)	0 –	Chest pain	2	(0.8%)	1 (0.8%)	Pulmonary arterial hypertension	2	(0.4%)	2 (0.9%)
Gastritis	2	(1.2%)	0 –	Haemoptysis	2	(0.8%)	0 –	Dyspnoea	1	(0.2%)	2 (0.9%)
Pulmonary hypertension	2	(1.2%)	0 –	Pneumonia	2	(0.8%)	0 –	Cardiac arrest	0	–	2 (0.9%)
Respiratory failure	2	(1.2%)	0 –	Renal failure acute	2	(0.8%)	0 –	Gastritis	4	(0.8%)	0 –
Catheter site haemorrhage	2	(1.2%)	0 –					Pneumonia	4	(0.8%)	0 –
Renal failure chronic	2	(1.2%)	0 –					Chest pain	3	(0.6%)	1 (0.5%)
								Gastroenteritis	3	(0.6%)	0 –
								Renal failure acute	3	(0.6%)	0 –
								Pulmonary hypertension	3	(0.6%)	0 –

Note: N for the pooled riociguat group includes the capped dose treatment group in PATENT-1, but N for the riociguat group in PATENT-1 reflects only the individual dose treatment group.
Incidences are based on the number of subjects, not the number of events. Although a subject may have had ≥2 AEs, the subject is counted only once in a category. The same subject may appear in different categories.