Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Riociguat

Proprietary Product Name: Adempas

Sponsor: Bayer Australia Pty Ltd

First round evaluation 10 October 2013
Second round evaluation 27 November 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of commonly used abbreviations

Abbreviation	Meaning
6MWD	6 minute walk distance
6MWT	6 minute walk test
ADME	absorption / distribution / metabolism / elimination
AE	adverse event
Aefeces	amount of drug excreted via feces
Aeur	amount of drug excreted via urine
AFIB	atrial fibrillation
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical Classification System
AUC	area under the concentration vs. time curve from zero to infinity
BCRP	Breast Cancer Resistance Protein
bid	bis in die (twice a day)
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
BPM	beats per minute
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
cGMP	cyclic guanosine monophosphate
CLCR	creatinine clearance
CLR	clearance of riociguat

Abbreviation	Meaning
CT	computed tomography
Ctrough	trough concentration
CLsys	systemic (plasma) clearance
Cmax	maximum drug concentration in measured matrix after single dose administration
Cmax/D	maximum drug concentration in measured matrix after single dose administration divided by dose
CO	cardiac output
CSR	clinical study report
CT	computed tomography
CTD	connective tissue disease
CTEPH	chronic thromboembolic pulmonary hypertension
CTX	type I collagen C-telopeptides
CV	coefficient of variation
CYP	cytochrome P450 isoenzyme
CYP1A1	cytochrome P450 isoenzyme 1A1
CYP1A2	cytochrome P450 isoenzyme 1A2
CYP2C8	cytochrome P450 isoenzyme 2C8
CYP2C9	cytochrome P450 isoenzyme 2C9
CYP2J2	cytochrome P450 isoenzyme 2J2
CYP3A4	cytochrome P450 isoenzyme 3A4
DBP	diastolic blood pressure
ECG	electrocardiogram
EMA	European Medicines Agency
EQ-5D	European quality of life 5-dimensions instrument
ERA	endothelin receptor antagonist

Abbreviation	Meaning
EU	European Union
Fabs	absolute bioavailability
FC	functional class
FDA	Food and Drug Administration
FPAH	familial pulmonary arterial hypertension
GFR	glomerular filtration rate
gSD	geometric standard deviation
h	hour (s)
HPAH	heritable pulmonary arterial hypertension
HIV	human immunodeficiency virus
HR	heart rate
IC50	inhibitory concentration (50% inhibition)
ICH	International Conference on Harmonisation
IDT	individual dose titration
ILD	interstitial lung disease
INR	international normalised ratio (prothrombin time)
IPAH	idiopathic pulmonary arterial hypertension
IR	immediate release
ITT	intention to treat
IVRS	interactive voice response system
LC-MS/MS	high-pressure liquid chromatography with tandem mass spectrometric detection
LFT	liver function test
LPH	Living with Pulmonary Hypertension
LS mean	last square mean
LTE	long term extension

Abbreviation	Meaning
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important clinical different
n	number
N/A	not applicable
NO	nitric oxide
NONMEM	non-linear mixed effect model
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NTX	N-terminal cross-linking telopeptides of type I collagen
NYHA	New York Heart Association
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PCH	pulmonary capillary haemangiomatosis
PD	pharmacodynamic
PDE5	phosphodiesterase 5
PE	pulmonary embolism
PEA	pulmonary endaterectomy
P-gp	P-glycoprotein
PH	pulmonary hypertension
PK	pharmacokinetic
PP	per protocol
PPH	primary pulmonary hypertension
PT INR	prothrombin time – international normalised ratio
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance

Abbreviation	Meaning
RAP	right atrial pressure
RHC	right heart catheter
RV	right ventricle
RVF	right ventricular failure
RVH	right ventricular hypertrophy
RVSP	right ventricular systolic pressure
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
sGC	soluble guanylate cyclase
SMQ	standardised MedDRA query
SOC	system organ class
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
TAPSE	tricuspid anular plane systolic excursion
Tei index	myocardial performance index (isovolumic contraction time plus isovolumic relaxation time divided by ejection time)
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
tid	ter in die (3 times a day)
tmax	time to reach maximum drug concentration in plasma after single (first) dose
TPR	total peripheral resistance
TTCW	time to clinical worsening
ULN	upper limit of normal
US(A)	United States (of America)

Abbreviation	Meaning
VKA	vitamin K antagonist
Vss	apparent volume of distribution at steady state
VTE	venous thromboembolism
WHO	World Health Organization
WHO FC	World Health Organization functional class

1. Clinical rationale

Riociguat is the first member of a novel class of compounds, the soluble guanylate cyclase (sGC) stimulators and has been developed to treat patients with chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). The sponsor has stated that riociguat is a direct and specific sGC stimulator. *In vitro* and *in vivo* riociguat stimulates sGC and increases production of the second messenger cyclic guanosine monophosphate (cGMP). It does this independent of nitric oxide (NO) and, in the presence of NO, it enhances the effects of NO. This mechanism of action is stated as unique in the setting of CTEPH and PAH.

Both CTEPH and PAH are rare and life-threatening forms of pulmonary hypertension (PH). These conditions share similar pathological features and are characterised by pulmonary arterial micro-vascular remodelling, dysregulation in vascular cell proliferation and in situ thrombosis, leading to increased pulmonary vascular resistance (PVR), abnormal pulmonary vascular tone, progressive right ventricular dysfunction/failure and, ultimately**,** premature death. The rate of disease progression is highly variable and depends on the type and severity of the pulmonary hypertension. It is defined by a mean pulmonary artery pressure (PAP) >25 mmHg.

The classification system for PH endorsed by the World Health Organization (WHO) is shown in Table 1 (below).

Table 1. Classification of Pulmonary Hypertension.

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH (IPAH)
1.2 Heritable PAH (HPAH)
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4 Associated with (APAH)
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5. Schistosomiasis
1.4.6. Chronic haemolytic anaemia
1.5 Persistent Pulmonary Hypertension of the Newborn (PPHN)
1' Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)
2. Pulmonary hypertension owing to left heart diseases
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3.Pulmonary hypertension owing to respiratory disease and /or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Haematological disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Source: (13)

For patients in Group 4 PH, pulmonary endarterectomy (PEA) surgery is the treatment of choice for patients with symptomatic, operable CTEPH. There are, however, a proportion of patients who are not suitable for surgery (30-40%) or who have persistent PH after surgery (~30%). In these patients medical therapy is warranted. There are currently no approved pharmacotherapies for CTEPH and patients are frequently treated off-label. Anticoagulation may prevent further embolism and in situ thrombosis but not necessarily disease progression.

There are no effective primary therapies for most types of Group 1 PAH that address the disease cause and as a result advanced therapy is often needed. This may include treatment with prostanoids, endothelin receptor antagonists (ERA), phosphodiesterase 5(PDE-5) inhibitors or occasionally calcium channel blockers.

Riociguat (BAY 63-2521) was discovered in-house by Bayer. The sponsor stated that a combination of pre-clinical investigations in animal models, together with early signs of efficacy studies in patients, have suggested that sGC is a valid therapeutic target for patients with PH. The submission seeks authorisation of riociguat for treatment of PH patients in Group 1 and also in Group 4. The sponsor stated that riociguat is also currently being developed in PH due to left heart disease (WHO Group 2) and due to interstitial lung disease (WHO Group 3.2).

1.1. Guidance

In the TGA pre-submission planning letter, the TGA requested the Sponsor clarify the indication in relation to whether the indication was to cover all types of PAH or specific subsets. The sponsor revised the indication.

Overall the clinical development program was conducted in accordance with relevant CHMP guidelines on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (EMA 2009).[1] The exception to this was that the pivotal trials were not sufficiently long for demonstrating an improvement in time to clinical worsening where a minimum of 6 months is necessary.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5
  - 30 clinical pharmacology studies, including 28 that provided pharmacokinetic data and 12 that provided pharmacodynamic data.
  - 2 integrated analyses of pharmacology studies
  - 6 population pharmacokinetic analyses.
  - 2 pivotal efficacy/safety studies (11348 [CHEST-1] and 12934 [PATENT-1]).
  - 2 Phase II studies, one uncontrolled (12166) and one controlled (15096).
  - 3 long term extension studies (11349 [CHEST-2], 12935 [PATENT-2] and extension of 12166).
  - 7 integrated analysis reports.
  - 16 other clinical reports. These included 5 studies with the major metabolite (BAY 60-4552) and (2 associated reports), 4 studies (with 3 additional reports) in different patient populations to that proposed in the indication, one safety listing report and one report on QT assay sensitivity.

2.2. Paediatric data

There is a paediatric development program for riociguat in the following indications:

- Treatment of primary pulmonary arterial hypertension (PAH).
- Treatment of persistent pulmonary hypertension of the Newborn (PPHN).

The Paediatric Investigation Plan (PIP) accepted by the European Medicines Agency is for film-coated tablets and oral liquid. For the film-coated tablets, there is a waiver in place for ages from birth to less than 6 years of age. The current submission included paediatric pharmacokinetic data in Study 15463 (a physiologically based pharmacokinetic [PBPK] modelling study to predict the pharmacokinetic properties of riociguat in the paediatric population). There are two planned studies with completion dates in 2016 and 2017, one in children 28 day to 18 years with PAH and one in neonates with pulmonary hypertension of the newborn.

[1] EMA (2009). Committee for medicinal products for human Use (CHMP). Guideline on the clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. EMEA/CHMP/EWP/356954/2008.

2.3. Good clinical practice

The sponsor declared that all studies were conducted according to Good Clinical Practice guidelines as well as local ethical and regulatory requirements.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 2 (below) shows the studies relating to each pharmacokinetic topic.

Table 2. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK	11910	Absolute BA
		11258	BA relative to an oral solution
		14769	BE of 0.5 mg tablet used in clinical trials and 0.5 mg tablet intended for marketing
		14845	BE of 1.0 mg tablet used in clinical trials and 1.0 mg tablet intended for marketing
		14986	Paediatric formulation - BA and food effects
		11525	Dosage forms - Routes of administration
		11259	Effect of food
		13010	Effect of food 2
		13009	Dose proportionality
		11260	Multiple doses and dose escalation
		11911	Mass Balance
PK in special populations	Target Population	11874	Patients with pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension or interstitial lung disease
	Hepatic Impairment	11916	Population which included smokers and non-smokers
		15001	In a non-smoking population
	Renal Impairme	11915	Population which included smokers and non-smokers

PK topic	Subtopic	Study ID	*
	nt	15000	Non-smoking population
	Other population characteristics	11914	Age and Gender
		12639	Young Japanese males - single dose
		12640	Japanese males - multiple doses
		14361	Chinese males - single and multiple doses
Drug- drug Interaction Studies	With respect to absorption	11262	Omeprazole
		11890	Maalox
		13790	Ranitidine (H2-antagonist)
	With respect to elimination and metabolism	11261	Ketoconazole
		13284	Clarithromycin
		14982	Midazolam
	Other factors	11918	Warfarin
		14204	Aspirin
Population PK Studies		12489	Structural PK for riociguat and metabolite M-1
		14362	PK model for riociguat and M-1 in renally and hepatically impaired patients
		15593	PK model for riociguat and M-1 in renally and hepatically impaired patients
		12653	Exploratory PPK analysis of riociguat in patients with pulmonary hypertension
		13817	PK model for riociguat and M-1 based on the data from four Phase III studies
		14851	PK properties[1] of riociguat in adult non-smokers and smokers
		15463	PK properties of riociguat in children of various age groups.
		14678	Evaluation of possible sparse sampling designs for the planned paediatric study

BA – bioavailability BE – bioequivalence PPK – population pharmacokinetic * Indicates the primary aim of the study. [1]Sponsor clarification: PBPK=physiology-based pharmacokinetic
† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

3.2.1. Detection methods

High-pressure liquid chromatography and tandem mass spectrometric detection (LC-MS/MS) assays with different working ranges were developed and fully validated for the simultaneous determination of riociguat (BAY 63-2521) and its metabolite M-1 (BAY 60-4552) in plasma and urine. Sample processing for plasma and urine involved protein precipitation followed by a reverse phase chromatographic separation and MS/MS detection. Method validation and analysis of the study samples were performed in accordance with the FDA guideline on bioanalytical validation.

The lower limit of quantification (LLOQ) in plasma ranged from 0.1 µg/L to 2.0 µg/L for riociguat and between 0.2 µg/L to 2.0 µg/L for M-1. The upper limit of quantitation (ULOQ) was between 100 µg/L and 500 µg/L for both analytes.

In urine, the LLOQ was in the range from 1.0 µg/L to 10 µg/L for riociguat and M-1. ULOQ was between 100 µg/L and 1000 µg/L for both analytes. Concentrations above LLOQ were determined with a precision better than 15%, and accuracy within 85 - 115%, respectively 20% and 80 to 120% at LLOQ in accordance to internal SOPs and pertinent guidelines on method validation.

3.2.2. Pharmacokinetic analysis

Area under the curve (AUC), maximum concentration (Cmax), time to maximum concentration (Tmax), and elimination half-life ($t_{1/2}$) were calculated using non-compartmental methods by KINCALC (a program developed by Bayer Pharma AG; Wuppertal, Germany) or WinNonlin software (Pharsight Corporation, Mountain View/CA, USA). The linear-logarithmic trapezoidal method was used to calculate AUC, and $t_{1/2}$ was calculated by linear least squares regression after logarithmic transformation of the terminal concentrations. Cmax and AUC values were in addition either dose-normalised (Cmax/D and AUC/D) or dose and body weight normalised (Cmax, norm and AUCnorm, according to the dose in milligram per kilogram body weight). Further plasma PK parameters are presented if appropriate, for example, apparent oral clearance.

If applicable, urinary concentrations of riociguat and urine volumes were used to calculate the amounts of riociguat excreted in the urine (Aeur) and to determine its renal clearance (CLR).

Plasma concentration–time courses of riociguat (calculated if two thirds or more of individual values were greater than the lower limit of quantification, LLOQ, at the scheduled time) are in general presented as geometric mean values including geometric standard deviations.

Pharmacokinetic parameters (except Tmax and Aeur) are presented as geometric mean values including geometric coefficient of variation [%CV] and, optionally, range. Results for Tmax are presented as median [range] and for Aeur as arithmetic mean [arithmetic coefficient of variation].

3.3. Pharmacokinetics in healthy subjects

3.3.1. Absorption

3.3.1.1. Sites and mechanisms of absorption

Following oral administration of a 1.0 mg IR tablet of riociguat in healthy male subjects, riociguat was rapidly absorbed with the maximum concentration (Cmax) occurring 45 min following dosing and the mean elimination half-life ($t_{1/2}$) was 6.78 hours.

3.3.2. Bioavailability

3.3.2.1. Absolute bioavailability

In **Study 11910**, which examined the PKs of riociguat after single oral IR tablet and intravenous doses of 1.0 mg riociguat in 22 healthy male subjects, the absolute bioavailability of riociguat was 94.3%.

3.3.2.2. Bioavailability relative to an oral solution or micronised suspension

The relative bioavailability of an oral tablet to an oral solution dose of 2.5 mg riociguat in healthy male subjects was 84.1%.

3.3.2.3. Bioequivalence of clinical trial and market formulations

Study 14769 examined the bioequivalence of the 0.5 mg tablet used in clinical trials and the 0.5 mg tablet intended-for-marketing in 24 healthy Japanese males. In this study the point estimates (90% CIs) for the AUC and Cmax of the marketed/trial formulations were 1.002 (0.96, 1.04) and 0.98 (0.91, 1.06), respectively, indicating that the two 0.5 mg tablet formulations were bioequivalent.

Study 14845 examined the bioequivalence of the 1.0 mg tablet used in clinical trials and the 1.0 mg tablet intended-for-marketing in 24 healthy Japanese males. In this study the point estimates (90% CIs) for the AUC and Cmax of the marketed/trial formulations were 0.96 (0.88, 1.05) and 1.06 (0.99, 1.14), respectively, indicating that the two 1.0 mg tablet formulations were bioequivalent.

3.3.2.4. Bioequivalence of different dosage forms and strengths

Study 14986 examined the oral bioavailability of liquid formulations of riociguat (0.15, 0.3 and 2.4 mg) intended for paediatric use in 30 fasted subjects. Riociguat was rapidly absorbed with median Tmax of 1.0 to 1.5 h after all doses. AUC/D and Cmax/D were similar for the paediatric high- (0.3 and 2.4 mg) and low-(0.15 mg) concentration suspensions in the fasted state (geometric mean AUC/D: 0.30 to 0.33 h/L; Cmax/D: 0.033 /L for all paediatric formulations) and comparable to the 1.0 mg IR tablet (AUC/D: 0.31 h/L, Cmax/D: 0.036 /L).

Mean $t_{1/2}$ ranged between 6.8 h (0.15 mg paediatric low-concentration suspension) and 9.2 h (2.4 mg paediatric high-concentration suspension). The 1.0 mg IR tablet as reference had a terminal half-life of 7.9 h.

Study 11525 investigated the PKs of riociguat after topical release of riociguat granules via the Enterion capsule in the distal small bowel and ascending colon, respectively, and riociguat solution via the Enterion capsule in the ascending colon in comparison with oral administration of riociguat solution in nine healthy males. Following administration of 1.0 mg riociguat granules to the distal small bowel, the AUC/D, $AUC_{(0\text{-}tn)}$ and $AUC_{(0\text{-}tn)}$ of riociguat were 43%, 52% and 84% lower, respectively, than following oral administration and following administration to the ascending colon, the AUC/D, $AUC_{(0\text{-}tn)}$ and $AUC_{(0\text{-}tn)}$ of riociguat were 81%, 88% and 97% lower, respectively, than following oral administration.

3.3.2.5. Bioequivalence to relevant registered products

Not applicable.

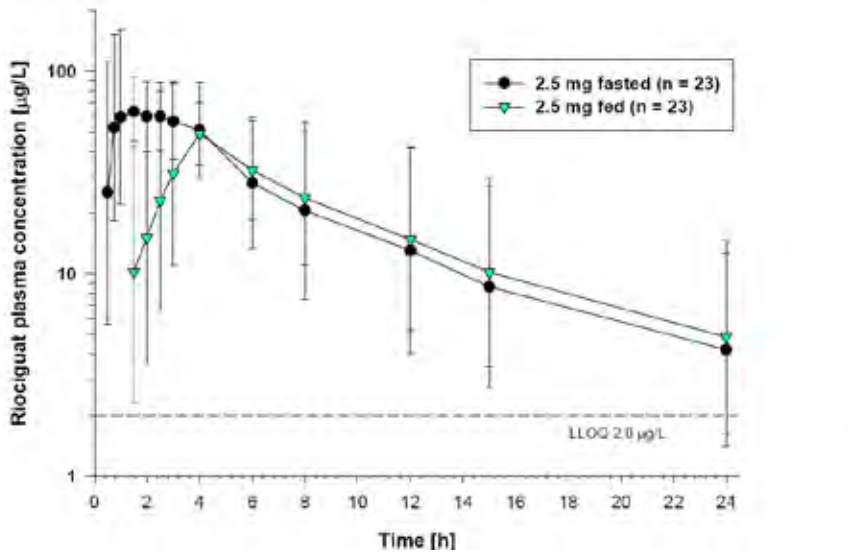
3.3.2.6. Influence of food

Two studies (**11259** and **13010)** examined the effects of a meal on the PK of riociguat.

Study 11259 investigated the PKs of riociguat after single oral doses of a 2.5 mg IR tablet with a high-fat, high-calorie breakfast in 12 healthy men. In this study the mean AUC and Cmax for riociguat were significantlyreduced by approximately 14 and 25%, respectively, and median Tmax was higher (3.0 versus 1.5 h), when 2.5 mg of the drug was given as a tablet either with or without a high-fat, high-calorie American breakfast.

Study 13010 also investigated the PKs of riociguat given orally as a 2.5 mg IR tablet with and without a high-fat, high-calorie American breakfast in healthy males. As in the previous study the median Tmax was delayed following a meal with a median Tmax of 4.0 hours compared with 1 hour in the fasted state (Figure 1). The 90% confidence intervals of the ratio "fed/fasted" for the AUC values of riociguat were fully contained in the bioequivalence range of 80 - 125%. By contrast the LS-mean Cmax of riociguat in the fed state was significant lower 35.3% irrespective of the smoking status. Therefore, a standardised high-fat, high-calorie American breakfast decreased the rate of absorption of riociguat but not its extent of absorption.

Figure 1. Geometric mean/geometric SD plasma concentration of riociguat following a single oral dose of 2.5 mg riociguat as IR tablet (semilogarithmic scale, all subjects valid for PK, n=23) Study 13010



Overall, intake of riociguat with food did not affect the AUC or Cmax to a clinically relevant extent; whereas by contrast, the Tmax was significantly increased by 2- to 4-fold. However, given the rapid rate of absorption and half-life of riociguat (Tmax 0.25 to 1.5 h and $t_{1/2}$ between 10 h and 12 h) in patients with suspected pulmonary hypertension (**Study 11874**) the increase in Tmax associated with food intake is unlikely to be of clinical relevance.

3.3.2.7. Dose proportionality

Study 13009 examined dose-proportionality of riociguat PKs when riociguat was given orally as 5 different single oral tablet doses (0.5, 1.0, 1.5, 2.0, and 2.5 mg) to 30 healthy male subjects. Riociguat was absorbed with a median Tmax of 0.75 - 1.0 hours after all 5 doses and the mean AUC/D and Cmax/D for riociguat were very similar. Mean $t_{1/2}$ of riociguat ranged from 5.4 hours to 7.2 hours with a high variability (1.0 - 19.2 hours, range). Smokers tended to have a shorter $t_{1/2}$ (1.0 - 7.1 hours), which was associated with a lower riociguat Cmax and AUC. The linear relationship between log transformed AUC and log dose had a slope (90% CI) of 1.0915 (1.0434; 1.1396). Similarly for log transformed Cmax and log dose the slope was 0.9866 (0.9307; 1.0424) indicating that riociguat PKs are dose proportional over the dose range from 0.5 mg to 2.5 mg.

3.3.2.8. Bioavailability during multiple-dosing

Study 11260 examined the PKs of riociguat following multiple oral doses of 0.5 mg, 1.0 mg, 1.5 mg TID, 2.5 mg BID or 2.5 mg TID given as IR tablet over 10 days in healthy male subjects. Steady state conditions for riociguat, characterised by constant trough concentrations, were reached after 3 days for all dosing regimens. Dose-proportional increases in $AUC_{(0\text{-}7)ss}$/$AUC_{(0\ to\ 12)ss}$ and of Cmax,ss were observed after 10 days. For TDS dosing, mean accumulation ratios for AUC(RAAUC) were between 110% and 157% and mean accumulation ratios for Cmax (RACmax) between 105 and 146%. After bid administration accumulation ratio RAAUC was 114%, RACmax was 98%.

3.3.2.9. Effect of administration timing

Not applicable.

3.3.3. Distribution

The following information regarding distribution, metabolism and excretion is primarily taken from the mass balance study (**Study 11911**), unless otherwise stated, which assessed the cumulative amount of drug-related, radio-labelled material excreted in urine and faeces, characterised the metabolic pattern in plasma, urine, and faeces, and quantified the total radioactivity and unchanged riociguat and M-1 concentrations in plasma and whole blood in four healthy male subjects.

3.3.3.1. Volume of distribution

Following a single dose 2 mL [^{14}C] riociguat oral solution 0.05%, 1.31 MBq per mL corresponding to 1 mg [^{14}C] riociguat solution, the apparent volume of distribution (Vz/f) ranged from 30.8 to 43.1 L in the four subjects.

At steady-state the volume of distribution (Vss) was approximately 30 L (0.38 L/kg) for riociguat as determined in the absolute bioavailability **Study 11910** indicating a low affinity for tissues.

3.3.3.2. Plasma protein binding

Plasma protein binding for riociguat in humans was high, approximately 95% *in vitro*, with serum albumin and α1-acidic glycoprotein being the main binding components. Mean protein-bound fraction determined *ex vivo* in healthy subjects was 96 to 97% for riociguat and 97% for M-1 (**Studies 11915, 15000, 11916, 15001 and 14204**).

3.3.3.3. Erythrocyte distribution

Approximately 20% of drug-related radioactivity following a 1 mg dose of [^{14}C] riociguat solution was distributed into blood cells.

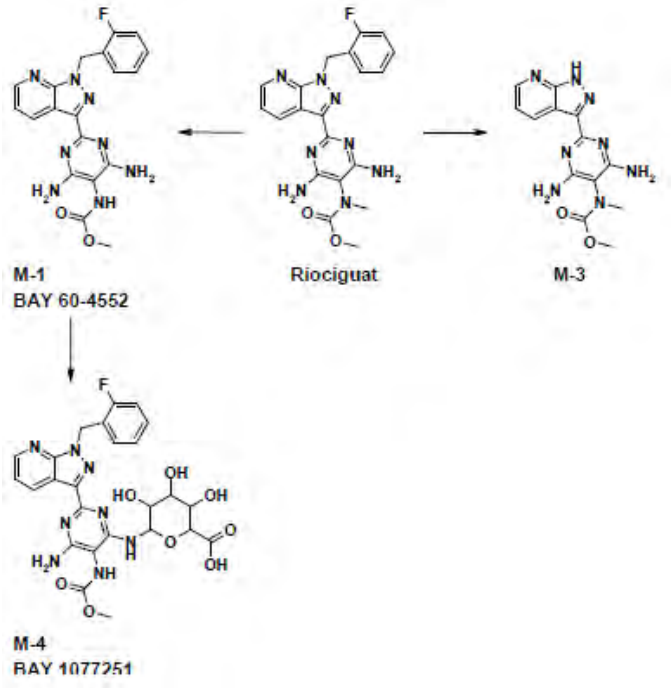
3.3.3.4. Tissue distribution

Tissue distribution of riociguat is predicted to be low.

3.3.4. Metabolism

The proposed metabolic pathways of riociguat in man are summarised in Figure 2, below.

Figure 2. Proposed metabolic pathways of riociguat (BAY 63-2521) in man



3.3.4.1. Interconversion between enantiomers

Not applicable.

3.3.4.2. Sites of metabolism and mechanisms / enzyme systems involved

In vitro CYP reaction phenotyping studies in human liver, intestinal and lung microsomes established that CYP2C8, CYP2J2, and CYP3A4 contribute to a similar extent to the formation of the major metabolite BAY 60-4552 (M-1) in the liver, whereas CYP3A4 and CYP2J2 almost equally catalyse 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 subjects most likely explain the 2- to 3-fold difference of riociguat clearance between smokers and non-smokers.

3.3.4.3. Non-renal clearance

The proportion of [^{14}C] riociguat associated radioactivity excreted in faeces ranged from 47.9% to 60.6%. The main portion (44.9% to 54.6%) was excreted within 96 hours after administration. Three subjects showed a more or less comparable pattern of metabolism and excretion, whereas the fourth was distinctly different and can be classified as a "slow" metaboliser with regard to M-1 formation.

3.3.4.4. Metabolites identified in humans

3.3.4.4.1. Active metabolites

M-1 exhibits pharmacological activity as soluble guanylate cyclase (sGC) stimulator but at 3- to 10-fold lower potency than that seen for riociguat.

3.3.4.4.2. Other metabolites

M-4 has been shown to be pharmacologically inactive.

3.3.4.5. Pharmacokinetics of metabolites

Following a single oral IR tablet dose of 1 mg riociguat the Cmax and AUC of the active and major metabolite of riociguat M-1 was 7.7 µg/L and 195.3 µg.h/L, respectively. The mean Tmax of M-1 occurs later than that of its parent compound (4h cf 0.75h, respectively) and it's $t_{1/2}$ is longer (13.2 h cf 6.8 h, respectively).

Subjects with high plasma concentrations of the parent compound had lower concentrations of M-1, whereas subjects with low plasma concentrations of riociguat had higher concentrations of M-1.

In man, metabolite M-1 is cleared via N-glucuronidation to metabolite M-4 (BAY 1077251), catalysed by UGT1A1 and 1A9. *In vitro* results suggest that M-1 has substrate properties for both P-gp and BCRP.

The renal clearance of M-1 of approximately 0.5 L/h indicates transporter-mediated active secretion ext to glomerular filtration (when assuming a human protein-bound fraction of 3.6%). Apparent (total) clearance of approximately 3 L/h indicates low clearance drug characteristics.

M-1 displayed linear PKs after single and multiple doses of riociguat IR tablets. The accumulation in AUC for M-1 following riociguat three-times daily was approximately 4- to 5-fold.

3.3.4.6. Consequences of genetic polymorphism

Study 35981 investigated whether genetic factors contribute to the absorption, distribution, metabolism and excretion of riociguat in healthy male volunteers. Regression analysis with demographic/environmental covariates from 147 Caucasian subjects such as age, dose, formulation, bodyweight and food-status showed that approximately 50% of the variability in exposure of the main metabolite M-1 can be explained by non-genetic factors, whereas, the variability observed in clearance, dose normalized AUC and $t_{1/2}$ could only marginally be explained. However, thorough examination of a panel of 1069 genetic variations in 172 drug metabolising genes and transporters failed to identify any genetic factors that contribute to the pharmacokinetic variability of riociguat in healthy male Caucasian and Japanese subjects.

3.3.5. Excretion

3.3.5.1. Routes and mechanisms of excretion

Riociguat is eliminated by both metabolic degradation as well as direct excretion of unchanged active compound.

3.3.5.2. Mass balance studies

In terms of exposure, riociguat (with 26-74%) and metabolite M-1 represented the majority of the radioactivity present in plasma (11-59%). Metabolite M4 accounted for 6-26 % of the total radioactivity present in plasma (**Study 11911**).

3.3.5.3. Renal clearance

The proportion of [^{14}C] riociguat associated radioactivity excreted in urine ranged from 33.4% to 45.6%. The main portion (28.0% to 41.9%) was excreted within 48 hours of administration.

The specific determination of riociguat accounted for 16.1%, 11.5%, 9.0%, and 51.0% of the total study drug-associated radioactivity excreted in urine in Subjects 011911-001 to 011911-004, respectively, whereas M-1 accounted for 52.6%, 53.3%, 44.3%, and 22.7%, respectively.

3.3.6. Intra- and inter-individual variability of pharmacokinetics

Inter-individual variability of riociguat PK was high with total variability (% coefficient of variation) of 76.9% for $t_{1/2}$, 89.7% for AUC/D, and moderate with 42.0% for Cmax/D. Intra-individual variability in various crossover studies was considerably lower with 18.4% for AUC/D and 23.9% for Cmax/D (**Pooled analysis of PK data**).

Inter-individual variability in population PK estimates for clearance from the Phase 3 trials, when correcting for relevant intrinsic and extrinsic factors as potential source of variability were in the range of 45%. Inter-individual variability in riociguat AUC across all doses was approximately 60% (PK/PD Study 13817 [PH-36960]). The intra-individual variability in PH patients was considerably lower with 35% for Ctrough, for instance, over the close to 4-year extension period of Phase 2 Study 12166.

3.4. Pharmacokinetics in the target population

Study 11874, which primarily examined pulmonary and systemic haemodynamics and gas exchange, also investigated the PKs of riociguat in patients with suspected pulmonary hypertension due to pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension or interstitial lung disease. Following a single-dose administration of 2.5 mg or 1 mg riociguat solution, plasma concentrations and AUC of riociguat and its metabolite M-1 increased dose-dependently with pronounced inter-individual variability, especially for the parent drug. Peak concentrations were reached after 0.25 to 1.5 h with $t_{1/2}$ between 10 h and 12 h for riociguat. PK results of 2.5 mg and 1 mg solution support dose-proportionality with regard to AUCnorm and Cmax,norm.

3.5. Pharmacokinetics in other special populations

3.5.1. Pharmacokinetics in subjects with impaired hepatic function

Two studies (**11916 and 15001**) examined the PKs of riociguat and its M-1 metabolite in subjects with hepatic impairment. Based on the preceding mass balance data, approximately 47% to 54% of the administered riociguat dose was excreted via the biliary/faecal route and up to 80% - at high variability - of the dose were actually recovered as metabolites. Therefore, hepatic impairment was expected to have a significant effect on riociguat metabolic clearance and elimination.

In **Study 11916** riociguat was readily absorbed with median Tmax of ≤1.25 hour in patients with Child Pugh A (n = 8) and Child Pugh B (n = 8) hepatic impairment and both control groups. However, the results were inconsistent with respect to the quantitative impact of the degree of hepatic impairment on the PKs of riociguat. For instance, although Child Pugh B subjects exhibited on average 30% higher riociguat plasma concentrations (AUC 329.9 µg*h/L) compared to the healthy control group B (AUC 233.8 µg*h/L), the Child Pugh A subjects (AUC 224.3 µg*h/L) had a lower mean exposure than that the healthy control group A (AUC 343.9 µg*h/L) and the lowest riociguat exposure of all 4 groups.

Prior to the commencement of the second study it was found that riociguat was, in part, metabolised via CYP1A1 which is known to be induced by smoking. As smokers have a considerably increased clearance of the parent compound riociguat to the metabolite M-1 it was therefore possible that the inconsistent results in **Study 11916** resulted from the combination of a number of factors including a higher number of smokers in the Child Pugh A group (5 smokers out of 8 subjects) compared to the matched healthy control group A; a high residual inter-subject variability of riociguat PKs, especially in AUC and the limited number of subjects per group.

Therefore, in an attempt to decrease the high inter-subject variability, the second study, **Study 15001**, examined the effects of hepatic impairment in a cohort of subjects who did not smoke. As in the preceding study, riociguat was rapidly absorbed with median Tmax of ≤ 1.5 hour in patients with Child Pugh A and Child Pugh B hepatic impairment and both control groups. The mean Cmax and Cmax,norm values of total riociguat were also similar in all 4 groups. By contrast, the mean $t_{1/2}$ of total riociguat was prolonged in Child Pugh A and Child Pugh B subjects (12.7 hours and 17.5 hours) compared to results in their healthy controls (9.2 hours and 8.9 hours). Exposure in terms of mean AUC of total riociguat was increased by 72% in Child Pugh A subjects and by 65% in Child Pugh B subjects compared to their healthy controls. Exposure in terms of mean AUC of unbound riociguat was increased by 60% in Child Pugh A subjects and by 88% in Child Pugh B subjects compared to their healthy controls, reflecting the increase in fraction unbound in Child Pugh B subjects. The group differences between "Child Pugh A / Control A" and "Child Pugh B / Control B" for riociguat total and unbound exposure are statistically significant. Therefore, when smoking subjects were excluded the rank order of AUC was Child Pugh B subjects > Child Pugh A subjects > healthy controls.

The antagonising effects - reduced rate of formation and impaired elimination of M-1 - lead to the differences in AUC of M-1 between Child Pugh A subjects (297 µg*h/L), Child Pugh B subjects (215 µg*h/L) and their matched healthy controls (235 µg*h/L and 221 µg*h/L). Therefore, an increased PD contribution of M-1 to the overall PDs in subjects with Child Pugh B hepatic impairment was not expected.

Mean renal clearance (CLr) of riociguat and M-1 was lower in Child Pugh A and Child Pugh B subjects compared to results in their healthy controls.

The high variability of riociguat PKs in **Study 11916** (geometric CVs up to 130%), which confounded the resulting PKs, was not observed in **Study 15001** (geometric CV of AUC for total riociguat 41 - 57%, geometric CV of Cmax for total riociguat 23 - 31% in the 4 groups). Therefore, the exclusion of smoking subjects allowed for a better assessment of the influence of the degree of hepatic impairment on riociguat PKs.

3.5.2. Pharmacokinetics in subjects with impaired renal function

Two studies (**11915 and 15000**) examined the PKs of riociguat and its M-1 metabolite in subjects with impaired renal function.

Study 11915 evaluated the PKs of riociguat and metabolite M-1 in subjects with mild to severe renal impairment, stratified according to creatinine clearance, and age-, weight-, and gender-matched healthy subjects. Overall, mean dose-normalised AUC and AUC/D values for riociguat and M-1 were higher in subjects with moderate or severe renal impairment compared to results in subject with normal renal. As in the initial study examining hepatic impairment (**Study 11916**) there was inconsistency in the results with respect to the quantitative impact of the degree of renal impairment on the PKs of riociguat, whereby, subjects with moderate renal impairment exhibit on average a more than 80% increase in riociguat plasma AUC compared to healthy controls or subjects with mild renal impairment, while riociguat PKs in subjects with severe renal impairment seemed to be hardly affected.

Therefore a second study, **Study 15000**, examined renal impairment in a cohort of non-smokers. In contrast to **Study 11915**, PK results in the non-smoking population demonstrated a consistent and substantial effect of renal impairment on clearance and elimination of riociguat: in all 3 groups of subjects with renal impairment, riociguat clearance was lower, $t_{1/2}$ was longer, and mean exposure in terms of AUC was higher (at least by 100%). Nevertheless, exposures observed in subjects with renal impairment were highly variable and the ranges of exposures observed in subjects with mild, moderate, and severe renal impairment overlapped those observed in healthy controls.

In addition, the observed influence of renal impairment on the mean exposure to riociguat was higher than anticipated from reported mass balance data, where approximately 9 - 16% of the

administered dose was found to be excreted as unchanged riociguat into the urine. Increase in exposure to riociguat did not increase strictly in parallel to decreasing renal function (creatinine clearance).

3.5.3. Pharmacokinetics according to age and gender

Study 11914 compared the PKs of riociguat, in young and elderly healthy volunteers of both genders, following a 2.5 mg oral tablet dose. In this study the AUC of riociguat was approximately 40% higher in elderly subjects compared to young subjects, possibly due to the decreased renal clearance in the elderly; however, this difference was not statistical significant, and was in part accounted for by the weight difference between the young and elderly. No notable age-related change in Cmax was observed. The effects of age on M-1 were less than those seen for the parent compound. Although females had higher Cmax values for both riociguat and M-1 compared to males, no differences in AUC were. The sponsor concluded that any effects due to age or gender were not sufficient to merit a dose adjustment.

3.5.4. Pharmacokinetics related to genetic factors

See Section *Intra- and inter-individual variability of pharmacokinetics*.

3.5.5. Pharmacokinetics {in other special population / according to other population characteristic}

Study 12639 examined the PKs and PD effects of riociguat after single oral doses of 0.5, 1.0 and 2.5 mg given to young healthy male subjects under the fasting condition. Riociguat Tmax ranged from 1 hour to 1.5 hours and $t_{1/2}$ ranged from 4.15 hours to 7.59 hours. Mean Cmax and AUC increased with dose, but AUC increased more than dose-proportionally over the dose range investigated. The $t_{1/2}$ was influenced by smoking status and the median value was 8.78 hours for non-smokers and 4.19 hours for smokers. A higher clearance and a lower exposure for riociguat were observed in smokers in comparison to non-smokers. Inter-individual variability in these parameters for smokers was larger than that for non-smokers. Mean urine excretion rate (Aeur0-72) ranged from 5.67% to 13.63% (geometric mean).

Study 12640 investigated the PKs of riociguat in healthy Japanese male subjects after multiple oral doses of 1.0 and 1.5 mg 3 times a day over 7 days. Plasma concentrations of riociguat and M-1 reached steady state during the 7-day multiple dosing period, regardless of dose. At steady state, riociguat Tmax was 1.5 hours and the $t_{1/2}$ ranged from 9.2 to 9.7 hours. The median $t_{1/2}$ on Day 9 for smokers and for non-smokers was 9.2 hours and 9.8 hours, respectively. The inter-individual variability on Day 9 was smaller than that on Day 1, regardless of the smoking status. Geometric means of AUC and Cmax of riociguat at steady state indicated dose proportionality. Cmax at steady state was 1.18 - 1.25 times higher than that on Day 1 (RACmax). $AUC_{(0-7)}$ at steady state was almost the same with AUC on Day 1. No major differences between smokers and non-smokers were observed in clearance, AUC/D or Cmax/D at steady state. Cumulative urine excretion rate of riociguat and M-1 throughout this study were about 15% and 23% of the administered dose, respectively.

Chinese subjects

Study 14361 examined the PKs of riociguat in healthy Chinese male subjects after a single dose and multiple oral doses of 1.0 mg and 2.0 mg 3 times a day over 6 days and a single dose on the seventh day of the multiple dosing regimen. The riociguat Tmax and Tmax,ss was 1 hour for both doses. Mean $t_{1/2}$ after a single dose and at steady state dosing of 1 mg and 2 mg riociguat was similar (about 3.5 hours after a single dose and about 5 hours at steady state). Mean dose- and weight- normalised exposure to riociguat was also similar following administration of 1 mg and 2 mg. Mean exposure to riociguat during the dosing interval increased at steady state (mean $AUC_{(0-7)ss}$, Day 9/$AUC_{(0-7)Day\ 1}$ was 176% and 156% in the 1 mg and 2 mg riociguat groups, respectively). Mean Cmax,ss,norm values of riociguat were similar in both groups (about 2.85 kg*h/L). Smoking reduced riociguat exposure after single dosing and at steady state (AUCnorm

and $AUC_{(0-7)ss,norm}$) by at least 60%. The decrease in Cmax,norm and Cmax,ss,norm of riociguat was less pronounced, i.e. by 20% and 44%, respectively. Smoking only slightly affected exposure to M-1.

3.6. Pharmacokinetic interactions

3.6.1. Pharmacokinetic interactions demonstrated in human studies

3.6.1.1. With respect to absorption

3.6.1.1.1. Omeprazole

Study 11262 investigated the pH-dependency of riociguat absorption when riociguat was given as a single IR tablet dose (2.5 mg) with and without a 4 day pre- and co-treatment of omeprazole (40 mg od). Pre- and co-treatment with omeprazole decreased riociguat bioavailability with Cmax and AUC decreasing by 35% and 26%, respectively, indicating a relevant PK interaction. Riociguat $t_{1/2}$ increased from 7.9 to 9.0 h and total body clearance (CL/f) increased from 4.3 to 5.8 L/h when riociguat was given concomitantly with omeprazole. Pre- and co-treatment with omeprazole did not influence the exposure of the metabolite M-1 to any relevant degree.

3.6.1.1.2. Maalox[2]

Study 11890 examined the effects of co-administration of 10 mL Maalox 70 mval suspension on the PKs of riociguat given as a single oral 2.5 mg IR tablet dose in comparison to a single oral 2.5 mg IR tablet dose given alone. Co-administration with Maalox resulted in reductions in riociguat Cmax and AUC of 56% and 34%, respectively. In addition, riociguat $t_{1/2}$ increased from 5.9 to 8.6 h and CL/f increased from 5.3 to 8.1 L/h. Co-administration with Maalox also led to reductions in M-1 Cmax and AUC of 44% and 33%, respectively. In addition, M-1 $t_{/2}$ increased slightly from 12.2 to 14.2 h and CL/f increased from 3.7 to 5.4 L/h.

3.6.1.1.3. Ranitidine

Study 13790 examined PKs of riociguat (2.5 mg TDS) following co-administration with the H2-antagonist ranitidine 150 mg od. in non-smoking subjects. $AUC_{(0-7)}$ of riociguat after co-administration with 150 mg ranitidine was 393 µg*h/L after the first dose compared to 439 µg*h/L in the previous multiple dose escalation study, where riociguat was given alone (**Study 11260**).

3.6.1.2. With respect to elimination and metabolism

3.6.1.2.1. Ketoconazole - strong CYP3A4 and P-gp inhibitor

Study 11261 examined the effect of multiple doses of 400 mg ketoconazole once-daily on the PKs of riociguat and its main metabolite M-1 given as a single oral dose of 0.5 mg riociguat in comparison to a single oral dose of 0.5 mg riociguat given alone. Pre- and co-treatment with ketoconazole increased riociguat Cmax and AUC increasing by 46% and 150%, respectively. Riociguat $t_{1/2}$ increased from 7.3 h to 9.2 h and CL/f decreased from 6.1 L/h to 2.4 L/h. The amount of riociguat excreted via urine increased from 7.9% to 17.1%. Renal clearance decreased slightly from 0.41 L/h to 0.38 L/h. Pre- and co-treatment with ketoconazole decreased M-1 mean Cmax by approximately 49% and mean AUC by 24%. M-1 $t_{1/2}$ increased slightly from 16.2 h to 18.3 h when riociguat was given concomitantly with ketoconazole. The amount of M-1 excreted via urine decreased from 15.0% to 10.2%. Renal clearance decreased

[2] Maalox (Cassella-med, Germany) contains aluminium hydroxide and magnesium hydroxide, whereby a 10 mL suspension has a neutralizing capacity equivalent to 70 mval HCl.

from 0.77 L/h to 0.64 L/h. A single dose of riociguat did not affect the bioavailability of ketoconazole.

3.6.1.2.2. Clarithromycin - strong and selective CYP3A4 and weak-to-moderate P-gp inhibitor.

Study 13284 examined the effect of a 4-day pre-treatment and a 1-dose co-treatment of 500 mg clarithromycin twice daily on the PKs of 1 mg riociguat given as a single oral dose in comparison to when riociguat was given alone. The 4-day pre-treatment and subsequent co-administration of clarithromycin increased the AUC of riociguat and M-1 by 41% and 19%, respectively, but did not significantly affect Cmax.

3.6.1.2.3. Midazolam - sensitive CYP3A4 probe substrate

Study 14982 investigated the effect of multiple doses of riociguat on the PKs of a single oral dose of midazolam in healthy male subjects. The PKs of midazolam were unaffected following 3-day TDS pre-treatment and concomitant administration with 2.5 mg riociguat compared to the respective mono-treatment with midazolam. The AUC of the CYP3A4-mediated metabolite 1-hydroxy-midazolam was not affected by co-administration of riociguat, whereas the lower border of the confidence interval of Cmax was slightly below [76.08] the pre-specified 80% - 125% range after 3-day TDS pre-treatment and concomitant administration with 2.5 mg riociguat compared to the respective mono-treatment with midazolam.

3.6.1.2.4. Warfarin - CYP2C9 substrate

Study 11918 examined the PK interaction, with respect to Coumadin (warfarin), when riociguat and warfarin were co-administered to healthy subjects. Steady-state riociguat did not affect the AUC and Cmax of warfarin. Single-dose administration of warfarin led to a 16% decrease in riociguat Cmax,ss, whereas it did not affect riociguat $AUC_{t,ss}$ or the PKs of M-1.

3.6.1.2.5. Aspirin

Study 14204 examined the effect of Aspirin (500 mg) on the PKs of a single dose of 2.5 mg riociguat. Mean PK parameters of riociguat and M-1 were virtually identical or at least very similar after administrations of riociguat with and without co-administration of Aspirin.

3.6.2. Clinical implications of in vitro findings

In vitro studies identified that:

- At therapeutic plasma concentrations, riociguat and its metabolite M-1 did not inhibit the major CYP isoforms CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2 and 3A4. Nor did they inhibit UGT1A1, 1A4, 1A6, and 2B7 isoforms and SULT.
- Riociguat and its metabolite M-1, however, revealed inhibitory potential on CYP1A1 (Ki value of 0.6 μM). Clinically relevant drug-drug interactions with co-medications which are significantly cleared by metabolism via CYP1A1 cannot be ruled out. However, only few drugs are known, for example, erlotinib or granisetron, where CYP1A1 significantly contributes to the overall clearance.
- No inducing potential on major CYP isoforms CYP1A2 and 3A4 was observed for riociguat and its major metabolite M-1.
- At therapeutic plasma concentrations, riociguat and M-1 are neither P-gp nor BCRP inhibitors. No clinically relevant drug-drug interactions due to inhibition of P-gp or BCRP by riociguat are expected.
- Due to the involvement of CYP1A1, CYP3A4, CYP2C8 and CYP2J2 in the riociguat metabolism and BCRP/P-gp in its biliary/faecal excretion, riociguat could be prone to PK interactions with strong inducers or inhibitors of these enzymes/transporter proteins.

3.7. Population PK studies

A large number of population PK (PPK) modelling studies were undertaken by the sponsor.

Study 12489 defined a structural PK for riociguat and active metabolite M-1 using data derived from **Study 11260**. In this study the PKs of riociguat and its active metabolite M-1 were adequately described by a two compartment model for each compound with first order absorption of riociguat. No systematic effects of dose or time on the PK parameters were found. There was a high intra-individual variability for the absorption rate, which could not be determined unambiguously in this study. The inter-individual variability of the clearance of riociguat is relatively high (63.8%), while the clearance of M-1 and other PK parameters show moderate inter-individual variability.

Study 14362 confirmed the structural PK models for riociguat and M-1 in renally and hepatically impaired patients following a single oral dose of 1.0 mg or 0.5 mg riociguat in Phase I study numbers **11915** and **11916**. In this analysis smoking had a pronounced effect on the conversion of riociguat to the metabolite M-1, explaining at least partly the high variability of the clearance of riociguat. The renal clearance of both riociguat and M-1 was mainly determined by the renal activity as measured by the creatinine clearance. There was a clear effect of moderate and severe renal impairment on renal clearance; however, due to the limited contribution (less than 10% for riociguat, approximately 20% for M-1) of renal clearance to total drug clearance, the influence of renal impairment on the total clearance is only weak and alterations in exposure are expected to be moderate.

A further PPK study [**Study 15593**] re-examined the structural PK models for riociguat and M-1 in renally and hepatically impaired patients following a single oral dose of 1.0 mg or 0.5 mg riociguat using plasma and urine concentration data from the Phase I **Studies 15000** and **11915** and **Studies 15001** and **11916**. In this study, riociguat clearance was dominated by the conversion to the main metabolite M-1 (CNPM) with a typical value of 1.2 L/h. This clearance term displayed high variability with a high level of unexplained variability. The healthy groups also displayed high variability in this clearance term. The clearance contribution due to non-renal mechanism (CNPX) had a typical value of 0.34 L/h and was described in the final model as being proportional to the fraction unbound. The non-renal clearance of M-1 (CLNM) has a typical value of 1.76 L/h and described in the final model to be proportional to derived creatinine clearance at baseline.

No influence of biomarker for hepatic function (for example, albumin, bilirubin) and Child Pugh classification on any of the clearance contributions and thus on the total clearance could be established for either riociguat or M-1. The total clearance of riociguat CLP= 1.912 L/h was a sum of renal filtration CRFP= 0.174 L/h, renal secretion CRSP= 0.068 L/h, non-renal clearance CNPX= 0.496 L/h and the metabolism to M-1 CNPM= 1.2 L/h.

Study 12653 represented an exploratory population PK/PD analysis of riociguat in patients with pulmonary hypertension. The results indicated that the PKs of both riociguat and M-1 could be described by a one-compartmental models, parameterised in terms of apparent clearance, apparent volume of distribution, and a first-order absorption rate constant. There was no evidence for time- or dose-dependent alterations in riociguat/M-1 PKs over the three months course of the study. Age and bilirubin concentration (hepatic capacity) were identified as covariates inverse correlating with the individual apparent clearance of riociguat in the **Study 12166**. Co-medication with bosentan was also tested as a possible covariate, but did not reach the predefined level of significance probably due to the low number of positive cases (N=4), although the co-medication was estimated to lead to an 50% increase in the clearance of riociguat. Smoking, once again, appeared to be correlated with an increased clearance of riociguat. Overall the variability in the PK of riociguat was moderate to high, especially regarding the absorption rate and the clearance. Regarding the PK model of the metabolite M-1, a correlation between the bilirubin concentration and the apparent volume of distribution was

identified, probably caused by an inverse correlation between the bilirubin concentration and the formation of the metabolite M-1. In addition, the apparent clearance and apparent volume of distribution of M-1 were linearly related to the weight of the patient.

Study 13817 examined the PK models for riociguat and its active metabolite M-1 based on the data from four Phase III studies, **PATENT-1** (**12934**), **CHEST-1** (**11348**) and the respective long term extensions (LTE) **PATENT-2** (**12935**), and **CHEST-2** (**11349**) which examined patients with pulmonary arterial hypertension and thromboembolic pulmonary hypertension. As in the previous PPK study riociguat and M-1 PKs in the Phase III studies were well described by one-compartmental models, parameterised in terms of apparent CL, apparent V, and a first-order absorption rate constant.

Bilirubin concentration (hepatic capacity) was identified as covariate inversely correlating with the individual apparent CL of riociguat. The covariates effects (creatinine clearance, bilirubin, co-medication and smoking) on CL reduced the unexplained inter-individual variability (IIV) of CL from 48.3% to 41.2%. The effect of the covariate body weight on the V reduced the unexplained IIV of V from 27.1% to 25%.

Patients receiving bosentan as a co-medication showed higher CL (35.6% increase in the clearance of riociguat) compared to patients without bosentan as a co-medication. Smoking correlated with an increased CL of riociguat. CL of riociguat in smokers showed high variability, this can be explained by the different smoking intensity by different patients. This was also consistent with the estimated high CL in smokers and patients receiving concomitant bosentan showed in previous studies (**Studies 12653, 14362 and 11910**).

There was no evidence for time- or dose-dependent alterations in riociguat PKs over the time course of the Phase III studies.

Regarding the PK model of M-1, a correlation between bilirubin concentrations and the apparent V was identified. This covariate term (bilirubin on V) probably reflected the change in the “bioavailability” of M-1 , with less compound being generated out of riociguat with decreasing liver capacity (increasing bilirubin concentration). There were limited information/data to reliably estimate the absorption (metabolism) parameter. The covariate creatinine clearance on CL reduced the unexplained IIV of CL from 42% to 37%. A correlation between weight of the patients and apparent V of M-1 was also identified.

Study 14851 examined the PK properties of riociguat in adult non-smokers and smokers in regards to the induction of CYP1A1 by cigarette smoke. In this study cigarette smoking was associated with a very high inter-individual variability which could not be fully accounted for by the PBPK model using reported variabilities in the population simulations, especially if smoking status was not correctly indicated by individual subjects. For non-smokers, liver clearance (CLliv) accounted for 93% of total clearance on average, whereas lung and intestinal clearance contributions (CLlng, CLint) were <1% and 2%, respectively. Unchanged riociguat excreted in faeces also was <1% of total clearance, whereas excretion in urine via glomerular filtration accounted for 15% of total clearance. Biliary secretion (Bile) was 14% of hepatic clearance with CYP-mediated metabolism of riociguat accounting for 86% with individual clearances split according to their relative expression profiles. By contrast, for smokers, CLliv was reduced to 81% of total clearance on average whereas clearance in lungs, the site of highest exposure to polycyclic aromatic hydrocarbons in tobacco smoke and highest induction of CYP1A1, accounted for 4% of total clearance. The still very high contribution of liver as main eliminating organ is not surprising, since it contains a significantly higher microsomal content (45 mg/g liver) than lung (3.8 mg/g lung) This physiological effect was well described by the established PBPK model based on relative expression data for all relevant organs. Therefore, the liver was the most sensitive organ to relative changes in CYP1A1 contents. For one smoker as an example CYP1A1 contribution was 69% of hepatic clearance compared to only 6% in one non-smoker indicating a significant increase in protein activity for this enzyme.

Study 15463 investigated the expected PK properties of riociguat in children of various age groups. The existing adult[3] PPK model was expanded to the paediatric population using data from the ICRP database as well as information from the literature to cardiac output of PAH and PPHN patients and by applying physiological scaling. The paediatric PPK[3] models for riociguat were then used to explore the PK in this age group compared to adults. For PAH children, in the age range between 6 and 18 years, plasma exposure at steady state was comparable with the exposure in adults, when riociguat is dosed on a mg/kg basis. Below 6 years, there was a tendency towards lower plasma levels in paediatric PAH patients with a minimum around 1 to 2 years of age. Below one year, the riociguat plasma exposure tended to increase again and 1-month old children had a plasma exposure comparable to that of adults. Plasma exposure was similar on Day 1 and Day 21 comparing PPHN children with adults; on Day 7, however, exposure was approximately twice as high.

Study 14678 evaluated possible sparse sampling designs for the planned multiple-dose paediatric study and identified two related sparse sampling designs that allowed the accurate and precise estimation of AUC, Cmax and Ctrough both after the first dose and during steady state in the planned study.

4. Evaluator's overall conclusions on pharmacokinetics

4.1. Absorption

Riociguat was rapidly absorbed with a Tmax of 45 min and a $t_{1/2}$ of 6.78 h. The absolute BA of riociguat was 94.3%, whereas, the relative BA of an oral tablet to an oral solution was 84.1%. The 0.5 and 1.0 mg riociguat IR tablets used in clinical trials were bioequivalent with the corresponding doses of the to-be-marketed formulations. Topical release of riociguat granules via the Enterion capsule in the distal small bowel and ascending colon resulted in lower riociguat exposure than following oral administration. In general, following a high fat, high calorie meal, riociguat Cmax was 25 to 35% lower, AUC was slightly lower (14%) or unaffected and Tmax increased 2 to 4–fold compared with riociguat PKs in the fasted state. Following dose-escalation (0.5, 1.0, 1.5, 2.0, and 2.5 mg), the riociguat Tmax and $t_{1/2}$ ranged from 0.75 to 1.0 hours and 5.4 to 7.2 hours, respectively and AUC and Cmax were dose proportional. Riociguat steady state occurred 3 days following oral doses of 0.5 mg, 1.0 mg, 1.5 mg TID, 2.5 mg BID and 2.5 mg TID riociguat IR tablets. Dose-proportional increases in $AUC_{(0\text{-}7)ss}/AUC_{(0\text{ to }12)ss}$ and Cmax,ss were observed after 10 days. Following TID dosing, mean accumulation ratios for AUC were between 110% and 157% and mean accumulation ratios for Cmax between 105 and 146%.

4.2. Distribution

The apparent volume of distribution of riociguat ranged from 30.8 to 43.1 L indicating a low affinity for tissues. Plasma protein binding for riociguat in humans was approximately 95% *in vitro*, with serum albumin and α1-acidic glycoprotein being the main binding components. The protein-bound fraction determined *ex vivo* was 96 to 97% for riociguat and 97% for M-1. Approximately 20% of drug-related radioactivity following a 1 mg dose of [^{14}C] riociguat solution was distributed into blood.

[3] Sponsor correction: PBPK model (physiology based pharmacokinetic model)

4.3. Metabolism

In vitro CYP reaction phenotyping studies in human liver, intestinal and lung microsomes established that CYP2C8, CYP2J2, and CYP3A4 contribute to a similar extent to the formation of the major metabolite M-1 in the liver, whereas CYP3A4 and CYP2J2 almost equally catalyse M-1 formation in the intestine. CYP1A1 also significantly contributed to the N-demethylation of riociguat in microsomes from human liver and lung tissue. Biotransformation of riociguat was much more pronounced in lung microsomes of smokers. M-1 is a soluble guanylate cyclase (sGC) stimulator but has 3- to 10-fold lower potency than riociguat. Subjects with high plasma concentrations of the parent compound had lower concentrations of M-1, whereas, subjects with low plasma concentrations of riociguat had higher concentrations of M-1. Following single oral IR tablet doses of 1 mg riociguat the Cmax and AUC of M-1 was 7.7 µg/L and 195.3 µg.h/L, respectively. M-1 Tmax occurs later than that than that of riociguat (4h cf 0.75h, respectively) and its $t_{1/2}$ is longer (13.2 h cf 6.8 h, respectively). M-1 displayed linear PKs after single and multiple doses of riociguat IR tablets. The accumulation in AUC for M-1 following riociguat TDS was approximately 4- to 5-fold. Thorough examination of a panel of 1069 genetic variations in 172 drug metabolising genes and transporters did not identify any genetic factors that contribute to the PK variability of riociguat.

4.4. Excretion

Riociguat is eliminated by metabolic degradation and direct excretion of unchanged active compound. The proportion of [^{14}C] riociguat associated radioactivity excreted in urine and faeces ranged from 33.4% to 45.6% and 47.9% to 60.6%, respectively, with the main portions excreted with 48 hours and 96 hours, respectively. The renal clearance of M-1 was approximately 0.5 L/h.

4.5. Intra- and inter-individual variability

Inter-individual variability of riociguat $t_{1/2}$, AUC/D and Cmax/D was 76.9%, 89.7% and 42.0%, respectively, whereas, intra-individual variability for AUC/D and Cmax/D was 18.4% and 23.9%.

4.6. Special populations

No studies examined the PKs of riociguat in either pregnant or breast-feeding mothers or children.

4.6.1. Target population

In patients with suspected PH the Cmax and AUC of riociguat and M-1 increased dose-dependently. The Tmax occurred at 0.25 to 1.5 h and the $t_{1/2}$ was between 10 h and 12 h for riociguat.

4.6.2. Subjects with impaired hepatic function

In non-smokers, riociguat Tmax was ≤ 1.5 hour in patients with Child Pugh A and Child Pugh B hepatic impairment and healthy controls and the mean Cmax and Cmax,norm values of total riociguat were also similar. By contrast, riociguat $t_{1/2}$ was prolonged in Child Pugh A and Child Pugh B subjects (12.7 hours and 17.5 hours) compared to healthy controls (9.2 hours and 8.9 hours). Exposure in terms of mean AUC of unbound riociguat increased by 60% in Child Pugh A subjects and by 88% in Child Pugh B subjects compared to healthy controls.

4.6.3. Subjects with impaired renal function

In non-smokers with renal impairment, riociguat clearance was lower, $t_{1/2}$ was longer, and mean AUC was higher (at least by 100%) than in healthy controls. Nevertheless, exposures

observed in subjects with renal impairment were highly variable and the ranges of exposures observed in subjects with mild, moderate, and severe renal impairment overlapped those observed in healthy controls.

4.6.4. Age and gender

Riociguat AUC was approximately 40% higher in elderly compared to young subjects - this difference was in part accounted for by differences in weight. No notable age-related change in Cmax was observed.

4.6.5. Japanese subjects

Following single oral doses of 0.5, 1.0 and 2.5 mg riociguat in Japanese subjects riociguat Tmax and $t_{1/2}$ ranged from 1 hour to 1.5 hours and 4.15 hours to 7.59 hours, respectively. Cmax and AUC increased with dose, but AUC increased more than dose-proportionally.

Following multiple oral doses of 1.0 and 1.5 mg 3 times a day over 7 days in Japanese males, riociguat PKs achieved steady state regardless of dose. Riociguat Tmax,ss was 1.5 hours and $t_{1/2}$ ranged from 9.2 to 9.7 hours. Riociguat AUC_{ss} and Cmax,ss were dose proportional. Cmax,ss was 1.18 - 1.25 times higher than that on Day 1, whereas, the $AUC_{(0-7)}$ss was almost the same with AUC on Day 1.

4.6.6. Chinese subjects

Following single dose and multiple oral doses of 1.0 mg and 2.0 mg TDS over 6 days in Chinese subjects, riociguat Tmax and Tmax,ss was 1 h. Mean $t_{1/2}$ after a single dose and at steady state g was 3.5 hours 5 hours, respectively. Mean exposure increased at steady state by 176% and 156% for the 1 mg and 2 mg doses, respectively. Smoking reduced riociguat exposure by at least 60%.

4.7. Drug-drug interactions

4.7.1. Omeprazole

Pre- and co-treatment with omeprazole decreased riociguat Cmax and AUC by 35% and 26%, respectively. Riociguat $t_{1/2}$ and CL/f increased from 7.9 to 9.0 h and from 4.3 to 5.8 L/h, respectively. By contrast Omeprazole had no effect on M-1 exposure.

4.7.2. Maalox

Co-administration with Maalox decreased riociguat Cmax and AUC by 56% and 34%, respectively, whereas $t_{1/2}$ and CL increased from 5.9 to 8.6 h and 5.3 to 8.1 L/h, respectively. Co-administration of Maalox also decreased M-1 Cmax and AUC by 44% and 33%, respectively.

4.7.3. Ranitidine

In non-smoking subjects $AUC_{(0-7)}$ of riociguat after co-administration with 150 mg ranitidine was 393 µg*h/L after the first dose compared to 439 µg*h/L in the multiple dose escalation study, where riociguat was given alone.

4.7.4. Ketoconazole - strong CYP3A4 and P-gp inhibitor

Pre- and co-treatment with ketoconazole increased riociguat Cmax and AUC by 46% and 150%, respectively. Riociguat $t_{1/2}$ increased from 7.3 h to 9.2 h, whereas, CL decreased from 6.1 L/h to 2.4 L/h. The amount of riociguat excreted via urine increased from 7.9% to 17.1%. Renal clearance decreased slightly from 0.41 L/h to 0.38 L/h. Pre- and co-treatment with ketoconazole decreased M-1 Cmax and AUC by 49% and 24%, respectively.

4.7.5. Clarithromycin - strong and selective CYP3A4 and weak-to-moderate P-gp inhibitor

Co-administration of clarithromycin increased the AUC of riociguat and M-1 by 41% and 19%, respectively, but had no effect on Cmax values.

4.7.6. Midazolam - sensitive CYP3A4 probe substrate

PKs of midazolam were not affected by concomitant administration with 2.5 mg riociguat.

4.7.7. Warfarin - CYP2C9 substrate

Steady-state riociguat did not affect the AUC and Cmax of warfarin. Single-dose administration of warfarin led to a 16% decrease in riociguat Cmax,ss, whereas it did not affect the $AUC_{t,ss}$ of riociguat or M-1.

4.7.8. Aspirin

The PKs of riociguat and M-1 were not affected by co-administration of Aspirin.

4.8. Population PK studies

The major outcomes identified in the PPK studies included:

- Smoking correlated with an increased clearance of riociguat.
- CL of riociguat in smokers showed high variability.
- The renal clearance of both riociguat and M-1 was mainly determined by the renal activity as measured by the creatinine clearance.
- In subjects with hepatic or renal impairment, the biomarkers for hepatic function (for example, albumin, bilirubin) and Child Pugh classification did not affect the total clearance of either riociguat or M-1.
- In patients with pulmonary hypertension and thromboembolic pulmonary hypertension, riociguat and M-1 PKs could be described by a one-compartmental model each, parameterised in terms of apparent clearance, apparent volume of distribution, and a first-order absorption rate constant.

Bilirubin concentration (hepatic capacity) was identified as covariate inversely correlating with the individual apparent CL of riociguat.

The covariates effects (creatinine clearance, bilirubin, co-medication and smoking) on CL reduced the unexplained IIV of CL from 48.3% to 41.2%. The effect of the covariate body weight on the V reduced the unexplained IIV of V from 27.1% to 25%.

Patients receiving bosentan as a co-medication showed higher CL (35.6% increase in the clearance of riociguat) compared to patients without bosentan as a co-medication.

There was no evidence for time- or dose-dependent alterations in riociguat PKs over the time course of Phase III studies.

For M-1, a correlation between the bilirubin concentration and the apparent volume of distribution was identified. In addition, the apparent clearance and apparent volume of distribution of M-1 were linearly related to the weight of the patient.

- For non-smokers, liver clearance accounted for 93% of total clearance on average, whereas lung and intestinal clearance contributions were <1% and 2%, respectively. Unchanged riociguat excreted in faeces also was <1% of total clearance, whereas excretion in urine via glomerular filtration accounted for 15% of total clearance. Biliary secretion was 14% of hepatic clearance with CYP-mediated metabolism of riociguat accounting for 86% with individual clearances split according to their relative expression profiles.

- For smokers, CLliv was reduced to 81% of total clearance on average whereas clearance in lungs, the site of highest exposure to polycyclic aromatic hydrocarbons in tobacco smoke and highest induction of CYP1A1, accounted for 4% of total clearance.
- In children with PAH, in the age range between 6 and 18 years, plasma exposure at steady state was comparable with the exposure in adults, when riociguat is dosed on a mg/kg basis. Below 6 years, there was a tendency towards lower plasma levels in paediatric PAH patients with a minimum around 1 to 2 years of age. Below one year, the riociguat plasma exposure tended to increase again and 1-month old children had a plasma exposure comparable to that of adults.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 3 (below) shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 3. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on pulmonary and systemic haemodynamics	11874	Impact of riociguat (1, 2.5 and 5 mg doses) in patients with suspected PH
Secondary Pharmacology	Effect on bone resorption and formation markers	13790	Effect of multiple-dose riociguat (2.5 mg TDS over 14 days)
	Effect on haemodynamics	11258	Oral doses of 0.25, 0.5, 1.0, 2.5, 5.0 riociguat administered as solution and 2.5 mg as a tablet.
		11259	Effects of a high-fat, high-calorie meal
		11260	Multiple oral doses of 0.5 mg, 1.0 mg, 1.5 mg TID, 2.5 mg BID or 2.5 mg TID given as IR tablet over 10 days
Gender and Age-on PD Response	Effect of age and gender	11914	PDs of riociguat, in young and elderly healthy volunteers of both genders, following a 2.5 mg oral tablet dose
PD Interactions	Nitroglycerin	14360	Effect on BP and heart rate
	Sildenafil	11917	Impact on pulmonary and systemic haemodynamics

PD Topic	Subtopic	Study ID	*
	Omeprazole	11262	Haemodynamics
	Maalox	11890	Haemodynamics
	Warfarin	11918	Prothrombin time and factor VII
	Aspirin	14204	Bleeding time and platelet aggregation

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

6. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

6.1. Mechanism of action

Riociguat is a stimulator of the soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO).

When NO binds to sGC, the enzyme catalyses synthesis of the signalling molecule cyclic guanosine monophosphate (cGMP). Intra-cellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis and inflammation.

Pulmonary hypertension (PH) is associated with endothelial dysfunction, impaired synthesis of nitric oxide and insufficient stimulation of the NO-sGC-cGMP pathway.

Riociguat has a dual mode of action. It sensitises sGC to endogenous NO by stabilising 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.

6.2. Pharmacodynamic effects

6.2.1. Primary pharmacodynamic effects

6.2.1.1. Target population

Study 11874 examined the impact of riociguat (1, 2.5 and 5 mg doses) on pulmonary and systemic haemodynamics and gas exchange in patients with suspected pulmonary hypertension due to pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension or interstitial lung disease. Due to a large drop in systemic blood pressure (BP) following the 5 mg dose of riociguat in 1 subject in the first part of the study the dose escalation did not proceed beyond this level. The 2.5 mg dose was chosen from Study Part A as an effective dose with a good safety profile as the starting dose for Study Part B.

Riociguat 2.5 and 1 mg induced similar and clinically relevant and statistically significant reductions in pulmonary artery pressure (PAP), systolic blood pressure (SBP), pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR) and a clinically relevant and statistically significant increase in cardiac index (CI), (*P* between 0.0047 and <0.0001). Reductions in PVR and SVR were more pronounced in the riociguat 1 mg dose group (296

versus 168 dyn*s*cm-5 and 690 versus 546 dyn*s*cm-5, respectively), while CI increased slightly more in subjects receiving riociguat 2.5 mg (0.95 versus 0.65 L/min/m2).

Both doses of riociguat were superior in reducing SBP, PVR, and SVR and increasing CI than nitrous oxide (NO), (*P* between 0.0220 and <0.0001). The differences in PAP between riociguat for any of the 2 doses and NO did not reach statistical significance (*P* between 0.0546 and 0.0539).

The results demonstrate that riociguat favourably influenced all main hemodynamic parameters in subjects with pulmonary hypertension. The study outcome proves that sGC stimulation as exerted by riociguat has the expected positive hemodynamic effects in patients with this disease.

6.2.2. Secondary pharmacodynamic effects

6.2.2.1. Healthy subjects

Study 13790 investigated the effect of multiple-dose riociguat (2.5 mg TDS over 14 days) on bone resorption and formation markers. Mean cGMP concentrations in plasma increased by 48.6% from 5.67 nmol/L to 8.24 nmol/L during riociguat treatment. Mean excretion of cGMP into urine increased by 136%.

Mean bone formation parameters in serum such as PINP, bAP, and osteocalcin decreased significantly by 5.5%, 12%, and 8.3%, respectively, during riociguat treatment compared to placebo. Mean serum PTH during riociguat treatment was not different to mean PTH during placebo treatment. All PTH values were within the normal range and without an obvious treatment effect.

Riociguat also demonstrated direct effects on parameters of renal function. Directly after administration of the first 2.5 mg dose (0 to 4 hours), there was an increase in urinary excretion of calcium, sodium, potassium, and creatinine. These effects are considered as markers for an increase in GFR due to dilation of the *vas afferens* and an increased filtration pressure resulting in an increase in mean creatinine clearance by 7.5% (*P*<0.0001).

Over the whole 14 day-treatment period riociguat resulted in an increased urinary excretion of calcium by 0.97 mmol (approximately 40 mg) per day corresponding to an increase by 22% (*P*<0.0001) compared to placebo. This effect is considered to be biologically relevant.

Mean 24-hour urine volume and the amount of sodium and potassium excreted in urine per 24 hours were not significantly different between riociguat and placebo treatments. Mean serum calcium decreased significantly by 0.03 mmol/L (1.2%), serum uric acid by 27.5 µmol/L (7.9%), and creatinine by 5.1 µmol/L (5.4%) (*P*=0.0007, *P*<0.0001, and *P*<0.0001, respectively). All individual values remained within the normal range.

After 48 - 72 hours of riociguat treatment, red blood cell count (-0.15 T/L, -3.17%) haematocrit (-0.01, -3.57%), and haemoglobin (-5g/L, -3.56%) decreased significantly. This was associated with a significant increase in reticulocyte count after 6 - 7 days. There was no riociguat effect on MCV, MCH, and MCHC. Total serum protein and serum albumin decreased by 1.5% and 1.1%, respectively. All these observations, especially their mutual consistency, indicate a common underlying cause, i.e. haemodilution by increase in intravascular volume after administration of the vasodilator riociguat in healthy, young men.

Due to this haemodilution, parameters determined in serum/plasma were normalised to serum albumin. This normalisation resulted in small numerical changes but the qualitative results remained the same.

Normalisation of serum calcium to serum albumin decreased the difference between riociguat and placebo treatments to only 0.016 mmol/L or 0.69% (*P*=0.0107), which is considered as biologically not relevant. Following normalisation to albumin serum renin and cGMP significantly increased by 48.5 and 50.5%, respectively.

6.2.2.2. Single-dose escalation

Study 11258 investigated the secondary PDs of riociguat after single oral doses of 0.25, 0.5, 1.0, 2.5, 5.0 administered as solution and 2.5 mg as a tablet. Mean heart rate measured over 1 min increased dose dependently from 4 BPM in the 1.0 mg dose to 11 BPM in the 5.0 mg dose.

Changes observed with the 2.5 mg solution and 2.5 mg tablet were similar. Mean heart rate recorded as "vital sign" increased dose-dependently and reached peak values 1 to 2 h after administration of 1, 2.5, and 5 mg solution. Mean changes 1 to 2 h post-baseline ranged from 12.0 (2.5 mg solution) to 16.6 BPM (5 mg solution). Individual maximum increases in heart rate were 26 BPM (2.5 mg solution) and 28 BPM (5 mg solution) 2 h after drug administration and 38 BPM (2.5 mg solution) and 47 BPM (5 mg solution) 6 h after drug administration. The increase in heart rate is regarded as the most sensitive parameter for the reduction of the peripheral vascular resistance in healthy young subjects.

A decrease in diastolic blood pressure (DBP) 1 h after drug application was observed for the 2.5 mg and 5.0 mg dose. Mean DBP decreased dose-dependently. Mean changes 0.5 to 2 h post-baseline ranged from +2.8 mmHg (0.25 mg solution) to -7.7 mmHg (5 mg solution). Individual maximum decreases in DBP ranged from 3 mmHg (0.25 mg solution) and 20 mmHg (2.5 mg solution) 0.5 to 2 h post-baseline. The maximum individual decrease with the 5 mg dose was 12 mmHg; changes with placebo ranged between -4 and -10 mmHg during this observation period. SBP was not significantly reduced, since BP regulation in healthy young subjects keeps the BP in the normal range as far and long as possible.

Parallel to the reduction of peripheral vascular resistance, an increase of the PD-driven AEs were observed. Orthostatic hypotension was observed in 2 subjects each in the 2.5 mg tablet and 5.0 mg solution group, no orthostatic hypotension was observed in the 0.25 dose group.

Concurrently, plasma renin activity, noradrenaline, and plasma cGMP increased as expected with the application of a sGC stimulator. Again, statistically significant and dose-dependent changes from placebo were observed from doses of 1.0 mg onwards. Riociguat at the doses tested had no effect on angiotensin II, aldosterone, and platelet aggregation.

6.2.2.3. Effect of food

Study 11259 examined the effects of a high-fat, high-calorie American breakfast on the PDs of 2.5 mg dose riociguat IR tablet. Compared to baseline, mean heart rate increased for up to 3 h following the administration of study drug in both treatment groups. Following the 2.5 mg dose in fasted subjects the increase in heart rate ranged from 4.5 to 9.8 BPM and in the fed group ranged from 4.7 to 12.8 BPM.

6.3. Time course of pharmacodynamic effects

The hemodynamic effects of riociguat included a spontaneous increase in pulse rate by 8.3 BPM after the first 24 hours of riociguat treatment. This effect was reduced to 3.6 BPM after 14 days of riociguat treatment. Mean SBP was 114.8 mmHg at baseline. It decreased by 4.2 mmHg after the first 24 hours and by 10 mmHg after 14 days.

Study 11260 investigated PDs of riociguat following multiple oral doses of 0.5 mg, 1.0 mg, 1.5 mg TID, 2.5 mg BID or 2.5 mg TID given as IR tablet over 10 days in healthy subjects. A decrease in BP was not seen at the lowest dose (0.5 mg TID), however BP effects were seen for all other doses. Lowering of BP was more consistently observed and already seen at lower doses for the DBP than for the SBP. Maximum placebo-corrected mean decreases in SBP, i.e., lowest values, were 0.8, -1.7, 0.5, -10.1, and -6.3 mmHg on 0d, and -5.8, -7.9, 2.0, -11.8, and -10.1 mmHg on 9d for the 5 dose steps (0.5 mg TID, 1.0 mg TID, 1.5 mg TID, 2.5 mg BID, and 2.5 mg TID), respectively. Maximum placebo-corrected mean decreases of DBP, i.e., lowest values, were -1.1, -7.5, -6.5, -8.5, and -5.5 mmHg on 0d, and -3.0, -5.8, -1.5, -10.6, and -7.1 mmHg on 9d for the 5 dose steps, respectively. An increase of the heart rate was observed for all dose steps. Maximum

mean placebo-corrected differences to baseline were 4.3, 6.6, 11.2, 11.3, and 13.2 BPM on 0d, and 3.1, 8.4, 8.7, 7.0, and 6.9 BPM on 9d for the 5 dose steps, respectively. The effect on the heart rate was slightly more pronounced than at steady state.

Dose related effects which were less pronounced on day 9 were also seen for the increase of plasma renin activity (maximum placebo-corrected mean increases of 0.198, 0.175, 0.433, 0.415, and 0.545 ng/mL/h on day 0, and 0.223, 0.235, 0.265, 0.135, and 0.516 ng/mL/h on day 9 for the 5 dose steps, respectively).

For cGMP in plasma, dose related effects were more pronounced on 9d than on 0d (maximum placebo-corrected mean increases of -0.390, 1.785, 2.264, 1.387, and 0.437 nmol/L on 0d, and -0.151, 1.863, 2.442, 3.017, and 2.035 nmol/L on 9d for the 5 dose steps, respectively).

6.4. Relationship between drug concentration and pharmacodynamic effects

Riociguat plasma concentrations were significantly correlated with the reductions in PAP, SBP, PVR, and SVR and the increase in CI from baseline (Table 4). By contrast, **Study 13817**, which examined the PK/PD relationship for riociguat in four Phase III studies, identified that there was no correlation between the change from baseline in the 6MWD and the riociguat AUC on day 84 (Figures 3 and 4).

Table 4. Correlation between PAP, SBP, PVR, SVR and CI and BAY 63-2521 drug concentration

Statistics on Spearman correlation between PAP, SBP, PVR, SVR, and CI and BAY 63-2521 drug concentration (subjects valid for pharmacokinetic and pharmacodynamic analysis, n=19)

Parameter	Unit	Correla-tion	95% confidence interval	Two-sided *P*>|Z|
Mean pulmonary arterial pressure (PAP)	mmHg	-0.2550	[-0.3827 ; -0.1274]	<0.0001
Systolic systemic blood pressure (SBP)	mmHg	-0.5569	[-0.6531 ; -0.4607]	<0.0001
Pulmonary vascular resistance (PVR)	$dyn*s*cm^{-5}$	-0.4733	[-0.5815 ; -0.3650]	<0.0001
Systemic vascular resistance (SVR)	$dyn*s*cm^{-5}$	-0.5910	[-0.6879 ; - 0.4942]	<0.0001
Cardiac index (CI)	$L/min/m^2$	0.4543	[0.3411 ; 0.5674]	<0.0001

Figure 3. Study 13817 Individual changes in 6MWD in patients classified to WHO class 3 (3 and 4) vs. AUC stratified by smoking status, bosentan and iloprost co-medication in PATENT-1, PATENT-2, CHEST-1 and CHEST-2 studies, respectively

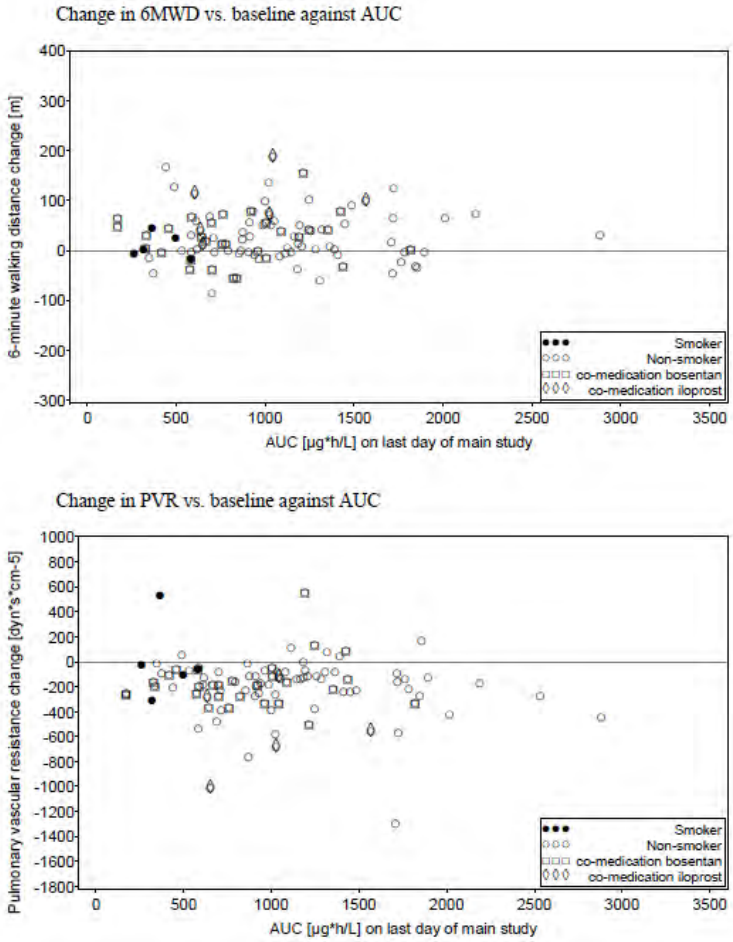
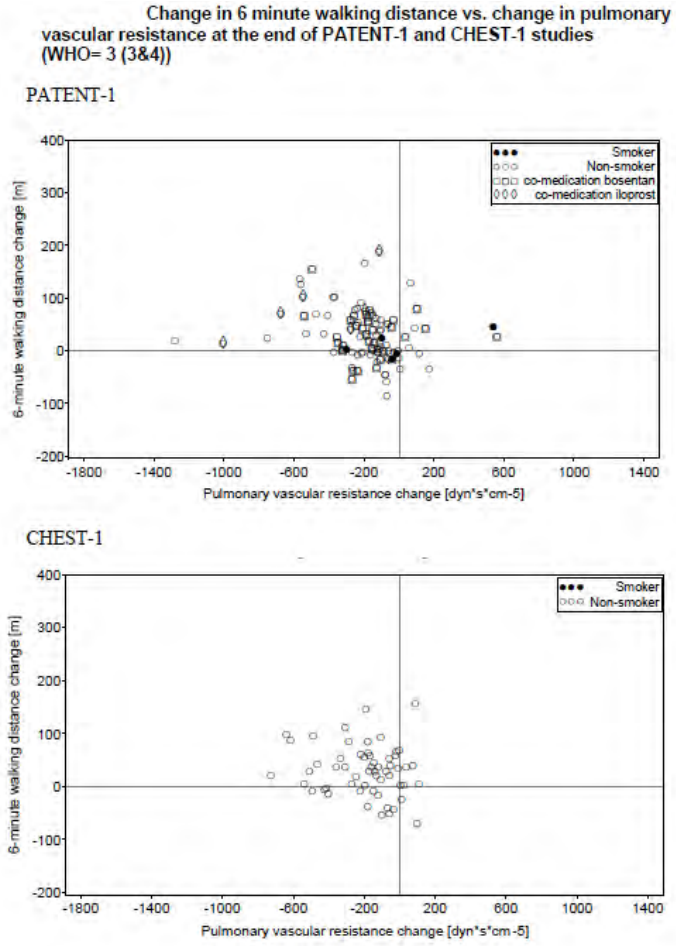


Figure 4. Study 13817 Relationship between change in 6MWD vs. the change in pulmonary vascular resistance (PVR).



6.5. Genetic-, gender- and age-related differences in pharmacodynamic response

Study 11914 compared the PDs of riociguat, in young and elderly healthy volunteers of both genders, following a 2.5 mg oral tablet dose. In this study there were no distinct trends for the subgroups (young males, young females, elderly males, and elderly females) for the change from baseline for the mean pulse rate and QRS intervals when comparing riociguat to the placebo group. The change from baseline in the mean QT was more variable although a greater decrease appears evident for the female subgroups compared to the male subgroups. However, for change from baseline in the mean QTcF interval, the effect of riociguat on this ECG variable is somewhat greater for the female subgroups compared to the male subgroups, a 6-12 msec prolongation compared to a 5-7 msec prolongation, respectively.

> Comment: In Australia, the European Union's Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs CHMP/ICH/2/04 has been adopted in Australia by the TGA, with the following notation:
>
> *"QT prolongation would be of regulatory concern if either the estimated QT prolongation was >5ms OR the upper bound of the 95% confidence interval was >10ms".*

QTcF in both the young and elderly female groups and the elderly male group were prolonged by >5msec one hour after dosing compared with the matching placebo groups. In the absence of

qualifying data from the Phase II and III studies this finding would in general warrant the need for a thorough QT study to be undertaken prior to drug registration. However, as discussed in Sections under *Safety, Electrocardiogram* and *Safety issues with the potential for major regulatory impact* of this report, healthy subjects do not tolerate riociguat administration; therefore, a Thorough QT study was not possible. In addition, the two pivotal clinical trials, did not identify any relevant changes in QT, QTcB and QTcF duration nor were there any events reported that were linked to QT prolongation.

6.6. Pharmacodynamic interactions

6.6.1. Nitroglycerin

Study 14360 evaluated the PD interaction (effect on BP and heart rate) between riociguat 2.5 mg and a standard dose of sublingual nitroglycerin in healthy male subjects. A single sublingual dose of 0.4 mg nitroglycerin administered 8 hours after pre-treatment with a single oral dose of 2.5 mg riociguat resulted in a significantly more pronounced maximum decrease in seated SBP than a single nitroglycerin dose after placebo pre-treatment. Such a significant difference was not detected when nitroglycerin was administered 24 hours after riociguat pre-treatment.

6.6.2. Sildenafil

Study 11917 examined the impact on pulmonary and systemic haemodynamics of single doses of 0.5 mg and 1 mg of riociguat in subjects with pulmonary arterial hypertension treated with sildenafil 20 mg TDS for at least the past 6 weeks. No significant post-baseline changes in the primary PD parameters PAPmean and PVR were observed after riociguat administration on top of a stable Sildenafil treatment. No significant effect on SBP was observed after riociguat administration on top of a stable sildenafil treatment. A significant although clinically irrelevant decrease in mean DBP (-3.1 mmHg) was observed after the 1 mg riociguat dose as well as a significant and clinically irrelevant increase in mean HR (+3.4 BPM) after the 0.5 mg riociguat dose. No clinically relevant changes in any of the blood gas parameters (PaO2, PaCO2, PvO2, SaO2, and SvO2) were detected after sildenafil and riociguat administrations.

6.6.3. Omeprazole

Study 11262 examined the PDs of riociguat following administration of riociguat given as a 2.5 mg IR-tablet single dose without and with a 4 day pre- and co-treatment of omeprazole 40 mg od. The mean heart rate increased continuously until 8 h after drug administration by a maximum of 12 BPM compared to baseline when riociguat was given alone and by a maximum of 10 BPM when given in combination with omeprazole. Mean SBP changes within 8 h post-baseline ranged between -3.2 and +1.0 mmHg when riociguat was given alone and between -3.8 and -0.8 BPM in combination with omeprazole. Mean DBP decreased by 4.3 to 8.7 mmHg within 2 and 8 h post-baseline when riociguat was given alone and by 0.8 to 4.2 mmHg when given in combination with omeprazole.

6.6.4. Maalox

Study 1189 examined the PDs of a single oral 2.5 mg IR tablet dose of riociguat when co-administered with 10 mL Maalox 70 mval suspension compared to a single oral 2.5 mg IR tablet dose alone in healthy male subjects. The mean heart rate increased by a maximum of 12.5 BPM 6 h after drug administration compared to baseline when riociguat was given alone and by a maximum of 10.4 BPM 6 h after drug administration when given in combination with Maalox. Mean SBP decreased by a maximum of 6.3 mmHg 4 h after drug administration compared to baseline when riociguat was given alone and by a maximum of 2.5 mmHg 6 h after drug administration when given in combination with Maalox. 8 h after drug administration, mean SBP had increased slightly by 0.2 mmHg when BY 63-2521 was given in combination with Maalox. The mean DBP decreased by a maximum of 3.4 mmHg 1.5 h after drug administration compared to baseline when riociguat was given alone and by a maximum of 3.2 mmHg 6 h after

drug administration when given in combination with Maalox. 1.5 h after drug administration, mean DBP had increased slightly by 0.7 mmHg when BY 63-2521 was given in combination with Maalox.

6.6.5. Warfarin

Study 11918 PD interaction, with respect to warfarin, when riociguat and warfarin and riociguat were co-administered to healthy subjects. The statistical analysis demonstrated that, in comparison to placebo, concomitant administration of riociguat 2.5 mg TDS at steady state did not influence the prothrombin time (PT) and factor VII % activity of warfarin, thus demonstrating no relevant PD interaction between riociguat and Coumadin. Regarding decreases in factor II % activity and factor X % activity, the results did not indicate any relevant effect of riociguat on these parameters.

6.6.6. Aspirin

Study 14204 investigated the influence of a combined treatment of a single dose of 2.5 mg riociguat and 500 mg Aspirin on bleeding time and platelet aggregation. Adding riociguat to Aspirin did not reveal a significant prolongation of bleeding time compared to bleeding time after Aspirin administration. In contrast, bleeding time after the combined treatment with riociguat and Aspirin was prolonged significantly in comparison to bleeding time after riociguat alone.

Following riociguat alone, the maximal platelet aggregation (collagen and arachidonic acid stimulations) remained virtually unchanged. Following Aspirin alone or Aspirin in combination with riociguat, mean maximal platelet aggregation (arachidonic acid stimulation) decreased to less than 1% and mean maximal platelet aggregation (collagen stimulation) decreased by approximately 10%.

Following Aspirin alone or Aspirin in combination with riociguat, a pronounced decrease in thromboxane B2 in serum was determined.

All 3 PD measures demonstrated the expected influence of Aspirin on platelet function. Those effects were not augmented by co-administration of Aspirin and riociguat. Riociguat alone did not show any influence on platelet function based on the PD measures performed.

7. Evaluator's overall conclusions on pharmacodynamics

7.1. Summary of the PD

The sponsor provided a wide range of PD studies, which examined the mechanism of action and dose-response relationship of riociguat. In addition, the studies also addressed the effects of riociguat on haemodynamic parameters, pulmonary effects and neurohormonal function, as well as other secondary effects such as bone formation and renal function.

7.1.1. Mode of action

Riociguat is a stimulator of the soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO).Riociguat has a dual mode of action. It sensitises sGC to endogenous NO by stabilising the NO-sGC binding. Riociguat also directly stimulates sGC via a different binding site, independently of NO.

7.1.2. Primary pharmacodynamic effects in the target population

Riociguat 2.5 and 1 mg induced similar and clinically relevant and statistically significant reductions in pulmonary artery pressure, systolic blood pressure, pulmonary vascular resistance and systemic vascular resistance and a clinically relevant and statistically significant increase in cardiac index (CI).

Reductions in PVR and SVR were more pronounced in the riociguat 1 mg dose group (296 versus 168 dyn*s*cm-5 and 690 versus 546 dyn*s*cm-5, respectively), while CI increased slightly more in subjects receiving riociguat 2.5 mg (0.95 versus 0.65 L/min/m^2).

Both doses of riociguat were superior in reducing SBP, PVR, and SVR and increasing CI than nitrous oxide (NO), (*P* between 0.0220 and <0.0001), whereas, the differences in PAP between riociguat for any of the 2 doses and NO did not reach statistical significance (*P* between 0.0546 and 0.0539).

7.1.3. Secondary pharmacodynamic effects in healthy subjects

Following administration of riociguat (2.5 mg TDS over 14 days) mean cGMP concentrations in plasma increased by 48.6% and mean excretion of cGMP into urine increased by 136%.

Riociguat induced an increase in pulse rate by 8.3 BPM after the first 24 hours of riociguat treatment. This effect was reduced to 3.6 BPM after 14 days of riociguat treatment.

Mean SBP decreased by 4.2 mmHg after the first 24 hours and by 10 mmHg after 14 days.

7.1.4. Bone formation

Mean bone formation parameters in serum such as PINP, bAP, and osteocalcin decreased significantly by 5.5%, 12%, and 8.3%, respectively, during riociguat treatment compared to placebo.

Mean serum PTH during riociguat treatment was not different to mean PTH during placebo treatment.

7.1.5. Renal function

Directly following 2.5 mg dose of riociguat (0 to 4 hours), there was an increase in urinary excretion of calcium, sodium, potassium, and creatinine.

Over the 14 day-treatment period riociguat increased urinary excretion of calcium by 22% (*P*<0.0001) compared to placebo.

Mean 24-hour urine volume and the amount of sodium and potassium excreted in urine per 24 hours were not significantly different between riociguat and placebo treatments.

Mean serum calcium decreased significantly by 1.2%, serum uric acid by7.9%, and creatinine by 5.4% (*P*=0.0007, *P*<0.0001, and *P*<0.0001, respectively); however, all individual values remained within the normal range.

After 48 - 72 hours of riociguat treatment, red blood cell count, haematocrit and haemoglobin were significantly reduced by 3.17%, 3.57% and 3.56%, respectively. These changes were associated with a significant increase in reticulocyte count after 6 - 7 days.

Riociguat did not affect mean corpuscular volume (MCV), Mean Corpuscular Hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Following normalisation of serum calcium to serum albumin, renin and cGMP significantly increased by 48.5 and 50.5%, respectively.

7.1.6. Dose escalation

Following single oral doses of 0.25, 0.5, 1.0, 2.5 and 5.0 mg riociguat mean heart rate measured over 1 min increased dose dependently from 4 BPM in the 1.0 mg dose to 11 BPM in the 5.0 mg dose and reached peak values 1 to 2 h.

Individual maximum increases in heart rate were 26 BPM (2.5 mg solution) and 28 BPM (5 mg solution) 2 h after drug administration and 38 BPM (2.5 mg solution) and 47 BPM (5 mg solution) 6 h after drug administration.

Mean changes 0.5 to 2 h post-baseline DBP ranged from +2.8 mmHg (0.25 mg solution) to -7.7 mmHg (5 mg solution).

Riociguat at the doses tested had no effect on angiotensin II, aldosterone, and platelet aggregation.

7.1.7. Effect of a meal

Following a 2.5 mg dose of riociguat IR tablets the heart rate increase ranged from 4.5 to 9.8 BPM in fasted subjects and from 4.7 to 12.8 BPM in subjects following a high-fat, high-calorie meal.

7.1.8. Steady-state versus single doses

Increases in heart rate and plasma renin activity were more pronounced following single doses than at steady state, whereas the effect on cGMP in plasma was more pronounced at steady-state than following a single dose.

7.1.9. Relationship between drug concentration and pharmacodynamic effects

Riociguat plasma concentrations were significantly correlated with reductions in PAP, SBP, PVR, and SVR and increases in CI. **By contrast there was no correlation between 6MWD and riociguat AUC[4].**

7.1.10. Gender and age

Following a 2.5 mg oral tablet dose there were no distinct trends for the subgroups (young males, young females, elderly males, and elderly females) for the change from baseline for the mean pulse rate and QRS intervals when comparing riociguat to the placebo group.

QTcF in both the young and elderly female groups and the elderly male group were prolonged by >5msec one hour after dosing compared with the matching placebo groups.

7.1.11. Effect on QTcF

QTcF in both the young and elderly female groups and the elderly male group were prolonged by >5msec one hour after dosing compared with the matching placebo groups. In the absence of qualifying data from the Phase II and III studies this finding would in general warrant the need for a Thorough QT study to be undertaken prior to drug registration. However, as discussed in sections under Safety, *Electrocardiogram* and *Safety issues with the potential for major regulatory impact* of this report, healthy subjects do not tolerate riociguat administration; therefore, a Thorough QT study was not possible. In addition, the two pivotal clinical trials, did not identify any relevant changes in QT, QTcB and QTcF duration nor were there any events reported that were linked to QT prolongation.

7.1.12. Pharmacodynamic interactions

7.1.12.1. Nitroglycerin

A single sublingual dose of 0.4 mg nitroglycerin administered 8 hours after pre-treatment with a single oral dose of 2.5 mg riociguat resulted in a significantly more pronounced maximum decrease in seated SBP than a single nitroglycerin dose after placebo pre-treatment. Such a significant difference was not detected when nitroglycerin was administered 24 hours after riociguat pre-treatment.

7.1.12.2. Sildenafil

No significant post-baseline changes in the primary PD parameters PAPmean and PVR were observed after riociguat administration on top of a stable Sildenafil treatment.

[4] Sponsor correction: By contrast there was no correlation between 6MWD and riociguat AUC (i.e. '*baseline'* deleted).

No significant effect on SBP was observed after riociguat administration on top of a stable sildenafil treatment, whereas, a significant decrease in mean DBP (-3.1 mmHg) and increase in mean HR (+3.4 BPM) were identified.

No clinically relevant changes in any of the blood gas parameters (PaO2, PaCO2, PvO2, SaO2, and SvO2) were detected after sildenafil and riociguat administrations.

7.1.12.3. Omeprazole

Mean heart rate increased continuously until 8 h after drug administration by a maximum of 12 BPM compared to baseline when riociguat was given alone and by a maximum of 10 BPM when given in combination with omeprazole.

Mean SBP changes within 8 h post-baseline ranged between -3.2 and +1.0 mmHg when riociguat was given alone and between -3.8 and -0.8 BPM in combination with omeprazole.

Mean DBP decreased by 4.3 to 8.7 mmHg within 2 and 8 h post-baseline when riociguat was given alone and by 0.8 to 4.2 mmHg when given in combination with omeprazole.

7.1.12.4. Maalox

Mean heart rate increased by a maximum of 12.5 BPM 6 h after drug administration compared to baseline when riociguat was given alone and by a maximum of 10.4 BPM 6 h after drug administration when given in combination with Maalox.

Mean SBP decreased by a maximum of 6.3 mmHg 4 h after drug administration compared to baseline when riociguat was given alone and by a maximum of 2.5 mmHg 6 h after drug administration when given in combination with Maalox.

Mean DBP decreased by a maximum of 3.4 mmHg 1.5 h after drug administration compared to baseline when riociguat was given alone and by a maximum of 3.2 mmHg 6 h after drug administration when given in combination with Maalox.

7.1.12.5. Warfarin

In comparison to placebo, concomitant administration of riociguat 2.5 mg TDS at steady state did not influence the prothrombin time and factor VII % activity of warfarin. Riociguat did not induce any relevant effects on factor II % and factor X % activity.

7.1.12.6. Aspirin

When riociguat was co-administered with Aspirin it had no significant effect on bleeding time and when given alone, riociguat had no effect on maximal platelet aggregation or platelet function.

8. Dosage selection for the pivotal studies

The sponsor's justification for the dose selection was as follows:

- The dose-ranging Study 11260 found that the rate of AEs increased with the highest dose of 2.5 mg TDS (7.5 mg) in healthy volunteers.
- Study 11258 found that 0.5 mg was the no effect dose in healthy volunteers and Study 11874 found haemodynamic effects in patients at doses of 1.0 mg and orthostatic hypotension at 5.0 mg.
- From this it was concluded that 1.0 mg was the minimum effective dose and 2.5 mg the maximum tolerated dose and this range was chosen for the Phase II Study 12166.
- Due to the high inter-individual variability in PK (Cmax and AUC) and the parallel reduction in pulmonary vascular resistance (PVR) with systemic vascular resistance (SVR), an

individual titration scheme was chosen according to peripheral systolic blood pressure (SBP).

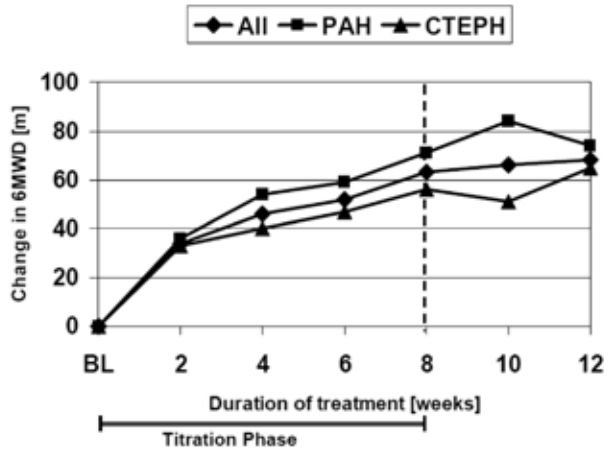
- While the PK steady state was noted at 3 days (**Study 11260**), the PD steady state (in terms of BP) was noted at 10 to 14 days (**Study 13790**), therefore dose titration was selected to be each 2 weeks.

This strategy was implemented in S**tudy 12166**. This was a multicentre, non-controlled, non-blinded Phase II study which assessed multiple doses of riociguat in 75 subjects with either PAH (33 subjects) or CTEPH (42 subjects) after 12 weeks treatment. Individual dose titration was assessed from a starting dose of 1.0 mg TDS and within a range of 0.5 mg TDS to 2.5 mg TDS. Subjects were up-titrated (0.5 mg TDS increments) each 2 weeks if SBP was >100 mmHg, or down-titrated with SBP <90 mmHg. There were 20 subjects with PAH and 30 with CTEPH who had end of study right heart haemodynamics assessed. Titration to the highest level of 2.5 mg TDS occurred in 68% of the study population.

In the total population, data show statistically significant improvement in systolic, diastolic and mean pulmonary artery pressure (PAP) as well as systemic SBP, DBP, pulmonary and systemic vascular resistance and cardiac output. These changes were more noted in those with WHO functional class III/IV. Significant changes were also noted on echocardiograph for the total population and the CTEPH subgroup. There was a statistically significant improvement in the 6MWD in the total population (LS mean change of 68 m) and the subgroups of PAH and CTEPH (LS mean change from baseline of 73 and 64 m, respectively) with improvement seen from Week 2 and increasing to Week 8 during dose titration (**Figure 5**). Treatment was tolerated within this dose range and in the 6 subjects on concomitant bosentan. Changes in mean heart rate were not clinically meaningful.

> Comment: Study 12166 demonstrated positive effects, in both the PAH and CTEPH populations, on haemodynamics and acceptable safety with the individual dose titration regimen guided by SBP within the range of 0.5 mg to 2.5 mg TDS. The study did however lack a control group so the extent of efficacy and the minimum and maximum effective dose was unable to be determined. Only 68% of subjects were able to tolerate the maximal dose of 2.5 mg TDS.

Figure 5. Study 121166 6 minute walk test mean changes in walking distance over time (population valid for PD and PK, n=72)



9. Clinical efficacy

9.1. Pulmonary arterial hypertension (WHO group 1)

9.1.1. Pivotal efficacy study

9.1.1.1. Study 12934 (PATENT-1) report A62510

9.1.1.1.1. Study design, objectives, locations and dates

Study 12934 was a Phase III, randomised, double-blind, placebo-controlled, multicentre, multinational study to evaluate the efficacy and safety of oral riociguat (1 mg, 1.5 mg, 2 mg, or 2.5 mg TDS) in patients with symptomatic pulmonary arterial hypertension (PAH). The study was conducted between December 2008 and May 2012 at 124 sites in 30 countries as follows: Argentina (1), Australia (6), Austria (3), Belgium (2), Brazil (4), Canada (3), China (5), Czech Republic (1), Denmark (1), France (9), Germany (9), Greece (1), Israel (2), Italy (5), Japan (15), Mexico (6), New Zealand (1), Poland (1), Portugal (4), Russia (2), Singapore (2), South Korea (4), Spain (3), Sweden (3), Switzerland (1), Taiwan (3), Thailand (2), Turkey (3), United Kingdom (4) and USA (18). The study used central laboratories and centralised reading of ECGs and there was a Steering Committee and Data Monitoring Committee (DMC) for the riociguat Phase III program which reviewed unblinded data.

The study consisted of a pre-treatment phase of up to 2 weeks and a 12 week treatment period with 8 weeks titration and 4 weeks maintenance therapy. Subjects then entered a 30 day follow up period or continued in an open label extension study (PATENT-2) at their optimised dose.

The study's objectives were to assess the efficacy and safety of oral riociguat in treatment naïve subjects and subjects pre-treated with an endothelin receptor antagonist (ERA) or a prostacyclin analogue (PCA) with symptomatic PAH. The optimised dose reached after individual dose titration (starting with 1 mg TDS and if tolerated up-titrated in steps of 0.5 mg dose increases every 2 weeks up to 2.5 mg TDS) was to be compared with placebo (main comparison). There was also an exploratory riociguat group with capped dose titration from 1.0 mg to 1.5 mg TDS.

9.1.1.1.2. Inclusion and exclusion criteria

Inclusion criteria were:

- Male and female adults aged 18 to 80 years.
- Symptomatic PAH (Group 1, Venice Clinical Classification of PH) with an eligibility and 6MWD test between 150 m and 450 m, a pulmonary vascular resistance (PVR) >300 dyn*sec*cm-5 and a mean pulmonary arterial pressure (PAP) >25 mmHg.
- PAH could be: idiopathic; familial; associated with connective tissue disease; associated with congenital heart disease (if subjects underwent surgical correction more than 360 days before study inclusion); due to portal hypertension with liver cirrhosis (without clinically relevant hepatic dysfunction); due to anorexigen or amphetamine use.
- Treatment-naïve subjects or subjects pre-treated with an ERA or a prostacyclin analogue (IV prostacyclin analogues excluded). Pre-treated subjects needed to be on a stable dose for 90 days prior to randomisation.[5]

[5] Note: In Japan, simultaneous treatment with oral beraprost 180 µg per day and an endothelin receptor antagonist was allowed (amendment 7). In Spain and Argentina, inclusion of treatment-naïve subjects was not allowed (amendments 3 and 5).

- Nonspecific treatments for PH such as oral anticoagulants, diuretics, digitalis, calcium channel blockers or oxygen supplementation were permitted.
- Right heart catheterisation must have been within 6 weeks at the participating centre under standardised conditions.
- Women with childbearing potential required a negative pregnancy test and contraception.

Exclusion criteria were: pregnancy; substance abuse; life expectancy anticipated at less than 2 years; unable to perform a valid 6MWD test; a relative difference of >15% in the 6MWD between eligibility and baseline; the 6MWD was not between 150 and 450 metres; use of prohibited medication (IV prostacyclin analogues, specific or nonspecific PDE inhibitors, NO donors such as nitrates).

Pulmonary disease exclusions: all types of PH except subtypes of Venice Group I specified in the inclusion criteria; moderate to severe obstructive lung disease (forced expiratory volume in one second <60% predicted); severe restrictive lung disease (total lung capacity <70% predicted); and severe congenital abnormalities of the lungs, thorax, and diaphragm.

Blood gas exclusions: oxygen saturation (SaO_2) <88% at Visit 0 despite supplemental oxygen therapy; arterial partial oxygen pressure (PaO_2) <55 mmHg at Visit 0 despite supplemental oxygen therapy; and arterial partial pressure of carbon dioxide ($PaCO_2$) >45 mmHg at Visit 0.

Cardiovascular exclusions (occurring with last 90 days): uncontrolled arterial hypertension; SBP >180 mmHg and/or DBP >110 mmHg at Visit 0 and/or Visit 1 before randomisation; uncontrolled arterial hypotension; SBP <95 mmHg at Visit 0 and/or Visit 1 before randomisation; resting heart rate in the awake subject <50 beats per minute (BPM) or >105 BPM at Visit 0 and/or Visit 1; atrial fibrillation or atrial flutter; left heart failure with an ejection fraction <40%; pulmonary venous hypertension indicated by baseline PCWP >15 mmHg (if age is between 18 and 75 years at Visit 1) or >12 mmHg (if age is >75 years at Visit 1); hypertrophic obstructive cardiomyopathy; severe proven or suspected coronary artery disease; clinical evidence of symptomatic atherosclerotic disease (for example, peripheral artery disease with reduced walking distance, history of stroke with persistent neurological deficit etc.); and congenital or acquired valvular or myocardial disease if clinically significant apart from tricuspid valvular insufficiency due to PH.

Exclusions related to disorders in organ function: clinical relevant hepatic dysfunction indicated by bilirubin >2 times upper limit normal (ULN) and/or ALT or AST >3 times ULN and/or signs of severe hepatic insufficiency; and severe renal insufficiency indicated by a glomerular filtration rate <30 mL/min at Visit 0, for example, calculated based on the Cockcroft formula or the Modification of Diet in Renal Disease Study Group (MDRD) formula.

9.1.1.1.3. Study treatments

Five dose strengths of riociguat were used (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg). Tablets were identical in appearance. Matching placebo tablets were used. The starting dose was 1.0 three times a day (tid). Treatment was given with or without food with doses 6 to 8 hours apart.

In the titration phase, the dose of study medication was titrated every 2 weeks based on the subject's peripheral SBP measured at trough before intake of the morning dose using the following algorithm ("individual dose titration scheme"):

- If trough SBP ≥95 mmHg, increase dose (+0.5 mg TDS)
- If trough SBP 90 – 94 mmHg, maintain dose
- If trough SBP <90 mmHg without symptoms of hypotension, reduce dose (–0.5 mg TDS)
- If any SBP <90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, stop study treatment; restart after 24 hours with reduced dose (–0.5 mg TDS).

The titration scheme for the 1.0 to 2.5 mg riociguat group is shown in Figure 6 and the 1.0 to 1.5 mg group in Figure 7. In the latter group, if the 1.5 mg dose was reached then no further up-titration was allowed and sham titration was undertaken.

Figure 6. Study 12934 PATENT-1 Titration scheme. Riociguat 1.0 to 2.5 mg group

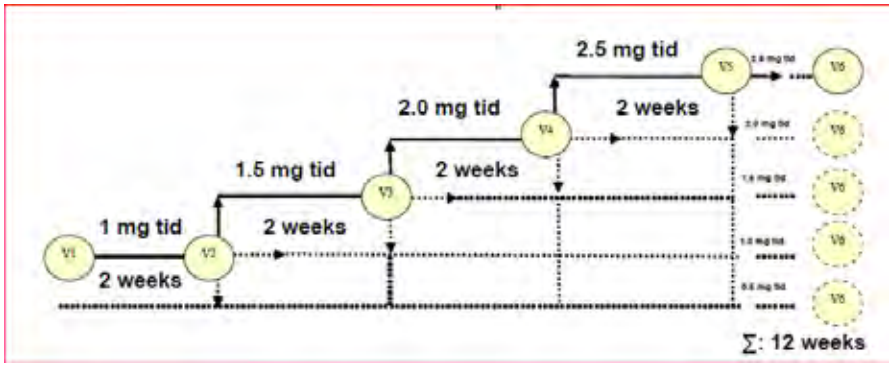
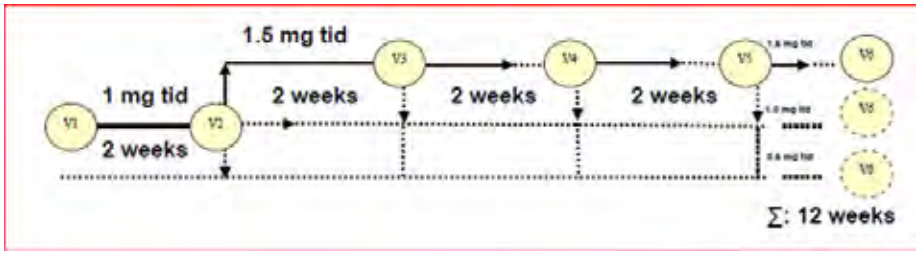


Figure 7. Study 12934 PATENT-1 Titration scheme. Riociguat 1.0 to 1.5 mg



At day 56, if SBP ≥90 mmHg the dose was maintained or if SBP <90 mmHg the dose was reduced. This was then deemed the "optimal dose" for the 4 week main study phase. Dose reductions for safety reasons were allowed. Subjects who had a treatment interruption of longer than 3 days were withdrawn. Subjects documented study drug intake in a diary.

Prohibited therapy included phosphodiesterase inhibitors and NO donors. The dose of endothelin receptor antagonists or prostacyclin analogues was not allowed to be altered.

9.1.1.1.4. Efficacy variables and outcomes

The primary efficacy variable was the 6 minute walking distance (6MWD). The primary outcome was the change from baseline in the 6MWD after 12 weeks treatment.[6]

Secondary efficacy variables were PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg CR10 or Modified Borg Dyspnoea Scale, EQ-5D and LPH questionnaires.

The secondary outcomes were:

- Change from baseline in PVR after 12 weeks.

[6] The 6MWD was performed according American Thoracic Society guideline. According to the guideline, the 6MWD test was to be carried out indoors, along a long, flat, straight, enclosed corridor with hard surface that is seldom travelled. The walking course was to be preferably 30 m in length, but not less than 25 m. The length of the corridor and turnaround points were to be marked. Subjects were instructed to walk alone, not run, from one end to the other end of the walking course, at their own pace, while attempting to cover as much ground as possible in 6 minutes. During the walk, subjects were allowed to stop, lean against the wall and rest, but were to resume walking as soon as they felt able to do so. The subjects were to sit at rest in a chair, located near the starting position, for at least 10 minutes before the start of the test. Investigators were not to walk with the subjects. Only standardised phrases for encouragement were to be used every minute during the test. The baseline test, and all following tests were to be performed under the same conditions (e.g. walking aids, use of oxygen).

- Change from baseline in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) after 12 weeks.
- Change from baseline in World Health Organization (WHO) functional class[7] after 12 weeks.
- Time to clinical worsening.[8]
- Change from baseline in Borg CR 10 Scale or Modified Dyspnoea Scale (measured at the end of the 6MWD test) after 12 weeks[9].
- Change from baseline in EQ-5D questionnaire after 12 weeks.[10]
- Change from baseline in Living with Pulmonary Hypertension (LPH) questionnaire after 12 weeks.[11]

Other outcomes included: exploratory biomarkers (carboxyterminal cross-linking telopeptide of bone collagen and osteopontin) and PK of riociguat and its main metabolite BAY 60-4552 in plasma.

9.1.1.1.5. Randomisation and blinding methods

After the pre-treatment phase, eligible subjects were randomised in a 4:2:1 ratio to the following 3 treatment groups:

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

Randomisation was stratified according to previous PAH treatment (treatment-naïve subjects and subjects pre-treated with an ERA or a PCA). Randomisation and titration were undertaken using an IVRS. Randomisation was in blocks of 7 with separate blocks for the therapy naïve and pre-treated subjects.

[7] WHO functional class:
I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

[8] The first occurrence of the following events of special interest was considered for the calculation of the combined endpoint of "Time to clinical worsening": death (all-cause mortality); heart/lung transplantation; atrial septostomy; hospitalisation due to persistent worsening of PH; start of new PH specific treatment or modification of pre-existing prostacyclin analogue; persistent decrease >15% from baseline or >30% compared to last measurement in the 6MWD due to worsening PH (confirmed on a second measurement after 14 days); persistent worsening of functional class due to PH (confirmed after 14 days)

[9] Modified Borg Dyspnoea Scale was replaced by the Borg CR 10 Scale in amendment 4. Exertion was ranked by the subjects by questioning immediate after the exercise test. The Borg Scale classifications are in **Table 7.3** (**p238**).

[10] The EuroQol EQ-5D is a self reported questionnaire assessing mobility, self care, usual activities, pain/ discomfort and anxiety/depression.

[11] The Living with PH (LPH) questionnaire was based on the Minnesota Living with Heart Failure questionnaire and modified for PAH patients. Subjects rated symptoms, functional limitations and psychological distress on their quality of life in the past week.

The study was double-blind, used matching active and placebo tablets and the placebo group underwent sham titration. The sponsor also stated that from Visit 2 onwards, the 6MWD test, Borg Scale assessment and evaluation of WHO functional class were performed by a second physician or person who was not involved in the process of study drug titration and was unaware of the immediate reaction of the subject's blood pressure and heart rate after dosing. The results of the NT-proBNP determination were not forwarded to the investigators before lock of the clinical database and the bioanalyst was blinded for analysis of PK samples.

9.1.1.1.6. Analysis populations

The intent to treat (ITT) population was all randomised subjects who received at least one dose of study medication (corresponding to the full analysis set). The safety population was also those randomised with at least one dose of study medication. The per protocol (PP) population consisted of subjects in the ITT with an adequate 6MWD at baseline and at week 12, or at the termination visit, or who was withdrawn due to death or clinical worsening and had no major protocol deviations affecting efficacy.

9.1.1.1.7. Sample size

Assuming a standard deviation (SD) of 70 m, 375 subjects in the ITT (250 in the riociguat 1.0 to 2.5 mg group, 125 in the placebo group, 4:2 randomisation) would be required to detect a placebo-adjusted difference of 25 m in 6MWD with a power of 90% and a two- sided significance level of 5%. The exploratory riociguat 1.0 to 1.5 mg group would have a sample size of one half of the placebo group, i.e. 63 patients. The total number of subjects required was 438 and, allowing for a 5% invalidity rate, a total sample size of 462 randomised subjects was chosen.

9.1.1.1.8. Statistical methods

The primary efficacy analysis was the change in 6MWD from baseline to week 12 (last observation until week 12) in the ITT population, with imputation of missing values for subjects who withdrew or died before 12 weeks. The values from the termination visit or last post baseline visit were used. If the subject died or withdrew from clinical worsening and had no measurements then the worst possible 6MWD value (0 metres) was used.

The riociguat 1.0 to 2.5 mg and placebo groups were compared using analysis of covariance (ANCOVA), with baseline 6MWD as a covariate and treatment group, stratification group (therapy-naïve / add-on) and region as main effects. If the Shapiro-Wilk test was significant at the 5% level, a non-parametric approach (stratified Wilcoxon test by region and stratification group) was used instead of the ANCOVA to formally determine statistical significance. Least squares (LS) mean and 95% confidence intervals (CIs) of the treatment difference were calculated based on the ANCOVA. Superiority of the riociguat 1.0 to 2.5 mg group over the placebo group was to be declared if the two-sided significance level was ≤0.05. The lower dose group (riociguat 1.0 to 1.5 mg) was only analysed descriptively. Secondary efficacy variables were tested in a sequential testing procedure in the order listed above. Time to clinical worsening was analysed using a stratified log-rank test with Kaplan Meier estimates. Sensitivity analyses on the 6MWD were undertaken using a mixed linear model (mixed model for repeated measure, MMRM).

There were 9 protocol amendments, 6 of which were country specific and 3 were global (amendments 4, 6 and 8). The major changes in these 3 amendments are as follows: amendment 4 increased the pre-treatment phase from 1 to 2 weeks, clarified inclusion exclusion criteria an study procedures and changed the Modified Borg Dyspnoea Scale to the Borg CR 10 Scale; amendment 6 increased the upper age limit from 75 to 80 years and reduced extended ECG measurements; and amendment 8 added calcium, phosphate and calcitriol measurements and changed the definition of treatment emergent AEs from up to 7 days to up to 2 days after the end of treatment.

9.1.1.1.9. Participant flow

There were 586 subjects enrolled, 445 randomised and 443 received study medication (254 in the riociguat 1.0 to 2.5 mg group, 126 in the placebo group, 63 in the riociguat 1.0 to 1.5 mg group). Of these, 405 (91.0%) completed the treatment phase. There were 38 randomised subjects who prematurely discontinued study medication and 2 who did not receive the study medication. The rate of premature withdrawal was 6.7%, 10.9% and 12.6% in the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups, respectively. The main reasons were adverse events (3.1%, 1.6% and 5.5%), withdrawal by subjects (2.4%, 3.1% and 2.4%) and protocol violation (0.4%, 4.7% and 2.4%, respectively.

9.1.1.1.10. Major protocol violations/deviations

The rate of major protocol deviations was 14.2%, 12.7% and 15.9% in the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups, respectively. The most frequent major deviations were 6MWD test not done at termination for non-completers and 6MWD test done >3 days post last study medication dose for non-completers.

There were 20 (4.5%) of randomised subjects who were incorrectly randomised with respect to the stratification on previous PAH therapy, 13 were stated to be therapy naïve when they were pre-treated and 7 the converse. Subjects were analysed by the correct pre-treatment situation. In addition there were 2 treatment errors reported and 8 subjects in the placebo group with plasma concentrations of riociguat. It was unknown if they had received incorrect medication or the laboratory samples were mixed. These subjects were excluded from the PP analysis. One subject was unblinded by the study site due to worsening of PH with no improvement on diuretic therapy. The subject received placebo.

Mean treatment compliance was ≥96% and the incidence of treatment compliance <90% was higher in the placebo group (8%) than the riociguat groups (3.1%-4.8%).

There were 443 subjects (99.6%) included in the ITT and safety populations and the PP population consisted of 379 subjects (85.8%, 85.9% and 83.5% or 218, 55 and 106 of the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups, respectively).

9.1.1.1.11. Baseline data

Treatment groups were balanced on demographics. Subjects were largely female (~80%), White (52-63%) or Asian (30-35%) with a mean age of 48.8-51.1 years and 22-26% were aged ≥65 years. The mean BMI was 26-27 kg/m^2. Most subjects had idiopathic PAH and this was higher in the placebo group (66.7%) than the riociguat groups (58.7% and 61.9%). The next most frequent primary diagnosis was PAH due to connective tissue disease which was greater in the riociguat 1.0 to 2.5 mg group (28.0%) than the placebo group (19.8%) and the riociguat 1.0 to 1.5 mg group (23.8%). Subjects had WHO functional class of II or III (91-98%) with a slightly higher rate of class III in the riociguat 1.0 to 1.5 mg group (62% versus 55% and 46%). There were 21-26% of subjects with a baseline 6MWD of <320 m. The mean PVR was 791-848 dyn*s*cm^{-5} and mean PAP was 47-52 mmHg.

About half the subjects were treatment naïve. Pre-treatment with an ERA occurred in 43-44.5% and with a PCA in 6-8%. Concomitant medication use was on the whole comparable between groups. For new concomitant medications commenced during the trial there was higher use of medications for acid related disorders in the riociguat 1.0 to 2.5 mg group (31% versus 22.% riociguat 1.0 to 1.5 mg and 14% placebo). The use of new specific PH medication was low and similar between groups, likewise new nonspecific PH medication use was similar between groups. There were 20 to 29% of subjects who had concomitant oxygen therapy.

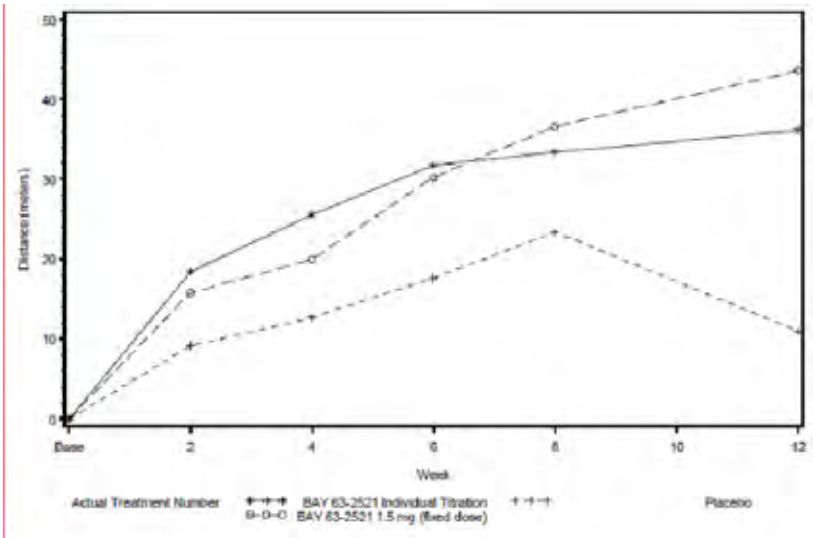
At the end of 12 treatment weeks in the riociguat 1.0 to 2.5 mg group, 74.6% of subjects were on 2.5 mg, 15.2% on 2.0 mg, 5.9% on 1.5 mg, 2.5% on 1.0 mg and 1.7% on 0.5 mg. In the riociguat 1.0 to 1.5 mg group, 94.7% were on 1.5 mg and 5.3% on 1.0 mg.

9.1.1.1.12. Results for the primary efficacy outcome

In the ITT population, the mean baseline 6MWD was 361.4-367.8 m. The mean change from baseline to last visit in the 6MWD was 29.6m, -5.6 m and 31.1 m in the riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups, respectively. The LS mean difference between riociguat 1.0 to 2.5 mg and placebo was 35.8 m (95% CI: 20.1, 51.5) which was statistically significant (p<0.001) (using the stratified Wilcoxon test). The improvement in distance walked over the 12 weeks treatment is shown in Figure 8.

These results were supported by analysis of the PP population, with a LS mean difference for riociguat 1.0 to 2.5 mg versus placebo of 33.5m (95% CI: 19.0, 48.0, p<,0.0001) as well as by sensitivity analyses (Table 5).

Figure 8. Study 12934 PATENT-1. . Mean change in 6 MWD from baseline (unadjusted values) ITT analysis set



Number of subjects at each timepoint

	Week 2	Week 4	Week 6	Week 8	Week 12
Riociguat 1.0-2.5 mg (individual dose titration)	N=247	N=243	N=241	N=235	N=233
Placebo	N=121	N=117	N=116	N=111	N=112
Riociguat 1.0-1.5 mg (capped titration)	N=63	N=59	N=56	N=58	N=56

Table 5. Study 12934 PATENT-1. Change in 6 MWD from baseline Sensitivity analysis ITT analysis set

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

[a] Riociguat 1.0 2.5 mg – placebo

Comment: There appeared little difference between the higher and lower riociguat dose titration groups in the primary efficacy endpoint of 6MWD in both the ITT and PP population.

Analysis of treatment differences between riociguat 1.0 to 2.5 mg and placebo in the 6MWD in a variety of subgroups was presented. The effect was consistent between treatment naïve (LS mean difference of 38.4m) and pre-treated subjects (LS mean difference 35.6 m). A positive response was also seen in subjects with idiopathic PAH (LS mean difference 42.8 m) and connective tissue disease (LS mean difference 28.1 m). The treatment effect was more notable in those with WHO class III/IV than I/II, whether pre-treated or treatment naïve. Response was also consistent across, age (<65, ≥65 years) and race though there were too few Black subjects to draw conclusions. There was no positive effect in the Americas but numbers were low and confidence intervals wide.

An exploratory responder analysis of "planned improvement" (defined as an improvement of 40 m for therapy naïve and 20 m for pre-treated subjects) was conducted. This found that in the riociguat 1.0 to 2.5 mg group the proportion of subjects with planned improvement was 49% and 53% for the therapy naïve and pre-treated subjects, respectively. Similar results were found for the lower dose group 1.0 to 1.5 mg with improvement in 56% and 48% of therapy naïve and pre-treated subjects, respectively. This compares to 20% and 35% in the respective placebo groups.

9.1.1.1.13. Results for other efficacy outcomes

The seven pre-specified secondary efficacy variables were analysed in a sequential testing procedure with statistically significant results for PVR, NT-proBNP, WHO functional class, time to clinical worsening and Borg Scale (but not for the EQ-5D and LPH questionnaires).

In the ITT population, both riociguat groups showed a decline in PVR with -223.3 and -167.8 mean change from baseline in the 1.0 to 2.5 mg and 1.0 to 1.5 mg groups, respectively compared to little change in the placebo group (-8.9). There was a significant LS mean difference for the 1.0 to 2.5 mg group compared to placebo of -225.7 (95% CI: 281, 170, p<0.0001). Subgroup analyses of the PVR were found to be supportive of overall results. Exploratory analyses of other haemodynamic parameters showed improvements with riociguat 1.0 to 2.5 mg (Table 6) and similar, albeit smaller, magnitude changes were also seen in the capped 1.0 to 1.5 mg riociguat group.

Table 6. Study 12934 PATENT-1. Change in haemodynamic parameters from baseline to last visit. Comparison of riociguat 1.0 to 2.5 mg and placebo. ITT analysis set.

Change in hemodynamic parameters from baseline to last visit: Comparison of riociguat 1.0-2.5 mg and placebo - ITT analysis set

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

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

There was a statistically significant decrease in NT-proBNP with riociguat 1.0 to 2.5 mg compared to placebo although the data showed high variability. There was a greater proportion of subjects treated with riociguat than placebo who improved in their WHO functional class (21% and 24% riociguat versus 14% placebo) and the treatment difference was significant (p=0.003).

In the ITT population, the rate of any clinical worsening was 1.2%, 6.3% and 3.2% in the riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups, respectively and the treatment comparison (using Mantel Haenszel estimate) was significant (p=0.028). The difference was not significant when the PP population was analysed.

The dyspnoea scale used was altered with amendment 4, however data were combined for analysis. There was a decrease in the mean Borg CR 10 scale by week 12 in both riociguat groups (-0.44 and -0.33) with little change in the placebo group (0.09). The difference between riociguat 1.0 to 2.5 mg and placebo was significant (p=0.002). As stated above, there was no significant treatment difference on the EQ-5D questionnaire between the riociguat 1.0 to 2.5 mg and placebo groups and while a significant difference was found on the LPH questionnaire this result cannot be considered due to the hierarchical testing procedure.

Summary: Study 12934 was a Phase III, randomised, double-blind, placebo-controlled, international study in 443 patients with symptomatic PAH treated for 12 weeks with an individual titration regimen of riociguat (1.0 to 2.5 mg TDS). The efficacy of a lower dose (1.0 to 1.5 mg TDS) was explored in a smaller group The study was positive as riociguat 1.0 to 2.5 mg was found to result in a significant improvement over placebo in the 6MWD of 35.8 m (95% CI: 20.1, 51.5). The effect was robust and supported by analysis of the PP population and sensitivity analyses. A positive treatment effect was also across subgroup analyses, in particular the treatment naïve and pretreated subjects. Positive results were seen in the secondary endpoints of PVR, WHO functional class, NT-proBNP and time to clinical worsening. Efficacy of the lower dose (capped at 1.5 mg TDS) was seen to be consistent with the higher dose on the primary outcome of 6MWD, although formal assessment of this was not undertaken and the study likely underpowered to make this assessment.

9.2. Other efficacy studies

9.2.1. Study 15096 (report number A57218)

Methods: Study 15096 was a Phase IIb, randomised, double-blind, placebo-controlled, 12 week interaction study of riociguat (1.0 to 2.5 mg TDS) on a background of stable sildenafil (phosphodiesterase 5 inhibitor) pre-treatment in subjects with symptomatic PAH. The study was conducted at 11 sites in Europe between August 2010 and June 2012, the long term extension was reported as still ongoing. The primary objective was to evaluate the effect of 1.0, 1.5, 2.0, and 2.5 mg riociguat TDS (dose titration) administered simultaneously with sildenafil on blood pressure in subjects with symptomatic PAH. The secondary objectives were: safety of the riociguat/sildenafil combination; changes in the 6MWD, WHO functional class, NT-proBNP, variables obtained during right-heart catheterisation, and PK of riociguat and sildenafil.

The study was planned in two parts with part 1 assessing the combination of riociguat with sildenafil 20 mg TDS. Part 2 was planned to assess any sildenafil dose used in clinical practice. The protocol was amended and Part 2 was not initiated. The rationale was that the interim analyses found decreased BP in both groups with a greater number in the sildenafil plus riociguat group, particularly during the long term extension. The CSR covers the period to 19 June 2012 and deaths to 2 November 2012.

Inclusion criteria were adults with symptomatic PAH (Group I Dana Point Updated Clinical Classification 2008), 6MWD of >150 m, PVR >300 dyn*s*cm-5, and a mean PAP ≥25 mmHg. Subjects needed to be on a stable dose of 20 mg TDS of sildenafil for at least 90 days and have SBP ≥95 mmHg and HR ≤105 BPM in the first 2 hours after intake of sildenafil. Exclusion criteria were similar to studies 12934 and 11348. Prohibited medications included specific PH medications (except sildenafil), alpha blockers and strong CYP3A4 inhibitors.

After a 2 week pre-treatment phase, subjects were randomised to riociguat (1.0 to 2.5 mg TDS) or matching placebo in a 2:1 ratio and commenced an 8 week titration period followed by a 4 week maintenance phase. Following this they could enter an optional long term extension phase on the optimal riociguat dose, and as blind was not broken, the placebo group the underwent blinded dose titration of riociguat. Riociguat was titrated as in previous studies according to peripheral SBP.

The primary endpoint was maximum change from baseline in supine SBP within 4 hours of dosing. Baseline SBP was on the background of sildenafil treatment alone. Efficacy endpoints of 6MWD, NT-proBNP, WHO functional class, Borg CR 10 scale, time to clinical worsening and right heart haemodynamics were exploratory. There was no formal statistical testing planned and no sample size calculation.

Results: Twenty-four subjects were enrolled, 18 randomised (12 on riociguat and 6 on placebo) and 17 continued to the long term extension phase. There were 16 (89%) subjects (11 riociguat and 5 placebo) eligible for efficacy and 18 for safety evaluation. Seventeen subjects entered the long term extension and 11 were ongoing at data cutoff.

The small numbers resulted in some imbalances between groups. Two thirds of subjects were female, all were White with an age range for 37 to 74 years. Most had idiopathic PAH (42% riociguat versus 67% placebo) or connective tissue disease (42% versus 17%). There were more riociguat subjects with a baseline 6MWD <320 m (42% versus 0%). The mean treatment duration with sildenafil was 505 (SD 421) and 394 (SD 306) days in the riociguat and placebo groups, respectively.

At baseline, there was a difference between groups in the primary PD endpoint as the mean maximum change in supine SBP after sildenafil dosing was 20.2 mmHg and -7.6 mmHg in the riociguat and placebo groups, respectively. At week 12 this change was maintained in the riociguat group (mean change of -20.7 mmHg). In the placebo group the mean change decreased

to -20.2 mmHg. At day 56 of the extension study the mean maximum change in supine SBP was -21.3 mmHg and -35.0 mmHg in the former riociguat and placebo groups, respectively.

There was a similar trend for standing SBP. For supine DBP, from a baseline mean maximum change of -13.6 and -9.4 mmHg respectively, at week 12 the maximum change was -13.7 and -13.8 mmHg in the riociguat and placebo groups respectively, showing no change with riociguat and a greater reduction in the placebo group.

Over the 12 weeks treatment, the mean change in 6MWD was 7.3 m and 30.2 m in the riociguat and placebo groups, respectively. There was a change in WHO functional class in only 2 of the riociguat and one the placebo subjects (all were improvements). The mean change from baseline in Borg CR 10 scale was -0.73 and -1.50 in the respective groups. Overall, the changes on right heart haemodynamics were favourable in both groups with a greater magnitude of change in the placebo group.

Summary: Study 15096 was a small Phase IIb randomised placebo controlled study assessing the interaction between sildenafil and riociguat in 18 subjects with PAH. While there did not appear to be an additive effect of riociguat in decreasing supine SBP, the small sample size led to baseline imbalances between groups and no formal statistical comparisons were undertaken.

> Comment: While there were no deaths in the main study there was one in the extension study and a further two were reported after database lock (17.6%). One was a fall with subdural haematoma, one decompensation of right heart failure and one cardiac arrest presumed related to the PAH. There was also a further 5 subjects (29%) who discontinued the extension due to AEs over an average period of 10 months.
>
> Given the safety findings reported in the extension study, the Sponsor concluded that the given the lack of an efficacy signal the benefit-risk was not positive and the combination is not recommended.

9.3. Chronic thromboembolic pulmonary hypertension (WHO group 4)

9.3.1. Pivotal efficacy study

9.3.1.1. Study 11348 (CHEST-1) report A62508

9.3.1.1.1. Study design, objectives, locations and dates

Study 11348 was a Phase III, randomised, double-blind, placebo-controlled, multicentre, multinational study to evaluate the efficacy and safety of oral riociguat (1 mg, 1.5 mg, 2 mg, or 2.5 mg TDS) in patients with chronic thromboembolic pulmonary hypertension (CTEPH). The study was conducted between February 2009 and June 2012 at 89 sites in 26 countries in North and South America, Asia, Europe and Australia (1 site). As with the previous study there was a centralised laboratory and centralised ECG reading and oversight by the steering committee and DMC.

The objectives were to assess the efficacy and safety of oral riociguat in subjects with inoperable CTEPH or recurrent or persisting pulmonary hypertension (PH) after surgical treatment. Riociguat was given at an individualised dose after dose titration (starting with 1 mg TDS and if tolerated up-titrated in steps of 0.5 mg dose increases every 2 weeks up to 2.5 mg TDS). The design was the same as Study 12934 (PATENT-1) with the following differences: there was no low dose group; the pre-treatment phase was approximately 4 weeks; and the treatment duration was 16 weeks (8 weeks titration and 8 weeks maintenance). Subjects who completed the study could enter an open label extension study (CHEST-2) on their optimal dose.

9.3.1.1.2. Inclusion and exclusion criteria

Inclusion criteria were:

- Male and female adults aged 18 to 80 years with CTEPH and an eligibility and baseline 6MWD test between 150 m and 450 m.
- CTEPH was defined either as inoperable (adjudicated by an experienced surgeon or a central adjudication committee[12]), with a PVR >300 dyn*sec*cm-5 measured at least 90 days after start of full anticoagulation and a mean PAP >25 mmHg, or as persisting or recurrent PH after pulmonary endarterectomy (subjects had to have a PVR >300 dyn*sec*cm-5 measured at least 180 days after surgery). The PVR inclusion criterion was changed from 480 to 300 dyn*sec*cm-5 by amendment 5).
- Nonspecific PH treatments (for example, oral anticoagulants, diuretics, digitalis, calcium channel blockers or oxygen supplementation) were allowed but anticoagulants must have started at least 90 days before Visit 1, diuretics stable for at least 30 days and oxygen therapy stable for at least 90 days.
- Right-heart catheterisation within 8 weeks of visit 1 and after ≥90 days of anticoagulation.
- Women were postmenopausal or confirmed non-pregnant and using contraception.

Exclusion criteria were essentially the same Study 12934 (PATENT-1). Subjects were not to be withdrawn from medically required treatments for the study. Prohibited treatments were: NO donors, endothelin receptor antagonists, prostacyclin analogues and phosphodiesterase inhibitors. That is, subjects were therapy naïve or had ceased PH-specific medication >30 days prior to right heart catheterisation. All types of PH were excluded except subtypes 4.1 and 4.2.

9.3.1.1.3. Study treatments

As in Study 12934, riociguat film coated tablets (doses of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg or 2.5 mg) or matching placebo were given 3 times a day. Titration was each two weeks based on peripheral SBP at trough with the same titration rules. The starting dose was 1.0 mg TDS. The placebo group underwent a sham titration. Prohibited medication included NO donors, phosphodiesterase inhibitors, endothelin receptor antagonists and prostacyclin analogues.

9.3.1.1.4. Efficacy variables and outcomes

As in Study 12934, the primary efficacy variable was the 6MWD while the primary efficacy outcome was the change from baseline in the 6MWD after 16 weeks (not 12 weeks as in PATENT-1). The secondary outcomes were the same as Study 12934 with the addition of haemodynamic parameters at 16 weeks and use of healthcare resources after 16 weeks.[13]

9.3.1.1.5. Randomisation and blinding methods

Subjects were randomised in a 2:1 ratio to riociguat 1.0 to 2.5 mg TDS or placebo TDS using an IVRS. Blinding was with matching placebo tablets, sham placebo titration, use of a second physician or person not involved in drug titration or subject's immediate BP and HR reaction post dosing for efficacy assessments, and not forwarding investigators results of the NT-proBNP.

[12] The inoperability assessment focused on the assessment of the technical operability taking into consideration the surgical accessibility of the organised thrombi and the concordance between surgical accessible vascular obstruction and PVR. In this context, the diagnosis of inoperability was established at least based on pulmonary angiogram supplemented by a ventilation-perfusion scan (preferred method) or alternatively CT pulmonary angiogram (minimum 64-slice spiral CT with contrast medium) supplemented by a ventilation-perfusion scan.

[13] Time to clinical worsening for this study was a combined endpoint of death (all cause), heart/lung transplantation, rescue PEA due to persistent worsening of PH, hospitalisation due to persistent worsening of PH, start of new PH-specific treatment due to PH worsening. Persistent decrease >15% from baseline or >30% from last 6MWD test and confirmed after 14 days, and persistent worsening of functional class.

9.3.1.1.6. Analysis populations

The primary analysis used the ITT population as in Study 12934 with supportive analysis of the PP population.

9.3.1.1.7. Sample size

Assuming an SD of 70 m, 261 subjects valid for ITT (174 in the riociguat 1.0 to 2.5 mg group, 87 in the placebo group, 2:1 randomisation) gave the study 90% power to detect a placebo-adjusted difference of 30 m (25 m was used in Study 12934) in 6MWD at a two-sided significance level of 5%. Allowing for an invalidity rate of 3%, a total of 270 randomised subjects were required.

9.3.1.1.8. Statistical methods

Statistical methods and imputation for missing values were the same as study PATENT-1. Secondary efficacy analyses were undertaken using the same sequential testing procedure.

There were 7 protocol amendments, 3 were country specific and 4 were global. Changes included increasing the upper age from 75 to 80 years, use of the Modified Borg Dyspnoea Score, specific imaging requirements for assessment of inoperability, change of baseline PVR from >480 to >300 dyn*sec*cm^{-5}, and addition of calcium, phosphate and calcitriol measurements.

9.3.1.1.9. Participant flow

Overall, 446 subjects were enrolled, 184 not randomised and 262 randomised with 173 in the riociguat 1.0 to 2.5 mg group, 88 in the placebo group and one subject randomised but not treated. Of these, 243 (92.7%) completed the treatment phase and 18 subjects prematurely discontinued study medication and one did not receive the study medication. Premature discontinuation was greater in the riociguat group than placebo group (8.0% versus 5.7%) and the most frequent reason was an adverse event (2.3% both groups. All 261 randomised and treated subjects were included in the ITT and safety analysis sets and 218 subjects (143 [82.2%] in the riociguat and 75 [85.2%] in the placebo group) were considered valid for per protocol analyses.

9.3.1.1.10. Major protocol violations/deviations

Major protocol deviations occurred in 17.3% and 14.8% of the riociguat and placebo groups, respectively. The most frequent major deviations were 6MWD test not done at the termination visit for non-completers (5.2% versus 1.1%), anticoagulation not taken for ≥90 days before baseline PVR (4.0% versus 5.7%), and baseline PVR ≤480 dyn*sec*cm-5 (3.5% versus 1.1%). Treatment compliance was high at >95% in both groups. There was one subject randomised in error and no study medication was received and a further 3 subjects with treatment errors, and two with riociguat concentrations in plasma despite being in the placebo group. These errors resulted in three subjects being excluded from the PP analysis.

9.3.1.1.11. Baseline data

Treatment groups were balanced on baseline demographic characteristics. Most subjects were female (riociguat versus placebo: 68% versus 61%) and White (69% versus 74%) or Asian (21% versus 23%). The mean age was 59 years with 41-43% aged ≥65 years. The mean BMI was 27-28 kg/m^2 and 53-65% of subjects had never smoked. Most subjects had inoperable CTEPH with a slightly higher rate in the placebo group (69.9% versus 77.3%) and postoperative CTEPH was slightly higher in the riociguat group (30.1% versus 22.7%). Subjects were in WHO functional class III (61.8% versus 68.2%) or II (31.8% versus 28.4%) and the baseline mean PVR was 790 and 779 dyn*s*cm-5 in the riociguat and placebo groups, respectively. General medical history and prior medication use was generally balanced between groups. New concomitant medication use showed a higher usage rate of drugs for acid related disorders (24.3% versus 14.8%) in the riociguat group and antithrombotics in the placebo group (50.9%

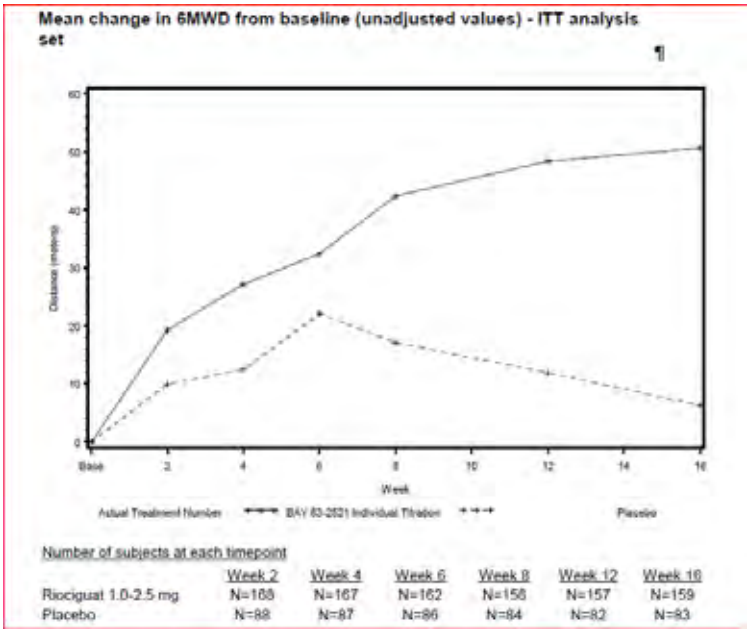
versus 60.2%. Specific PH medication use was prohibited and was reported in only 3 subjects (riociguat group) and there were two subjects with reported concomitant use of bosentan. Non-specific PH medication use was similar between groups apart from the higher rate of new oral antiocoagulants in the placebo group (25.4% versus 37.5%). New use of supplemental oxygen was reported in 5.8% and 4.5% of the riociguat and placebo groups, respectively.

At the end of 16 treatment weeks, 77% of riociguat subjects were on the highest dose of 2.5 mg, 12.5% on 2.0 mg, 6.3% on 1.5 mg, 3.8% on 1.0 mg, 0.6% on 0.5 mg.

9.3.1.1.12. Results for the primary efficacy outcome

In the ITT population, the mean baseline 6MWD was 342.3 m and 356.0 m in the riociguat 1.0 to 2.5 mg and placebo groups, respectively. The mean change from baseline to week 16 (with imputation for missing values) was 38.9 m and -5.5 m, respectively. The LS mean difference in the 6MWD was 45.7 m (95% CI: 24.7, 66.6) which was statistically significant (p<0.0001) using the stratified Wilcoxon test (non-parametric). Response divergence between groups was seen from 2 weeks and improved in the riociguat group until around week 12 and then appeared to plateau (Figure 9). Results were supported by the PP analysis which found a LS mean difference of 52.2m (95% CI: 30.5,73.9 p<0.0001). Sensitivity analyses were also supportive with estimated treatment differences of 38.7 to 44.4 m.

Figure 9. Mean change in 6MWD from baseline (unadjusted values) ITT analysis set



Subgroup analysis of the primary endpoint found that there was a consistent benefit in the riociguat group for those with inoperable CTEPH, WHO functional class III/IV, females, males, age <65 or ≥65 years, Whites and Asians and baseline 6MWD group. The placebo corrected mean change from baseline in those with inoperable CTEPH was 53.9 m (95% CI: 28.5, 79.3m) and for those with postoperative CTEPH was 26.7 m (95% CI: -9.7, 63.1). Those with postoperative CTEPH and in WHO functional I/II showed less improvement in the 6MWD and there was a more notable effect in China compared to other regions.

In an exploratory analysis, the proportion of subjects who had an improvement in the 6MWD of at least 30 m was 63.0% and 29.5%, and of at least 40 m was 52.6% versus 23.9%, of the riociguat and placebo groups, respectively. In further exploratory analyses, a significant negative correlation was found between the 6MWD and PVR, as well as 6MWD and NT-proBNP, however the level of correlation was low (0.27 and 0.21, respectively).

9.3.1.2. Results for other efficacy outcomes

On the hierarchical testing of secondary efficacy variables only the PVR, NT-proBNP and WHO functional class were statistically significant. The variable of time to clinical worsening was not significant (p=0.218). It was noted that there were a low number of clinical worsening events (n=4, 2.3% and n=5, 5.7% in the riociguat and placebo groups, respectively). Subsequent secondary variables of Borg CR 10 Scale, EQ-5D questionnaire and LPH questionnaire were then deemed not significant.

In the ITT population, a decline in the PVR was only seen in the riociguat group and there was a significant LS mean difference -246.4 (95% CI: -303,-189 p<0.0001). The positive change in PVR was seen across subgroups of inoperable and postoperative CTEPH, WHO functional class and baseline 6MWD (± 320m). Exploratory analyses of other haemodynamic parameters showed improvements with riociguat including reduction in PA pressures, right atrial pressure as well as increase in cardiac output and venous oxygen saturation.

NT-proBNP results demonstrated high variability however there was a statistically significant decrease in NT-proBNP with riociguat 1.0 to 2.5 mg compared to placebo. The rate of improvement of at least one level in the WHO functional class was greater in the riociguat than placebo group (32.9% versus 14.9%, p=0.00263).

In the ITT population, the rate of any clinical worsening was higher with placebo (2.3% versus 5.7%) but the result was not statistically significant (p=0.174). The difference was also not significant when the PP population was analysed.

The dyspnoea scale used was altered with amendment 3 from the Modified Borg to the Borg CR 10 Scale with data being combined for analysis. The hierarchical testing order found that no claims can be made for this endpoint, despite the greater reduction in the riociguat group (mean change of -0.83 versus +0.17 in the placebo group). Similarly, no conclusions are drawn on the "positive" results for the change from baseline of the EQ-5D questionnaire (LS mean difference of 0.13, 95% CI: 0.06, 0.21) or the LPH questionnaire results (LS mean difference of -5.76, 95% CI: -10.45,-1.06).

Summary: Study 11348 (CHEST-1) was a Phase III, randomised, double-blind, placebo-controlled, international study in 261 patients with inoperable or postoperative CTEPH treated for 16 weeks with an individual titration regimen of riociguat (1.0 to 2.5 mg TDS). The study was positive as riociguat 1.0 to 2.5 mg was found to result in a significant improvement over placebo in the 6MWD of 45.7 m (95% CI: 24.7, 66.6). The effect was robust and supported by analysis of the PP population and sensitivity analyses. A positive treatment effect was also found on subgroup analyses (age, sex baseline 6MWD and race), in particular subjects with inoperable CTEPH and postoperative CTEPH though the effect was less pronounced in the latter group. The effect was also greater in those in WHO functional class III/IV. Positive results were seen in the secondary endpoints of PVR, WHO functional class and NT-proBNP. The rate of clinical worsening was not significantly improved with riociguat.

9.4. Other efficacy studies (both indications)

9.4.1. Long term uncontrolled studies

There were three open label, long term extension studies in the dossier:

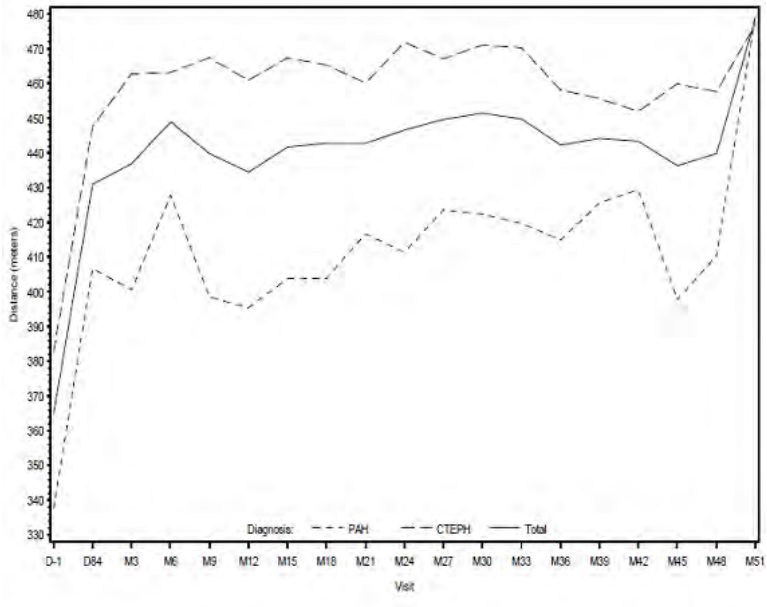
- Report A61224 was the 4.5 year follow up of the Phase IIa Study 12166.
- Report A62511, Study 12935 (PATENT-2) was the long term extension of Study 12934 (PATENT-1).
- Report A62509, Study 11349 (CHEST-2) was the long term extension of Study 11348 (CHEST-1).

These studies had safety and tolerability as the primary objective with efficacy and PK being secondary objectives. Efficacy assessments were conducted each 3 months and included the 6 minute walk test, the Borg dyspnoea score, WHO functional class and laboratory testing of NT-proBNP. Statistical analysis was descriptive and in studies 12935 and 11349, imputation for missing values was undertaken at week 12 (and planned for end of study). The studies were reported to be ongoing until commercial availability of riociguat.

In studies 12935 and 11349, subjects entered a blinded 8 week titration phase during which they were maintained on their riociguat dose level with sham titration, or if previously on placebo, they were titrated up each 2 weeks from 1.0 mg TDS to a maximum of 2.5 mg TDS. Those in Study 12935 who had been on low dose riociguat were titrated from their last dose. Titration rules were the same as the primary study, based on SBP and undertaken using an IVRS. After the titration period, the unblinded dose of riociguat could be altered by 0.5 mg TDS between the range of 0.5 mg and 2.5 mg TDS. Other specific PH treatments such as PCAs and ERAs were allowed (except during titration if treatment naïve) but phosphodiesterase inhibitors and NO donors were prohibited.

Study 12166 extension included 68 subjects with PAH or CTEPH with WHO functional class II - IV who were treatment naïve or pretreated with endothelin antagonists. Treatment duration was up to month 42 with a mean of 36.5 months. There were 47 (69%) subjects ongoing at the data cut-off of 1 November 2011. During the long term extension (LTE), 47% of subjects took concomitant ERAs. The improvement in the 6MWD seen in the primary study was generally maintained during the extension study (Figure 10). The modified Borg dyspnoea score was <1 during the extension study (indicating little clinical significance). Improvements in WHO functional class appeared to be maintained.

Figure 10. Study 12166 long term extension 6 min walking test-mean distance (m) by visit (derived visit analysis; n=68).



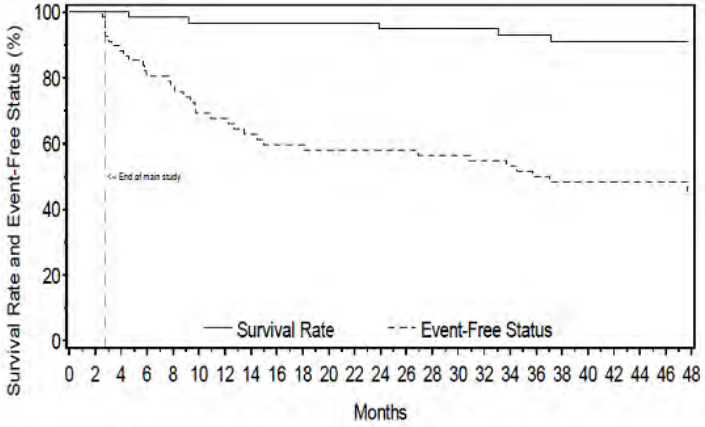
D = day; M = month

Comment: Subject numbers differ at the various time points and together with potential effects from subject discontinuation it is not possible to draw meaningful conclusions from these efficacy data.

There was high variability in NT-proBNP over time and also the inter-subject variability was high. The probability of survival at 47 months was >91% and event free survival (i.e. survival without heart/lung transplantation, atrial septostomy, pulmonary endarterectomy or start of

new pulmonary hypertension treatment) was 45%. Figure 11 shows the Kaplan Meier plot of time to clinical worsening.

Figure 11. Study 12166 long term extension Kaplan Meier plot of time to clinical worsening (months)-combined diagnosis group (n=68)*

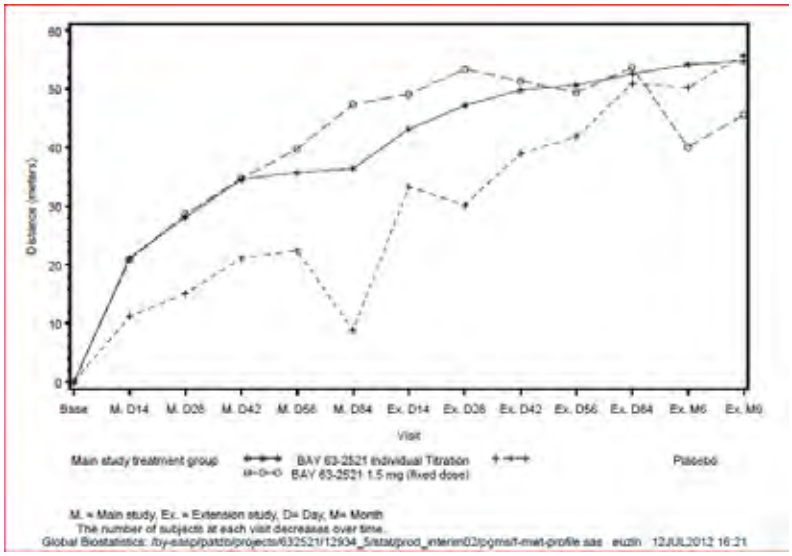


Note: The main study ended at 2.8 months.
a Subjects who withdrew prematurely from the study for reasons other than death are censored on the date of last study medication or on the date of last visit, which ever comes last. Subjects ongoing in the study are censored 01 NOV 2011 (cut-off date).
Censoring on the date of last study medication/last visit omits the death of Subject 12166-01-009 from the analysis. This subject, who withdrew due to an adverse event, died 64 days after the last dose of study medication.
Event-free status was defined as survival without heart/lung transplantation, atrial septostomy, pulmonary endarterectomy or start of new pulmonary hypertension treatment. For subjects with more than 1 event, only the first event was used in the analysis.

Study 12935 (PATENT-2) was analysed to a visit cut-off date of 16 April 2012. Of the 405 subjects completing the primary study, 396 entered the extension with 363 included in the interim analysis and 55 (15%) had prematurely discontinued at data cut-off. The main reasons for discontinuation were adverse events (7.2%) and death (3.9%). The extension study subjects had mainly idiopathic PAH (62.8%) or PAH due to connective tissue disease (23.7%). Treatment compliance was high the first 12 weeks with 95% of subjects reporting compliance between 90 to 110%. This decreased slightly to 88% in the 4 weeks post titration.

The mean change in 6MWD from baseline in PATENT-1 to week 12 in PATENT-2 (24 weeks on-study) was 52.5 m, 42.3 m and 45.2 m in the former 1.0–2.5 mg riociguat, placebo and 1.0–1.5 mg riociguat group, respectively. The unadjusted mean change from baseline was 51.2 m at 6 months (n=288), 53.7 m at 9 months (n=247), 48.4 m at 12 months (n=214), and 47.3 m at 18 months (n=151) (Figure 12).

Figure 12. Study 12935 (PATENT-2)

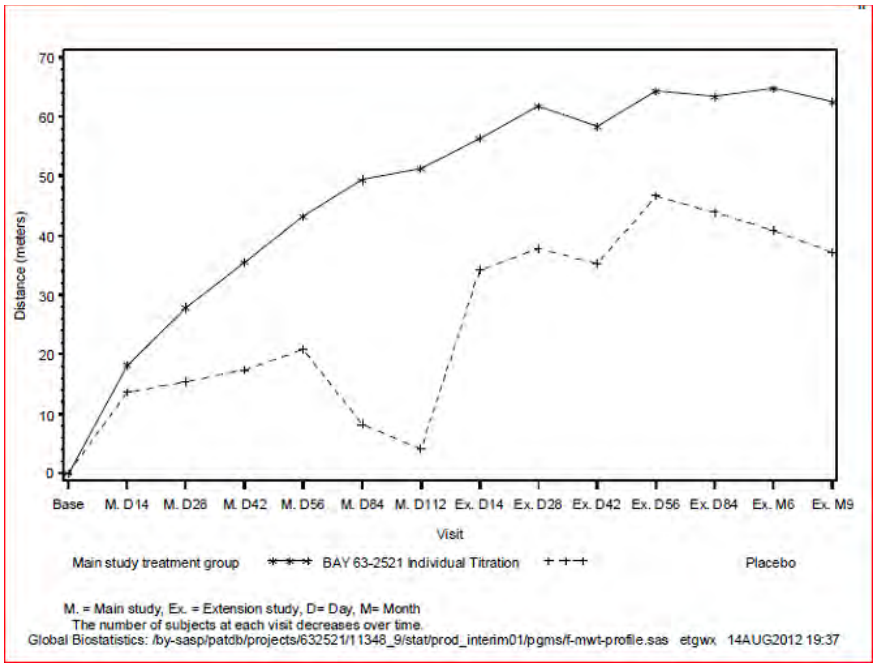


The data on NT-proBNP at week 12 of the extension study showed a maintenance in the mean reduction from baseline, although the high variability of these data make comparisons between groups difficult. At week 12 in PATENT-2, an improvement in WHO functional class compared to baseline was reported in 30.4%, no change in 65.2% and deterioration in 4.4%. At 18 months (in 159 subjects) the rate of improvement was 37.8% and deterioration was 8.8%, while the rate of any clinical worsening was 17.9%. Data on the Borg CR 10 scale, the EQ-5D and LPH also indicated efficacy maintenance.

Study 11349 (CHEST-2) was analysed using a data cut-off at 3 March 2012 when all subjects had completed the 8 weeks titration phase. Data were analysed at week 12 of the extension study with imputation for subjects who had not yet reached this visit due to death, withdrawal or the data cut. Of the 243 CTEPH subjects completing the primary study, 237 entered the extension, 194 were included in the interim analysis and 12 (6.2%) had prematurely discontinued. The most frequent reason for discontinuation was death (2.3% and 3.1% of the former riociguat and placebo groups, respectively). Concomitant medication specific for PH was low (about 10%) as it was prohibited during the titration phase. Treatment compliance was high with a mean of 98% during the first 12 weeks.

In the primary study, the mean change from baseline to week 16 in the 6MWD was 51.2 and 4.1 m in the riociguat and placebo groups, respectively. The mean change in 6MWD from baseline in the primary study to week 12 in CHEST-2 (28 weeks on study) was 63.3 m and 35.3 m in the former riociguat and placebo groups, respectively. The unadjusted mean change from baseline for the total group (n=194) was 56.5 m at 6 months (n=149), 54.0 m at 9 months (n=113), 47.6 m at 12 months (n=93) and 60.7 m at 18 months (n=63) (Figure 13).

Figure 13. Study 11349 (CHEST-2) Mean change in 6MWD from baseline by visit (unadjusted values)-long term safety analysis set



Compared to baseline, at week 12 in CHEST-2, 39.9% of subjects improved and 3.3% of subjects deteriorated in WHO functional class. The rate of 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). After the median treatment duration of 336 days, the rate of clinical worsening was 10.8%[14].

The decrease in mean NT-proBNP appeared to be maintained however the data were again highly variable. After 28 weeks of treatment the mean change from baseline in the Borg CR 10 Scale was -0.89 and -0.44 in the former riociguat and placebo groups, respectively, suggesting a maintenance of effect in those on riociguat and a lesser effect in those swapping from placebo.

Comments: Efficacy assessments in these extension studies point towards a persistence of effect (24 weeks in PATENT-2 and 28 weeks in CHEST-2).

- The improvement in those who had been treated with placebo in the primary study when treated with riociguat provides confirmatory efficacy evidence.
- However, the data were uncontrolled and open label, the analysis exploratory and descriptive and other PH medications could be commenced (from week 8 in PATENT-2 and CHEST-2).
- The data from the Phase II extension study also had variable subject numbers at visits and lacked imputation leading to a risk of bias from premature discontinuation.
- For these reasons the evaluator finds that the evidence for long term efficacy is only moderate.

9.4.2. Other studies

Module 5 also contained the following data:

[14] Clinical worsening was a composite of hospitalisation due to PH, start of new PH treatment, decrease in 6MWD due to PH, persistent worsening of functional class due to PH or death.

- **Report PH-37063** which included updated safety listings for riociguat studies 11348/11349 (CHEST), 12166,12934112935 (PATENT), 14308 (LEPHT) and 15096 (PATENT PLUS).
- **Report A50851**, **Study 13796**, was a randomised, double-blind, 2-way crossover, placebo-controlled study to investigate the influence of a single-dose of moxifloxacin 400 mg on the QTc interval in 56 healthy male and female subjects for positive control validation in selected centres of the PATENT-1 trial. The study was designed to test the ECG assay sensitivity of PATENT-1 at a subset of 5 PATENT-1 centres. In the 51 subjects available for QT analysis, the LS mean difference between moxifloxacin 400 mg and placebo 3 hours post dosing in the QTcF was 15.37 msec (95% CI: 11.9, 18.8) and for QTcF was 15.55 msec (95% CI: 10.1, 21.0). This indicated that the study setting ECGs were sensitive enough to detect potential QT prolongation induced by riociguat.

Five studies with riociguat's main metabolite, BAY 60-4552, as follows:

- **Report PH-35324, Study 12120**, was a relative bioavailability study to investigate safety, tolerability, pharmacokinetics of a 2.5 mg IR tablet of BAY 60-4552 in comparison to a 2.5 mg solution of BAY 60-4552, and to investigate the food effect of a fat, high calorie meal on a 2.5 mg IR tablet BAY 60-4552 in 12 healthy male subjects in a randomised, open-label, three-fold crossover design.
- **Report PH-35615, Study 12119**, was a single dose, basic Phase I dose escalation study in a randomised, single-blind, placebo-controlled, group-comparison design to investigate safety and tolerability of BAY 60-4552 and its pharmacodynamics and pharmacokinetics after oral dosing in 8 healthy male subjects per dose step. Report PH-36619, Study 12440, was the exploratory PK/PD analysis of this study.
- **Report PH-36011, Study 12835,** was a randomised, non-blinded, non-placebo-controlled, 2 fold crossover study to investigate the influence of co-administration of 10 mL Maalox on the safety, tolerability, and pharmacokinetics of a single oral dose of 10 mg BAY 60-4552 given as 4 x 2.5 mg IR tablets in healthy male subjects.
- **Report PH-36121, Study 12356**, was a proof of concept study to investigate safety, tolerability, pharmacokinetics and the impact on pulmonary and systemic haemodynamics of a single oral dose of BAY 60-4552 in patients with biventricular chronic heart failure and pulmonary hypertension in a non-randomised, non-blinded, dose escalation design. Report PH-36571, Study 12487, was an exploratory PK/PD analysis of this study.
- **Report PH-36125, Study 12121**, was a multiple dose basic Phase I dose escalation study, to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of BAY 60-4552 after oral dosing of 2.5, 5.0 or 7.5 mg od over 7 days given as a 2.5 mg IR-tablet and preceded by a single dose in 12 healthy male subjects per dose step in a randomised, single-blind, placebo-controlled, group-comparison design.

  Comment: These studies are of the active metabolite of riociguat (BAY 60-4552). The sponsor stated this was assessed in a separate development program which was terminated in 2011. Safety data are considered in the pooled analyses.

Four early phase studies of riociguat in different patient populations:

- **Report A54795, study14549**, was a Phase IIa multi-centre, randomised, double-blind, placebo-controlled study to assess the effects of a single dose of 1 mg riociguat (BAY 63-2521) on myocardial contractility and relaxation in patients with pulmonary hypertension associated with left ventricular systolic dysfunction (PH-sLVD). This study was prematurely terminated as only one subject of the 22 planned subjects was enrolled. No efficacy data on this subject were presented and the report was abbreviated.

- **Report A55138, Study 12916**, was a Phase II, multi-centre, non-randomised, non-blinded, non-controlled 12 week study to investigate the impact of multiple doses of riociguat (1.0 to 2.5 mg TDS) on safety, tolerability, pharmacokinetics, and pharmacodynamics in 22 patients with interstitial lung disease (ILD) associated pulmonary hypertension. The dossier included an interim report with a long term extension reported to be ongoing. There was also included **Report PH-36704, Study 13815,** which was the exploratory PK/PD analysis of this study.
- **Report A62512, Study 14308,** was a Phase II, randomised, double-blind, placebo-controlled, parallel group, 16 week, multi-centre study to evaluate the haemodynamic effects of Riociguat as well as safety and PK in 202 patients with pulmonary hypertension associated with left ventricular systolic dysfunction. The dose groups were riociguat 0.5 mg TDS fixed, up to 1 mg tid, up to 2 mg TDS and placebo. The primary PD endpoint was change from baseline in mean PAP at 16 weeks. The study found no significant improvement in mean PAP with riociguat 2.0 mg TDS compared to placebo group as the mean change from baseline to week 16 in the mean PAP was –2.71 mmHg (95% CI: –5.99, 0.57 mmHg, p=0.104). **Report PH-37047** was included in the dossier. This study report was stated to be the interim analysis for the database cutoff of 7 June 2012. It only included the tables in Section 14 which the Sponsor stated was "for technical reasons".
- **Report PH-36363, Study 12915**, was a proof of concept Phase IIa study to investigate safety, tolerability, pharmacokinetics and the impact on pulmonary and systemic haemodynamics, gas exchange and lung function parameters of a single-dose (1.0 mg and 2.5 mg) of BAY 63-2521 IR tablet in 23 patients with COPD associated pulmonary hypertension in a non-randomised, unblinded design. **Report PH-36428, Study 15027**, was the exploratory PK/PD analysis from Study 12915.

  Comment: These data are from different patient populations to the proposed indication and so do not provide relevant efficacy data for this submission. They are not discussed further in this section. Safety data from studies 12915, 12916, 14308, 14549 have been included in the pooled safety data analyses.

9.5. Analyses performed across trials (pooled analyses and meta-analyses)

Report PH-37088, was a technical report for the integrated analysis of efficacy of riociguat in patients with CTEPH and PAH. It included data from the pivotal Phase III studies 11348, 11349, 12934 and 12935. Subjects valid for safety and the ITT population were included and analysis was exploratory, stratified by indication. Efficacy data were represented in the Summary of Clinical Efficacy in Module 2.

There were 707 subjects randomised in studies 11348 and 12934 (446 into Study 11348 and 586 into Study 12934), with 704 in the ITT population, 427 subjects received individual dose titration (IDT) riociguat and 214 placebo (64 subjects in the riociguat 1.0 to 1.5 mg group in Study 12934 were not included in the integrated analysis) (Table 7).

Table 7. Subject populations-Pooled CTEPH studies (11349, 11349) and pooled PAH studies (12934 and 12935).

Indication / *Population* / Study	Main studies: Riociguat IDT		Main studies: Placebo		LTE studies: Former riociguat IDT		LTE studies: Former placebo	
CTEPH studies 11348 and 11349								
Randomized								
Study 11348 CHEST-1	174	(100%)	88	(100%)	-	-	-	-
Study 11349 CHEST-2 [a]	-	-	-	-	129	(74.1%)	65	(73.9%)
Valid for safety / ITT								
Study 11348 CHEST-1	173	(99.4%)	88	(100%)	-	-	-	-
Study 11349 CHEST-2 [a]	-	-	-	-	129	(74.1%)	65	(73.9%)
Per Protocol [b]								
Study 11348 CHEST-1	143	(82.2%)	75	(85.2%)	-	-	-	-
PAH studies 12934 and 12935								
Randomized								
Study 12934 PATENT-1	254	(100%)	127	(100%)	-	-	-	-
Study 12935 PATENT-2 [a]	-	-	-	-	215	(84.7%)	96	(75.6%)
Valid for safety / ITT								
Study 12934 PATENT-1	254	(100%)	126	(99.2%)	-	-	-	-
Study 12935 PATENT-2 [a]	-	-	-	-	215	(84.7%)	96	(75.6%)
Per Protocol [b]								
Study 12934 PATENT-1	218	(85.8%)	106	(83.5%)	-	-	-	-

a Numbers denote active treatment (combined for PATENT-1) or placebo group for the single study or the respective pooled population as described in Section 3.2. Population in the studies 11349 and 12935 is named "long-term safety analysis.
b Not applicable for LTE studies and the pooled analysis.

The main differences in baseline characteristics between the two studies were that in the PAH study there were more women (79% versus 66%), more Asians (30% versus 22%), less Europeans (47% versus 60%) and subjects with PAH were younger (51 years versus 59 years). In the CTEPH study population has slightly more severe disease with 62-68% of subjects in WHO functional class III and most others in class II. In the PAH study the proportion of subjects in WHO function class III was lower (46-55%) and higher in class II (43-48%). There were also more CTEPH than PAH subjects with baseline 6MWD of <320m (33% versus 24%). In CHEST-1, use of specific PH medication was not allowed, while in PATENT-1 pre-treatment (with mainly ERAs) occurred in about half the subjects (Table 8).

Tables 9, 10 and 11 present data on the primary efficacy endpoint, subgroup analysis of the primary endpoint and hierarchical testing of the secondary endpoints for the two studies side by side.

Table 8. Specific prior and concomitant PH medication-main CTEPH and PAH studies (safety-ITT analysis set)

Specific prior and concomitant PH medication – main CTEPH and PAH studies (safety/ITT analysis set)

Medication class/ category	11348 (CHEST-1) Riociguat IDT N=173 (100%)		11348 (CHEST-1) Placebo N=88 (100%)		12934 (PATENT-1) Riociguat IDT N=254 (100%)		12934 (PATENT-1) Placebo N=126 (100%)	
Endothelin receptor antagonists								
Prior medication	5	(2.9%)	1	(1.1%)	114	(44.9%)	54	(42.9%)
Any concomitant medication	2	(1.2%)	0	-	113	(44.5%)	52	(41.3%)
Any new concomitant medication	1	(0.6%)	0	-	4	(1.6%)	1	(0.8%)
Prostacyclins (incl. analogues)								
Prior medication	17	(9.8%)	9	(10.2%)	43	(16.9%)	24	(19.0%)
Any concomitant medication	0	-	0	-	22	(8.7%)	12	(9.5%)
Any new concomitant medication	0	-	0	-	4	(1.6%)	5	(4.0%)
Phosphodiesterase Type 5 inhibitors								
Prior medication	3	(1.7%)	4	(4.5%)	1	(0.4%)	1	(0.8%)
Any concomitant medication	0	-	0	-	0	–	1	(0.8%)
Any new concomitant medication	0	-	0	-	0	–	1	(0.8%)

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

Table 9. Primary efficacy analysis. Change in 6MWD (m) from baseline to last visit. Main CTEPH and PAH studies (safety and ITT analysis set)

Primary efficacy analysis: Change in 6MWD (meter) from baseline to last visit - main CTEPH and PAH studies (safety/ITT analysis set)

	11348 (CHEST-1)		12934 (PATENT-1)	
Statistic	**Riociguat IDT**	**Placebo**	**Riociguat IDT**	**Placebo**
	N=173	**N=88**	**N=254**	**N=126**
Baseline				
Mean (SD)	342.3 (81.9)	356.0 (74.7)	361.4 (67.7)	367.8 (74.6)
Median (Min-Max)	360.0 (150-557)	372.0 (152-474)	374.5 (160-468)	391.0 (150-450)
Change from baseline to last visit [a]				
Mean (SD)	38.9 (79.3)	−5.5 (84.3)	29.6 (65.8)	−5.6 (85.5)
Median (Min-Max)	42.0 (−376-335)	5.0 (−389-226)	30.0 (−430-279)	8.5 (−400-204)
Treatment comparison	**Riociguat IDT− placebo**		**Riociguat IDT− placebo**	
LS mean difference	45.69		35.78	
95% CI	24.74 to 66.63		20.06 to 51.51	
p-value (ANCOVA)	<0.0001		<0.0001	
p-value (stratified Wilcoxon test)	<0.0001		<0.0001	

ANCOVA model with baseline value, treatment group, and region as fixed effects, stratified Wilcoxon test by region (for PATENT-1 by stratification group in addition)

a Last visit = Last observed value (not including follow-up) for subjects who completed the respective 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

Abbreviations: IDT = individual dose titration (1.0-2.5 mg), SD = standard deviation, CI = confidence interval, ANCOVA = analysis of covariance

Table 10. Primary efficacy analysis. Mean treatment difference in change from baseline to last visit in 6MWD by pre-specified subgroups. Main CTEPH and PAH studies (safety and ITT analysis set)

Primary efficacy analysis: Mean treatment difference in change from baseline to last visit in 6MWD by pre-specified subgroups – main CTEPH and PAH studies (safety/ITT analysis set)

	11348 (CHEST-1)		12934 (PATENT-1)	
Subgroup	**LS mean difference (riociguat IDT − placebo)**	**95% CI**	**LS mean difference (riociguat IDT − placebo)**	**95% CI**
Inoperable CTEPH	53.92	28.53 to 79.31	-	-
Postoperative CTEPH	26.72	-9.86 to 63.13	-	-
Idiopathic/Familial	-	-	42.60	23.38 to 62.22
Connective tissue disease	-	-	26.11	-4.40 to 60.62
Associated (other forms) PAH	-	-	18.23	-32.50 to 68.96
Therapy-Naive	-	-	58.36	14.46 to 62.26
Pre-Treated	-	-	35.66	16.04 to 66.36
Pre-treated with ERA	-	-	25.89	5.31 to 46.48
Pre-treated with PCA	-	-	101.28	26.53 to 176.02
WHO I/II at Baseline	25.45	-8.85 to 59.75	12.14	-6.14 to 32.42
WHO III/IV at Baseline	62.97	26.50 to 79.43	59.70	36.44 to 82.96
Pre-Treated & WHO I/II at BL	-	-	8.43	-22.96 to 39.82
Pre-Treated & WHO III/IV at BL	-	-	54.15	26.69 to 81.61
Therapy-Naive & WHO I/II at BL	-	-	16.46	-10.86 to 43.78
Therapy-Naive & WHO III/IV at BL	-	-	71.72	29.80 to 113.64
Baseline 6MWD < 320m	44.25	2.94 to 85.56	57.33	20.48 to 94.18
Baseline 6MWD >= 320m	46.15	22.14 to 70.15	29.15	11.74 to 46.55
Baseline 6MWD < 380m	44.64	16.92 to 72.37	49.49	26.16 to 73.82
Baseline 6MWD >= 380m	47.45	15.10 to 79.79	24.98	4.37 to 45.58
Female	54.21	27.73 to 80.70	36.99	20.20 to 53.80
Male	39.80	8.60 to 71.00	31.38	-9.34 to 72.10
Age < 65	43.93	14.52 to 73.34	27.27	8.14 to 46.41
Age >= 65	48.63	18.85 to 78.41	54.77	30.18 to 79.37
White	44.34	20.41 to 68.27	37.99	17.88 to 58.10
Black or African American	63.63	-152.89 to 200.86	32.89	-70.29 to 136.07
Asian	55.42	3.01 to 107.24	38.78	10.93 to 66.63
Race not reported	5.79	-64.87 to 76.44	-4.73	-58.13 to 48.67
North America	18.53	-29.83 to 67.10	4.07	-49.32 to 57.46
South America	18.54	-37.85 to 74.66	-4.04	-39.36 to 31.28
Europe	46.83	19.59 to 73.67	46.10	21.47 to 70.73
China	101.85	38.94 to 164.76	40.13	6.48 to 86.79
Asia/Pacific	14.80	-77.48 to 107.08	40.67	8.29 to 73.05
Overall	**46.09**	**25.25 to 66.93**	**35.48**	**19.84 to 51.13**

Estimates and CIs are based on an ANCOVA model with baseline value and treatment effect as fixed effects.
Last visit = last observed value (not including follow-up) for subjects who completed the study or withdrew, except imputed worst value in case of death or clinical worsening without a termination visit or a measurement at that termination visit.
Abbreviations: IDT = individual dose titration (1.0-2.5 mg), CI = confidence interval, ANCOVA = analysis of covariance, BL = baseline

Table 11. Secondary efficacy variables. Summary of hierarchical testing. ITT analysis set

Secondary efficacy variables: Summary of hierarchical testing - ITT analysis set

Variable	Treatment effect ANCOVA p-value	Shapiro-Wilk test p-value	Stratified Wilcoxon test p-value	Statistically significant	Statistically significant in hierarchical testing
11348 (CHEST-1)					
6MWD (primary)	<0.0001	0.0001	**<0.0001**	Yes	Yes
PVR	<0.0001	0.0001	**<0.0001**	Yes	Yes
NT-proBNP	0.0293	0.0001	**<0.0001**	Yes	Yes
WHO functional class	–	–	**0.0026**	Yes	Yes
Time to clinical worsening	0.2180 a	–	**0.1724 b**	No	No
Borg CR 10 scale c	–	–	**0.0035**	Yes	No
EQ-5D questionnaire	0.0002	0.0001	**<0.0001**	Yes	No
LPH questionnaire	0.0165	0.0001	**0.1220**	No	No
12934 (PATENT-1)					
6MWD (primary)	<0.0001	0.0001	**<0.0001**	Yes	Yes
PVR	<0.0001	0.0001	**<0.0001**	Yes	Yes
NT-proBNP	0.0157	0.0001	**<0.0001**	Yes	Yes
WHO functional class	–	–	**0.0033**	Yes	Yes
Time to clinical worsening	0.0285 a	–	**0.0046 b**	Yes	Yes
Borg CR 10 scale d	–	–	**0.0022**	Yes	Yes
EQ-5D questionnaire	0.0197	0.0001	**0.0663**	No	No
LPH questionnaire	0.0009	0.0001	**0.0019**	Yes	No

P-values used to determine statistical significance are given in bold.
a Mantel-Haenszel estimate p-value for incidence of clinical worsening
b Stratified log-rank test p-value for time to clinical worsening.
c Subjects enrolled before amendment 3 used the Modified Borg Dyspnoea Scale.
d Subjects enrolled before amendment 4 used the Modified Borg Dyspnoea Scale.

Comment: Efficacy data were presented side by side for CHEST-1 and PATENT-1 but were not pooled due to the different PH diagnosis, different treatment duration (16 versus 12 weeks) and different baseline treatment regimens allowed and resultant disease characteristics. For these reasons further data from the integrated analysis have not been presented.

9.6. Evaluator's conclusions on clinical efficacy for PAH and CTEPH

The efficacy of riociguat in PAH and CTEPH was based on two Phase III randomised, double-blind, placebo-controlled, international studies, one in each indication. The PAH study (PATENT-1) included 443 patients with symptomatic PAH (WHO group 1) which was primarily idiopathic (59-67%) or due to connective tissue disease (20 to 28%). These PAH subjects could be treatment naïve (about half the subjects) or pre-treated with an ERA or prostacylin analogue. The CTEPH study (CHEST-1) included both subjects with inoperable CTEPH (70-77%) or with PH persisting after pulmonary endarterectomy (23-30%). Subjects with CTEPH received oral anticoagulation but not specific PH medication. The studies included patients with a 6MWD between 150-450 m, a PVR of >300 dyn*sec*cm^{-5} and a mean PAP of >25 mmHg. The vast majority of subjects were WHO FC II and III at baseline.

The trials employed an individual dose titration (IDT) regimen with a starting dose of 1.0 mg TDS and increases of 0.5 mg TDS each two weeks based on the subject's peripheral SBP. The dose range was between 0.5 mg and 2.5 mg TDS and there was a separate arm in study PATENT-1 which assessed a titration regimen capped at 1.5 mg TDS. Controlled treatment was for 16 weeks in the CHEST-1 and 12 weeks in PATENT-1. At week 16 in CHEST-1, 77% of subjects were on riociguat 2.5 mg TDS and 12% were on 2.0 mg TDS. At week 12 in PATENT-1, 75% of the 1.0 to 2.5 mg group were on 2.5 mg TDS and 15% on 2.0mg TDS and in the capped 1.0 to 1.5 mg group, 95% were on 1.5 mg TDS. Subjects could then enter open label long term extensions.

The primary efficacy endpoint in both studies was the mean change from baseline in the 6MWD compared to placebo in the ITT population with imputation for missing values. Secondary endpoints were tested in a hierarchical procedure in the following order: PVR, NT-proBNP, WHO functional class, Time to clinical worsening, Borg CR 10, EQ-5D and LPH.

Premature treatment discontinuation was lower in the riociguat group than the placebo group (6.7% versus 12.6%) in the PAH study, but this was not seen in the CTEPH study (8.0% versus 5.7%) (Table 12).

Table 12. Primary reasons for premature termination of study treatment. Main and extensions CTEPH and PAH studies (randomised subjects).

Primary reasons for premature termination of study treatment - main and extension CTEPH and PAH studies (randomized subjects)

	11348 (CHEST-1)				12934 (PATENT-1)			
	Riociguat IDT		Placebo		Riociguat IDT		Placebo	
Completed treatment	160	(92.0%)	83	(94.3%)	237	(93.3%)	111	(87.4%)
Prematurely discontinued	14	(8.0%)	5	(5.7%)	17	(6.7%)	16	(12.6%)
Adverse event	4	(2.3%)	2	(2.3%)	8	(3.1%)	7	(5.5%)
Death	2	(1.1%)	2	(2.3%)	0	-	2	(1.6%)
Lack of efficacy	2	(1.1%)	1	(1.1%)	0	-	1	(0.8%)
Lost to follow-up	0	-	0	-	1	(0.4%)	0	-
Non-compliance with study drug	1	(0.6%)	0	-	1	(0.4%)	0	-
Protocol violation	3[a]	(1.7%)	0	-	1	(0.4%)	3[a]	(2.4%)
Withdrawal by subject	2	(1.1%)	0	-	6	(2.4%)	3	(2.4%)
	11349 (CHEST-2)				12935 (PATENT-2)			
	Former riociguat IDT		Former placebo		Former riociguat IDT		Former placebo	
Prematurely discontinued	7	(5.4%)	5	(7.7%)	32	(14.9%)	19	(19.8%)
Adverse event	2	(1.6%)	0	-	17	(7.9%)	8	(8.3%)
Death	3	(2.3%)	2	(3.1%)	6	(2.8%)	6	(6.2%)
Lack of efficacy	1	(0.8%)	1	(1.5%)	1	(0.5%)	1	(1.0%)
Non-compliance with study drug	0	-	0	-	0	-	2	(2.1%)
Protocol violation	0	-	0	-	2	(0.9%)	0	-
Withdrawal by subject	1	(0.8%)	2	(3.1%)	5	(2.3%)	2	(2.1%)
Other	0	-	0	-	1	(0.5%)	0	-

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

Both studies were positive with statistically significant and clinically meaningful improvement in exercise capacity. In CHEST-1 in the CTEPH population, the LS mean improvement in the 6MWD after 16 weeks with riociguat compared to placebo was 46 m (95% CI 25,67, p<0.0001) (Table 13). In PATENT-1 in the PAH population, riociguat treatment (1.0 to 2.5 mg TDS regimen) resulted in improvement over placebo in the 6MWD after 12 week of 36 m (95% CI: 20-52, p<0.0001) (Table 14).

Table 13. Study 11348 (CHEST-1) Summary of efficacy results for predefined variables in the hierarchical testing order. ITT analysis set.

Variable	LS mean (treatment difference of riociguat IDT to placebo)	95% CI	Stratified Wilcoxon test p-value	Statistically significant	Statistically significant in hierarchical testing
6MWD (m) (primary)	46	25 to 67	<0.0001	Yes	Yes
PVR (dyn*s* cm^{-5})	-246	-303 to -190	<0.0001	Yes	Yes
NT-proBNP (pg/mL)	-444	-843 to -45	<0.0001	Yes	Yes
WHO functional class	32.9%[a] riociguat 14.9% [a] placebo	N/A	0.0026	Yes	Yes
Time to clinical worsening	2% [b] riociguat 6% [b] placebo	N/A	0.1724 [c]	No	No
Borg CR 10 score [d]	-0.8 [e] riociguat 0.2 [e] placebo	N/A	0.0035	Yes	No
EQ-5D questionnaire	0.13	0.06 to 0.21	<0.0001	Yes	No
LPH questionnaire	-5.76	- 10.45 to -1.06	0.1220	No	No

Abbreviations: LS = least square; CI = confidence interval; IDT = individual dose titration (riociguat 1.0 to 2.5 mg); 6MWD = 6 minute walking distance; PVR = pulmonary vascular resistance; EQ-5D = European quality of life 5-dimensions instrument; LPH = Living with Pulmonary Hypertension

[a] Improvement by at least 1 WHO functional class in the respective treatment group

[b] Percentage of subjects with any clinical worsening event in the respective treatment group

[c] Stratified log-rank test p-value for time to clinical worsening.

[d] Subjects enrolled before amendment 3 used the Modified Borg Dyspnoea Scale.

[e] Change from baseline to last visit in the respective treatment group

Table 14. Study 12934 (PATENT-1) Summary of efficacy results for predefined variables in the hierarchical testing order. ITT analysis set.

Summary of efficacy results for pre-defined variables in the hierarchical testing order- Study 12934 (PATENT-1), ITT analysis set

Variable	LS mean (treatment difference of riociguat IDT to placebo)	95% CI	Stratified Wilcoxon test p-value	Statistically significant	Statistically significant in hierarchical testing
6MWD (m) (primary)	36	20 to 52	<0.0001	Yes	Yes
PVR (dyn*s* cm^{-5})	-226	-281 to -170	<0.0001	Yes	Yes
NT-proBNP (pg/mL)	-432	-782 to -82	<0.0001	Yes	Yes
WHO functional class	20.9%[a] riociguat 14.4% [a] placebo	N/A	0.0033	Yes	Yes
Time to clinical worsening	1% [b] riociguat 6% [b] placebo	N/A	0.0046 [c]	Yes	Yes
Borg CR 10 scale [d]	-0.4 [e] riociguat 0.1 [e] placebo	N/A	0.0022	Yes	Yes
EQ-5D questionnaire	0.06	0.01 to 0.11	0.0663	No	No
LPH questionnaire	-6.17	- 9.79 to -2.54	0.0019	Yes	No

Abbreviations: LS = least square; CI = confidence interval; IDT = individual dose titration (riociguat 1.0 to 2.5 mg); 6MWD = 6 minute walking distance; PVR = pulmonary vascular resistance; EQ-5D = European quality of life 5-dimensions instrument; LPH = Living with Pulmonary Hypertension

[a] Improvement by at least 1 WHO functional class in the respective treatment group

[b] Percentage of subjects with any clinical worsening event in the respective treatment group

[c] Stratified log-rank test p-value for time to clinical worsening.

[d] Subjects enrolled before amendment 3 used the Modified Borg Dyspnoea Scale.

[e] Change from baseline to last visit in the respective treatment group

The results were robust in both studies, being supported by sensitivity analyses using different imputation methods and by the PP population analysis. In addition, efficacy on the primary endpoint of 6MWD was demonstrated across subgroups. This included inoperable CTEPH (LS mean difference 54m) and postoperative CTEPH (LS mean difference27 m), therapy naïve PAH patients (LS mean difference of 38m) and pre-treated PAH subjects (LS mean 26 m CHECK), WHO functional class (I/II or III/IV), gender, age group (± 65 years), baseline 6MWD (± 380 m, ± 320 m), race (White, Asian). The efficacy was noted to be greater in those with more impaired WHO FC and to have less of an effect on those PAH patients already on background PH specific medication.

Efficacy was supported by statistically significant results for secondary endpoints of PVR, NT-proBNP level and WHO functional class in both studies. While there was a trend in favour of riociguat in time to clinical worsening and the Borg CR 10 score for dyspnoea in both studies, this was only significant in the PAH study. It is noted that the duration of the pivotal trials (12-16 weeks) was less than the EMA recommended 6 months for studies aiming to demonstrate improvement in time to clinical worsening (EMA 2009).[15] Improvements on the QOL questionnaires did not reach significance in either study. The efficacy data were also supported by positive effects on haemodynamic parameters of PVR, CO, SVR and mean PAP in both studies.

In the long term open label studies, the mean exposure was 388 and 438 days in CHEST-2 and PATENT-2, respectively. Persistence of efficacy, as measured by 6MWD and WHO functional class maintenance, was found and the addition of PH medication was low at 6.2% and 12.1% in CHEST-2 and PATENT-2, respectively. There are however no controlled data past 12 weeks PAH and 16 weeks in CTEPH on which to confirm these findings.

There were no specific withdrawal studies and no studies assessing switching between medications.

The efficacy data on the capped titration regimen (1.0 to 1.5 mg TDS) were very similar to the higher titration regimen across all parameters. The low dose group had a small sample size

[15] EMA (2009). Committee for medicinal products for human Use (CHMP). Guideline on the clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. EMEA/CHMP/EWP/356954/2008.

(n=63) and there were no formal comparisons of the two dose groups. This means it is not possible to draw conclusions on the relative efficacy of one dose compared to the other.

The interaction of riociguat with the PDE inhibitor sildenafil was assessed in a small study (15096) in PAH patients and found a negative benefit risk balance so the combination must be avoided.

10. Clinical safety

10.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

10.1.1. Pivotal efficacy studies

There were four Phase III studies: Study 11348 (CHEST-1) and its long-term extension Study 11349 (CHEST-2); and Study 12934 (PATENT-1) and its long-term extension Study 12935 (PATENT-2). In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs).
- AEs of particular interest were: syncope (also predefined as an SAE); hypotension; SBP <90 mmHg; bleeding events; increased ALT >3xULN with increased bilirubin >2xULN; decrease in creatinine clearance >30 mL/min, creatinine clearance <90 mL/min; events included in the time to clinical worsening efficacy endpoint.
- Laboratory tests included haematology, coagulation, clinical chemistry including calcium phosphtate and 1,25-dihydroxy vitamin D, cystatin C, pregnancy testing, NT-proBNP (considered as a secondary efficacy endpoint).
- Vital signs after 10 minutes rest supine.
- 12 lead ECGs.
- Blood gas analysis SaO_2 (%), PaO2, $PaCO_2$ (mmHg).

Safety assessments were conducted every 2 weeks (apart from blood gas analysis) during the primary study and during the first 8 weeks of the extension study, then on a 3 monthly basis.

10.1.2. Phase II studies

There were seven Phase II studies: Study 12166 and its long-term extension (LTE), Study 15096 (PATENT PLUS), Study 12915 (PH due to COPD), Study 12916 (PH due to ILD), Study 14308 (PH due to LVD) and Study 14549 (PH due to LVD). The studies included 265 subjects and the daily dose range varied from 1.0 to 9.0 mg. These studies provided data on TEAEs, laboratory variables, vital signs (BP and HR), ECGs and blood gas analysis.

10.1.3. Phase I studies

There were 30 Phase I studies on riociguat including 768 healthy subjects and patient volunteers. There were 5 Phase I studies on the active metabolite of riociguat BAY 60-4552. In 25 these Phase I studies riociguat was administered as a single agent. The safety analysis set included 738 subjects. Single dose studies assessed doses from 0.25 to 5 mg in 543 subjects and multi-dose studies assessed doses from 1.5 mg to 7.5 mg in 189 subjects.

Due to differing aetiologies, safety data have been presented for each indication, PAH and CTEPH, separately. In addition the Sponsor pooled safety data as follows:

- Pool 1: the two Phase III placebo-controlled studies and their two non-controlled extension studies

- Pool 2: all multi-dose studies in CTEPH and PAH (the 4 Phase III studies plus studies 12166 and 15096)
- Pool 3: all Phase II and III riociguat studies (Pool 2 plus studies 12915, 12916, 14308 and 14549).

The sponsor stated that for the integrated analysis of safety *to ensure that all events which occurred in an extension study/phase are completely counted and not masked by events in the main study, all subjects in the extension study/phase were counted as additional subjects. Consequently, the number of analyzed subjects is higher than the number of enrolled subjects*.

10.2. Pivotal studies that assessed safety as a primary outcome

None.

10.3. Patient exposure

Exposure to riociguat in the Phase II studies was summarised : There were 265 subjects treated with riociguat with a mean treatment duration in the various studies ranging from 2 days to 36 months.

In the Phase III program where data available are for the safety analysis, there were 317 subjects with PAH and 173 with CTEPH exposed to riociguat in the primary studies and (due to the swap from placebo to active in the long term extension studies) the number rose to 363 and 194 in the respective long term extension studies (Table 15 below).

Table 15. Exposure to Riociguat and placebo in the Phase III clinical studies.

Study type/ Indication	Controlled studies		Uncontrolled studies
	Riociguat	Placebo	Riociguat
Clinical pharmacology			
Indication PAH			
Pivotal	317#	126	
Long term extension			363*
Indication CTEPH			
Pivotal	173	88	
Long term extension			194**
TOTAL	490	214	557

254 riociguat 1.0 to 2.5 mg and 63 riociguat 1.0 to 1.5 mg; *At cut off of 16 April 2012, 363 of 396 subjects in the extension were included in the safety analysis. **At cut off of 3 May 2012, 194 of the 237 subjects were included in the safety analysis

The mean treatment duration in PATENT-1 was 81.4 days (± 15.6), 80.0 days (± 18.9) and 78.2 days (± 20.5) in the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups,

respectively. The average total dose received was 457 mg (± 122.5) and 335.8 (± 86.1) in the 1.0 to 2.5 mg and 1.0 to 1.5 mg groups, respectively. At week 12, 74.6% of the riociguat 1.0 to 2.5 mg group were on the highest dose of 2.5 mg, 15.3% were on 2.0 mg, 5.9% were on 1.5 mg, 2.5% on 1.0 mg, and 1.7% on 0.5 mg. In the riociguat 1.0 to 1.5 mg group, 94.7% were on 1.5 mg.

In the long term extension study (PATENT-2), the mean treatment duration was 436.2 days (± 268.9) in the former riociguat 1.0 to 2.5 mg grou, 426.1 days (± 261.7) in the former placebo group and 470.1 days (± 282.2) for the former riociguat 1.0 to 1.5 capped dose group. There were 325 subjects who received treatment for 8 weeks (titration phase), 290 subjects for 24 weeks, 221 subjects for 48 weeks, 162 subjects for 72 weeks and 52 subjects (14.3%) for 108 weeks. The total exposure was 435.7 person-years. The mean cumulative exposure was 3082.5 mg (± 1994.3).

The mean treatment duration in CHEST-1 was 108.2 days (± 21.2) and 110.2 days (± 14.8) in the riociguat 1.0 to 2.5 mg and placebo groups, respectively. The average total dose received was 645 mg (± 166.5). At week 16, 76.9% (123/160) were on the highest dose of 2.5 mg tid, 12.5% were on 2.0 mg tid, 6.3% were on 1.5 mg tid, 3.8% on 1.0 mg tid, and 0.6% on 0.5 mg TDS.

In the extension study (CHEST-2), the mean treatment duration was 388.3 days (± 276.3). There were 187 subjects who received treatment for 8 weeks (titration phase), 97 subjects for 48 weeks and 39 subjects (20.1%) for 96 weeks. The total exposure was 206.2 person-years. The mean cumulative treatment exposure was 2732 mg (± 2015).

The demographics of patients in the two Phase III studies and in the pooled population were summarised in the submission.

10.4. Adverse events

10.4.1. All adverse events (irrespective of relationship to study treatment)

10.4.1.1. Pivotal studies

PAH: In PATENT-1. The rate of AEs was 90.6%, 88.1% and 93.7% and the rate of treatment emergent AEs (TEAEs)[16] was 89.4%, 85.7% and 92.1% in the riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups, respectively. Most events were mild or moderate and the rate of severe TEAEs was highest in the placebo group (11.0%, 15.1% and 9.5%, respectively). The rate of AEs after cessation (>2 days) of study treatment was 3.5%, 5.6% and 1.6%, respectively.

The most frequently involved SOC was gastrointestinal (55.1%, 37.3%, 60.3%). The following TEAEs occurred more frequently with riociguat than placebo (riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups, respectively): headache (27.2%, 19.8% and 31.7%), dyspepsia (18.9%, 7.9% and 12.7%), peripheral oedema (17.3%, 11.1% and 22.2%), dizziness (15.7%, 11.9% and 23.8%), hypotension (9.8%, 2.4% and 3.2%), anaemia (8.3%, 2.4% and 1.6%), pyrexia (3.1%, 3.2% and 9.5%) and gastritis (1.6%, 0% and 6.3%).

Dyspnoea (6.3%, 11.1% and 6.3%), cough (4.7%, 10.3% and 4.8%) and fatigue (2.8%, 6.3% and 0%) all occurred at higher rate in the placebo than riociguat groups.

In the long term extension study PATENT-2, the rate of TEAEs was 90.2% with 25.3% of subjects reporting a severe TEAE. The most frequently reported events were nasopharyngitis (19.8%), dizziness (18.5%), peripheral oedema (17.9%), headache (16.5%), cough (14.3%), diarrhoea (13.8%), nausea (12.4%) and dyspepsia (10.5%).

[16] Treatment emergent adverse events were defined as any event occurring in the period after the first dose of study medication up to 2 days after the last dose of study medication.

CTEPH: In CHEST-1, the rate of TEAEs was 92.5% in the riociguat compared to 88.6% in the placebo group. The rate of severe TEAEs was similar between groups (11.0% versus 11.4%). The rate of post-treatment AEs (AE starting >2 days after stopping study drug) was also similar (1.2% riociguat versus 1.1% placebo). The most frequently involved SOC was nervous system disorders (49.1% versus 30.7%) followed by gastrointestinal disorders (48% versus 30.7%) (Table 16).

Table 16. Most common TEAEs (≥5% of subjects in any treatment group) by MedDRA system organ class/preferred term (safety population of the Phase III studies 11348 and 11349 CETPH indication

	11348 CHEST-1				11349 CHEST-2	
MedDRA *Primary system organ class* / preferred term	Riociguat 1.0 – 2.5mg		Placebo		TOTAL [a]	
N (= 100%)	173		88		194	
ANY EVENT	159	(91.9%)	76	(86.4%)	173	(89.2%)
Cardiac disorders	20	(11.6%)	14	(15.9%)	43	(22.2%)
Palpitations	6	(3.5%)	4	(4.5%)	11	(5.7%)
Right ventricular failure	6	(3.5%)	3	(3.4%)	10	(5.2%)
Eye disorder	13	(7.5%)	3	(3.4%)	20	(10.3%)
Gastrointestinal disorders	83	(48.0%)	27	(30.7%)	82	(42.3%)
Constipation	10	(5.8%)	1	(1.1%)	9	(4.6%)
Diarrhoea	17	(9.8%)	4	(4.5%)	23	(11.9%)
Dyspepsia	31	(17.9%)	7	(8.0%)	19	(9.8%)
Nausea	19	(11.0%)	7	(8.0%)	15	(7.7%)
Vomiting	17	(9.8%)	3	(3.4%)	8	(4.1%)
General disorders & administration site conditions	55	(31.8%)	31	(35.2%)	60	(30.9%)
Chest pain	7	(4.0%)	4	(4.5%)	12	(6.2%)
Oedema peripheral	27	(15.6%)	18	(20.5%)	30	(15.5%)
Infections and infestations	65	(37.6%)	29	(33.0%)	90	(46.4%)
Bronchitis	6	(3.5%)	3	(3.4%)	14	(7.2%)
Nasopharyngitis	26	(15.0%)	8	(9.1%)	42	(21.6%)
Upper respiratory tract infection	10	(5.8%)	4	(4.5%)	15	(7.7%)
Injury, poisoning and procedural complications	11	(6.4%)	5	(5.7%)	33	(17.0%)
Fall	1	(0.6%)	0	-	5	(2.6%)
Investigations	31	(17.9%)	22	(25.0%)	46	(23.7%)
Blood creatinine increased	3	(1.7%)	5	(5.7%)	4	(2.1%)
International normalised ratio increased	10	(5.8%)	4	(4.5%)	10	(5.2%)
Metabolism and nutrition disorders	15	(8.7%)	10	(11.4%)	21	(10.8%)
Musculoskeletal and connective tissue disorders	34	(19.7%)	19	(21.6%)	58	(29.9%)
Arthralgia	5	(2.9%)	1	(1.1%)	16	(8.2%)
Back pain	7	(4.0%)	5	(5.7%)	17	(8.8%)
Muscle spasms	4	(2.3%)	2	(2.3%)	10	(5.2%)
Pain in extremity	3	(1.7%)	5	(5.7%)	8	(4.1%)
Nervous system disorders	85	(49.1%)	27	(30.7%)	60	(30.9%)
Dizziness	39	(22.5%)	11	(12.5%)	33	(17.0%)
Headache	43	(24.9%)	12	(13.6%)	10	(5.2%)
Syncope	4	(2.3%)	3	(3.4%)	10	(5.2%)
Psychiatric disorders	8	(4.6%)	8	(9.1%)	15	(7.7%)
Insomnia	4	(2.3%)	6	(6.8%)	6	(3.1%)
Respiratory, thoracic and mediastinal disorders	43	(24.9%)	32	(36.4%)	67	(34.5%)
Cough	9	(5.2%)	16	(18.2%)	19	(9.8%)
Dyspnoea	8	(4.6%)	12	(13.6%)	16	(8.2%)
Epistaxis	2	(1.2%)	2	(2.3%)	10	(5.2%)
Pulmonary hypertension	4	(2.3%)	0	-	10	(5.2%)
Vascular disorders	29	(16.8%)	13	(14.8%)	20	(10.3%)
Hypotension	16	(9.2%)	3	(3.4%)	11	(5.7%)

Note: Numbers denote number and percentage of subjects with events per treatment group. Multiple mentions per subject are possible.

[a] TOTAL refers to the 194 subjects in CHEST-2 included in the interim analysis (cut-off 3 May 2012).

The TEAE profile was similar to that seen in PATENT-1. Events with a rate at least 5% greater with riociguat than placebo were: headache (24.9% versus 13.6%), dizziness (22.5% versus 12.5%); dyspepsia (17.9% versus 8.0%), nasopharyngitis (15.0% versus 9.1%), diarrhoea (9.8% versus 4.5%), vomiting (9.8% versus 3.4%) and hypotension (9.2% versus 3.4%). While

higher rates in the placebo groups were seen for peripheral oedema (15.6% versus 20.5%), cough (5.2% versus 18.2%) and dyspnoea (4.6% versus 13.6%).

In the long term extension study CHEST-2, the rate of TEAEs was 92.8% and the rate of severe TEAEs was 17.0%. The most frequently reported events were nasopharyngitis (21.6%), dizziness (17.0%), peripheral oedema (15.5%), diarrhoea (11.9%), dyspepsia (9.8%) and cough (9.8%).

Pooled data: Tables 17 and 18 summarise the adverse event data and most frequent TEAEs in the two Phase III studies and in the pooled data from these studies. Exposure adjusted pooled data from the extension studies shows the most frequent TEAEs (per 100 person-years) were nasopharyngitits (26.8), dizziness (21.7), peripheral oedema (19.8), headache (17.7) and diarrhoea (15.7).

Table 17. Overall summary of number of subjects with adverse events-safety population of controlled Phase III studies 11348 and 12934

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 TEAE	159	(91.9%)	76	(86.4%)	227	(89.4%)	108	(85.7%)	444	(90.6%)	184	(86.0%)
Any study drug-related TEAE	103	(59.5%)	36	(40.9%)	162	(63.8%)	66	(52.4%)	304	(62.0%)	102	(47.7%)
Any severe TEAE	19	(11.0%)	10	(11.4%)	28	(11.0%)	19	(15.1%)	53	(10.8%)	29	(13.6%)
Any drug-related severe TEAE	4	(2.3%)	2	(2.3%)	15	(5.9%)	5	(4.0%)	20	(4.1%)	7	(3.3%)
Any serious TEAE	34	(19.7%)	14	(15.9%)	29	(11.4%)	23	(18.3%)	74	(15.1%)	37	(17.3%)
Any study drug-related serious TEAE	6	(3.5%)	1	(1.1%)	8	(3.1%)	5	(4.0%)	16	(3.3%)	6	(2.8%)
Any TEAE 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 TEAE leading to death	2	(1.2%)	3	(3.4%)	2	(0.8%)	*4	(3.2%)	5	(1.0%)	*7	(3.3%)

* One TEAE 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 (A62510 [Study 12934 in Module 5.3.5.1] Section 10.4.3.1). This subject died from *metastatic malignant melanoma*; the case was assessed as a post-treatment death (see also end of Table 7-18).

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.

Table 18. TEAEs: Most frequent MedDRA preferred terms-safety population of controlled Phase III studies 11348 and 12934

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 TEAEs 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.

10.4.1.2. AEs of interest

10.4.1.2.1. Syncope

In PATENT-1 the rate of syncope (loss of consciousness, presyncope and syncope) TEAEs was higher in the placebo group (3.1%, 5.6% and 3.2%). In PATENT-2 the rate of syncope in the

overall population was 7.2%. In PATENT-1, there were 3 severe events, with one occurring in each treatment group, all of which resolved.

In CHEST-1, the rate of syncope was 3.5% and 3.4% in the riociguat and placebo groups, respectively and two cases, one in each group, were severe. In the extension study, the overall rate was 6.7% with 6 severe cases. There were no withdrawals for syncope.

In pooled analysis (Pool 1), the rate of syncope TEAE was 14.8 versus 20.6 events per 100 person-years (riociguat versus placebo) and in the LTE studies was 8.1 events per 100 person-years.

10.4.1.2.2. Hypotension

In PATENT-1, the rate of hypotension (hypotension and BP decreased) TEAEs was highest with riociguat 1.0 to 2.5 mg (10.2% versus 3.2% placebo, 4.8% riociguat 1.0 to 1.5 mg). One patient withdrew from the study due to moderate hypotension. In PATENT-2 the rate of hypotension was 8.0%, there were 2 severe cases and no withdrawals due to hypotension.

In CHEST-1, the rate of hypotension was higher with riociguat (11.5% versus 4.5%) with one severe case. In CHEST-2, the rate was 6.2% and there were no withdrawals due to this event.

Pooled analysis (Pool 1) found hypotension more frequent with riociguat than placebo (10.0% versus 3.7%) with serious hypotension occurring in 0.4% (vs 0% in placebo) and one riociguat subject discontinuing due to hypotension. Hypotension was more frequent in subjects aged ≥65 years (16.4% versus 5.2% placebo). The rate of SBP <90 mmHg was also greater with riociguat (17.8% versus 9.8%) and the rate of combined hypotension due to TEAE or SBP <90 mmHg was 23.3% versus 12.1%. In the pooled LTE studies the rate of hypotension TEAE was 7.1 per 100 person-years and of SBP <90 mmHg was 49.5 per 100 person-years.

10.4.1.2.3. Bleeding events

The rate of bleeding events (haemorrhages and anaemia) in PATENT-1 was 12.2%, 10.3% and 11.1% in the riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups, respectively. Severe events only occurred in the riociguat groups (1.6% and 3.2%) and the 6 cases included 2cases of haemoptysis and 1 case each of intra-abdominal haemorrhage, subdural haematoma, vaginal haemorrhage and haematemesis. In PATENT-2, the rate was 24.5% and the most frequent bleeding events were epistaxis and haemoptysis. Serious bleeding events occurred in 4.7% in the extension study. In PATENT-1 approximately half the subjects were on anticoagulants and in the extension study the overall rate was 62%.

In the CTEPH population where over 95% of subjects were on anticoagulants, the reported rate of TEAEs due to bleeding events was 13.3% versus 11.4% in the riociguat and placebo groups, respectively. The most frequent events were haemoptysis and epistaxis. There were 6 (3.5%) serious bleeding events (3 were haemoptysis) all of which were in the riociguat group. In the extension study CHEST-2, the rate of bleeding events was 17.5% with serious bleeding events occurring in 3.6% and 3 of these subjects has serious gastrointestinal haemorrhage.

In pooled analysis (Pool 1), the differential in bleeding events (19.8% versus 15.4%) was driven by a higher rate of anaemia in the riociguat group (5.7% versus 1.9%). The rate of serious bleeding events was higher with riociguat (2.4% versus 0%). The rate of bleeding events was 49.3 per 100 person-years in the pooled LTE studies.

10.4.1.2.4. Gastrointestinal disorders

GI disorders were common and more frequent with riociguat (52.0% versus 33.6% in the pooled Phase III controlled studies). Serious GI disorders occurred in 1.6% versus 0.9% of the pooled placebo group and 2 subjects discontinued (one riociguat and one placebo). In the extension studies, while the rate of GI disorders remained high (89.8 events per 100 person-years) the rate of discontinuation due to this event was low (0.4%).

10.4.1.2.5. Tachycardia

In Pool 1, the rate of tachycardia TEAEs was not higher with riociguat (2.9% versus 4.7%) and the rate was 12.1 per 100 persons-years. This dropped to 3.1 per 100 person-years in the LTE studies.

10.4.1.2.6. Renal failure

See *Kidney function* below.

10.4.2. Other studies

In the 22 single dose Phase I studies, the most frequent TEAEs were headache and flushing. Orthostatic hypotension was noted after a single dose of 5 mg. In three multidose studies, the most common events were headache, dyspepsia, gastro-oesophageal reflux and increased ALT (none >2xULN).

In the Phase II studies, the AE profile was similar to the pivotal studies with the most frequent events being headache, dizziness, peripheral oedema, hypotension and nasopharyngitis.

10.5. Treatment-related adverse events (adverse drug reactions)

10.5.1. Pivotal studies

PAH: The rate of treatment-related TEAEs was higher with riociguat that placebo (63.8%, 52.4% and 61.9% in the riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups, respectively). The treatment-related TEAEs that were more frequent with riociguat than placebo were headache, dyspepsia, dizziness, hypotension, nausea, palpitations and peripheral oedema. Diarrhoea and flushing was reported more frequently with placebo.

CTEPH: In CHEST-1, the rate of treatment-related TEAEs was higher with riociguat than placebo (59.5% versus 40.9%), with headache, dizziness, dyspepsia and hypotension being the most common events and occurring at a greater rate than placebo.

In the pooled long term studies, the most frequent treatment-related TEAEs were dizziness (8.3%), dyspepsia (7.0%), headache (6.5%), hypotension (5.4%), nausea (3.9%), diarrhoea (3.6%), peripheral oedema (3.1%), palpitations (2.5%) and gastro-oesophageal reflux disease (2.3%).

10.5.2. Other studies

The profile of treatment-related TEAEs was similar in the Phase I and II studies.

10.6. Deaths and other serious adverse events

10.6.1. Pivotal studies

10.6.1.1. Deaths

PAH: In PATENT-1, the death rate was slightly higher in the placebo group (0.8%, 2.4% and 1.6%). The four deaths in riociguat-treated subjects were due to sepsis, haemoptysis, right ventricular failure and PAH and in the placebo group were due to PAH, anxiety, respiratory failure and circulatory collapse.

CTEPH: In CHEST-1, there were 5 deaths (3 riociguat and 2 placebo) and the death rate was also lower in the riociguat group (1.2% versus 3.4%). The deaths in riociguat-treated subjects were due to cardiac failure, anaemia, catheter site haemorrhage and acute renal failure and in the placebo group were due to cardiac arrest and cardiopulmonary failure. The death due to acute renal failure was classed as treatment-related.

The rate of death in the pooled Phase III controlled studies was 1.0% in the riociguat compared to 3.3% in the placebo group. The rate in the pooled LTE studies was 4.3% over a mean treatment duration of 422.8 days.

10.6.1.2. SAEs[17]

PAH: The rate of SAEs was lowest in the riociguat 1.0 to 2.5 mg group (11.4% versus 18.3% placebo and 17.5% riociguat 1.0 to 1.5 mg) (Table 19). The most frequent SAEs were syncope (1.2%, 4.0%, 0%), right ventricular failure (0.8%, 0.8%, 4.8%), chest pain, haemoptysis and pneumonia.

In the extension study, the SAE rate was 38.6%.

Table 19. Serious TEAEs: Most frequent MedDRA preferred terms-safety population of controlled Phase III studies (11348 and 12934)

12934)

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 TEAEs 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.

CTEPH: The rate of SAEs was 19.7% and 15.9% in the riociguat and placebo groups, respectively (Table 19). Higher incidence rates in the riociguat treatment group were reported for right ventricular failure (3.5% versus 3.4% placebo), haemoptysis (1.7% versus 0%), gastritis (1.2% versus 0%), catheter site haemorrhage (1.2% versus 0%), chronic renal failure (1.2% versus 0%), pulmonary hypertension (1.2% versus 0%) and respiratory failure (1.2% versus 0%).

In the pooled Phase III controlled studies, the rates (riociguat versus placebo) of the most frequent SAEs were as follows: syncope 1.4% versus 3.7%, RV failure 2.2% versus 1.9% and haemoptysis 1.0% versus 0%.

In the pooled Phase III extension studies, the most common SAEs were: syncope (5.4%), pulmonary arterial hypertension (4.5%), right ventricular failure (4.1%), pulmonary hypertension (2.9%), cardiac catheterisation (2.7%), pneumonia (2.0%), haemoptysis (1.3%), bronchitis (1.1%), dyspnoea (1.1%), atrial fibrillation (0.9%) and atrial flutter (0.9%). There were two patients (0.4%) with pulmonary venous occlusive disease (PVOD) and one (0.2%) acute pulmonary oedema in the LTE studies.

In the pooled controlled studies Phase III studies, the rate of haemoptysis SAE was 4.93 and 0 events per 100 person-years in the pooled riociguat and placebo groups, respectively. This reduced to 1.24 events per 100 person-years in the pooled LTE studies.

[17] Syncope was predefined as an SAE in the Phase III studies.

In the controlled studies, the rate of atrial fibrillation SAE was 1.64 events in the pooled riociguat group and no events in the pooled placebo group and in the pooled LTE studies was 0.78 events per 100 person-years.

10.6.2. Other studies

There were no deaths in the Phase I studies and the rate of SAEs was 0.8% (6/738). The events were: hypotension; tinnitus; orthostatic hypotension and syncope with concomitant nitroglycerin; sinus bradycardia and syncope also with nitroglycerin; fall from a ladder with excoriation and contusion 7 days post riociguat; and increased CK 15 days post riociguat dose.

In Study 14308 in patients with PH and LV systolic dysfunction, the rate of treatment emergent SAEs was 34.3%, 21.2%. 25.0% and 29.0% in the riociguat 2mg, 1mg, 0.5 mg and placebo groups, respectively. Differences were noted for atrial fibrillation (4.5% riociguat 2.0 mg versus 0% placebo) and cardiac failure (10.4% riociguat 2.0 mg versus 0% placebo). There were 3 deaths in this study, one in each riociguat group (ventricular fibrillation, pneumonia, heart transplant and complications).

In the Phase II Study 12166, there was one death from progressive right heart failure 50 days post medication cessation. There were 11 subjects with 17 SAEs which included three bleeding events and one pulmonary oedema. In the LTE there were 7 deaths 6 of which occurred on riociguat treatment and five were due to progression of the PAH. The rate of serious TEAEs was 69.1% and the most frequent SAEs were syncope (17.6%), right ventricular failure (11.8%), PAH (10.3%), cardiac failure (8.8%), PH (7.4%), atrial flutter (5.9%) and pneumonia (5.9%).

In Study 15096 (interaction with sildenafil), there were 2 SAEs (RV failure and erysipelas) both in the riociguat group (16.7% versus 0%) and no deaths. In the LTE (n=17) over an average treatment period of 10 months, three deaths were reported, two from cardiac causes and one from a subdural haematoma following a fall. There were 8 SAEs (47.1%), three of which were classed as treatment-related (2 hypotension and one colitis).

> Comment: The high death rate (3/17, 17.6%) in the extension study combined with a high treatment discontinuation rate due to AEs (5/17, 29.4%) led the Sponsor to conclude there was a negative benefit-risk balance for the combination of riociguat with sildenafil. Concomitant use of riociguat with PDE inhibitors should be avoided.

10.7. Discontinuation due to adverse events

10.7.1. Pivotal studies

PAH: The rate of study medication discontinuation due to a TEAE was highest in the placebo group in PATENT-1 (7.1% versus 3.1% and 1.6%in the riociguat 1.0 to 2.5 and 1.0 to 1.5 mg groups, respectively) and in the extension study the rate was 7.7%. The most frequent events in the controlled study were in the respiratory disorders (0.4%, 4.0% and 0%) and cardiac disorders (0.8%, 0.8%, 1.6%), while in the extension studies were PAH (1.1%) and PH (0.8%).

CTEPH: The rate of TEAEs leading to discontinuation of study drug was similar between groups (2.9% riociguat versus 2.3% placebo) in the controlled study. In the LTE study, the TEAE discontinuation rate was 1.5% with the most common reason being PH (1.0%).

The pooled rate of discontinuation due to TEAEs was 2.9% and 5.1% in the riociguat and placebo groups, respectively in the short term studies. In the long term extensions, the pooled rate was 5.6% with the reasons being cardiac failure, cardiac shock, right ventricular failure, hypoxia, PAH, pulmonary haemorrhage, PH, PVOD and respiratory failure.

10.7.2. Other studies

In the Phase I program the rate of premature discontinuation was 3.9% (29/738) with 2.3% (17) due to adverse events. The AE discontinuation rate in Study 14308 was 9.0%, 12.1%, 9.4%

and 7.2% in the riociguat 2.0 mg, 1.0 mg, 0.5 mg and placebo groups, respectively. In Study 12166 the AE discontinuation rate was (3/75, 4%) one of which was unmasking of PVOD and in the LTE of study the rate was 11.7% (8/68). As mentioned above, the AE discontinuation rate in the small study with sildenafil was 5.5% in the primary study and this rose to 29% in the extension study with 4 out of the 5 events being hypotension.

10.8. Laboratory tests

10.8.1. Liver function

10.8.1.1. Pivotal studies

PAH: Treatment emergent shifts in LFTs were reported more frequently in the placebo than riociguat groups. There was one case (0.4%) of ALT >3xULN in the riociguat 1.0 to 2.5 mg group and 3 (2.6%) in the placebo group. In the LTE, the rate of increased ALT, AST (>3xULN) and bilirubin (>2xULn) was 0.9%, 0.3% and 3.2%, respectively.

CTEPH: Liver function changes were unremarkable. There was one case of ALT >3xULN in a riociguat treated subject (0.6% versus 0%) and none in the LTE study (. There were no cases of abnormal LFTs meeting Hy's Law criteria in the pivotal studies.

10.8.1.2. Other studies

In the Phase I single dose studies, the rate of treatment emergent high (>1xULN) ALT was 4.8% versus 0% with placebo. The rate for ALT >3x ULN and AST >3x ULN was 0.1% each in the riociguat treated subjects, there were no cases of bilirubin >2x ULN. In the Phase I multi-dose studies there were no subjects treated with riociguat who had LFT levels >2x ULN. There were no cases of AST/ALT >3x ULN with bilirubin >2x ULN in the Phase II studies.

10.8.2. Kidney function

10.8.2.1. Pivotal studies

PAH: The rate of an increase in creatinine of >0.3 mg/dL was higher with riociguat 1.0 to 2.5 mg (9.6%, 6.1%, 1.7%) as was an increase >0.5 mg/dL (2.9%, 0.9%, 0%). Treatment emergent low creatinine clearance was higher with riociguat 1.0 to 2.5 mg than placebo (24.4% versus 19.2%) while the rate of eGFR calculated using the MDRD formula was not higher (7.9% versus 9.6%). Treatment emergent low eGFR was noted in 15% of subjects in PATENT-2.

CTEPH: The rate of treatment emergent high creatinine was slightly higher with riociguat than placebo (27.0% versus 23.8%) but the rate of an increase in creatinine of >0.3 mg/dL was similar (8.6% versus 9.8%). The rate of emergent low creatinine clearance was also lower than placebo (19.6% versus 33.3%) but comparable using the MDRD formula (18.0% versus 21.6%). In CHEST-2, the rate of emergent low creatinine clearance was 32.3%.

There were two SAEs of acute renal failure in the PATENT-1 study (both treated with riociguat 1.0 to 2.5 mg). In CHEST-1, there were 4 (2.3%) subjects treated in the riociguat 1.0 to 2.5 mg group with SAEs of renal failure, one of which was fatal, (compared to one case [1.1%] of serious renal impairment in the placebo group). There were 4 (2.0%) reported SAEs of renal failure in CHEST-2.

The rate of serious TEAEs of renal failure was 1.3% in the pooled riociguat subjects compared to 0.3% in the pooled placebo subjects (Pool 3). Two of the cases had not resolved and one was fatal.

10.8.2.2. Other studies

Creatinine change was not remarkable in the Phase I single or multidose studies. In Study 14308 the rate of TEAEs of increased creatinine was lower in the riociguat than placebo group (3.0% versus 11.6%).

10.8.3. Other clinical chemistry

10.8.3.1. Pivotal studies

Mean changes from baseline in clinical chemistry parameters were unremarkable in the two Phase III studies. It was noted that 20.5% of PAH subjects in the riociguat 1.0 to 2.5 mg group had treatment emergent low calcium with none reported in the lower dose or placebo group. For CTEPH subjects the rate of low calcium was also higher with riociguat (11.1% versus 0%).

> Comment: Calcium measurement was added as a protocol amendment and the subject numbers are small which may have resulted in the imbalances seen.

10.8.3.2. Other studies

In the Phase I single dose studies, the rate of treatment emergent high (>1xULN) CK was 9.8% versus 0% with placebo. There were no associated cardiac events in these subjects. Seven subjects (1.1%) had lipase > 2xULN and one of these (0.2%) was > 4xULN. There was no evidence of pancreatitis. In the Phase I multi-dose studies there were two subjects (2.6%) with lipase >2xULN. Other clinical chemistry was unremarkable. In the Phase II Study 14308, high CK was noted in 19.6% of the riociguat 2.0 mg group compared to 10.2% of the placebo group.

10.8.4. Haematology

10.8.4.1. Pivotal studies

PAH: The mean change from baseline in haemoglobin was -0.60, 0.08 and -0.44 g/dL in the riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups respectively. The rate of TEAEs of anaemia was noted to be higher with riociguat 1.0 to 2.5 mg (8.3%, 2.4%, 1.6%). In the long term extension anaemia was reported in 7.4% and treatment emergent low haemoglobin was reported in 37.1% of PATENT-2 subjects. There was a high rate of emergent high APTT and high INR but this corresponded to use of anticoagulant medication.

CTEPH: The mean change from baseline in haemoglobin was -0.69 and 0.02 g/dL in the riociguat and placebo groups respectively in CHEST-1. Treatment emergent low haemoglobin was however less frequent with riociguat (5.7% versus 10.1%). The rate of anaemia TEAEs was higher with riociguat (3.5% versus 1.1%). In the LTE study, the rate of emergent low haemoglobin was 28.7% and anaemia was reported in 4.1% of subjects.

10.8.4.2. Other studies

In the Phase I single dose studies, the rate of haemoglobin less than the LLN was 7.9% compared to 3.3% in the placebo group. In the Phase I multi-dose studies the rate of low haemoglobin was higher with riociguat (33.3% versus 16.4% placebo) but low haematocrit was similar (44.1% versus 44.9%). In the Phase II Study 14308, low haemoglobin (46.2% versus 29.4%) and low haematocrit (37.5% versus 18.9%) were more frequent with riociguat 2.0 mg than placebo.

10.8.5. Vital signs

10.8.5.1. Pivotal studies

10.8.5.1.1. Blood pressure

PAH: The mean decrease in SBP over the course of the primary study was greater in the higher riociguat than lower dose group (6.2-10.3 mmHg versus 1.5-6.4 mmHg). The mean decrease over the LTE ranged from 5.6 to 9.5 mmHg at each visit. The mean decrease from baseline in the DBP in the LTE study ranged from -5.3 to -6.9 mmHg. The rate of subjects with low SBP (<95 mmHg) ranged from 10.4% to 20.1% at each visit in the riociguat 1.0 to 2.5 mg group (compared to 9.7-14.9% in the placebo group). The frequency of low SBP in the LTE study was 13.7-19.2% at each visit.

CTEPH: Over the course of the primary study, from 10.45-15.9% of subjects treated with riociguat had low SBP 2 to 3 hours after medication dose. This compares to 1.1% to 5.7% of the placebo group. The frequency of low SBP in the LTE study ranged from 9.5% to 12.4% at each visit. In the extension study, the mean decrease in SBP was 10.47 mmHg and mean decrease in DBP was 8.49 mmHg.

The shift in BP was reflected in TEAEs of hypotension as discussed in *All adverse events* above.

HR: Small increases in heart rate were noted in the pivotal studies although ECG findings were unremarkable.

Weight: There were no notable changes in weight.

Blood gases: There were no notable changes or relevant intergroup differences in blood gas assessment.

10.8.5.2. Other studies

In the Phase I single dose Study 11258, an increasing frequency of orthostatic hypotension was noted with increasing riociguat dose with 3 out of 10 subjects in the 5.0 mg having such a reaction.

10.8.6. Electrocardiograph

10.8.6.1. Pivotal studies

In the two pivotal studies, there were no relevant changes in PR, QRS, QT, QTcB and QTcF duration. There were no events linked to QT prolongation reported.

10.8.6.2. Other studies

There were no clinically relevant effects on ECG noted from the Phase I or II studies. Further discussion on cardiovascular safety is in *Safety issues with the potential for major regulatory impact* below.

10.9. Postmarketing experience

None.

10.10. Safety issues with the potential for major regulatory impact

10.10.1. Cardiovascular safety

In Study 11914 there was a signal of QTcF prolongation of 6-12 msec in females and 5-7 msec in males. In addition, the Sponsor stated that *in vitro* studies noted minor effects of riociguat and its main metabolite on ventricular repolarisation while nonclinical studies in dogs found no adverse ECG effects.

Despite this, data from the Phase I single dose studies showed no cases with an absolute QTcF value of over 500 msec and one case of >60 msec prolongation over baseline. Similarly in the multiple dose Phase I studies there were no cases of an absolute value >500 msec and no cases of prolongation >60 msec compared to baseline.

A Thorough QT study was not conducted due to safety concerns with administering riociguat to healthy volunteers (the maximum well tolerated dose in healthy volunteers was 2.5 mg and 5 mg resulted in haemodynamic effects). As a consequence, ECG data were obtained from the subject population in the Phase III program. This included a randomised controlled study (**Study 13796**) in healthy volunteers conducted at study sites participating in PATENT-1 using the same ECG recording methods. The study was designed to validate ECG assay sensitivity for PATENT-1. Secondly there was extended ECG monitoring with centralised reading in 98

riociguat subjects (76 high dose, 22 low dose) and 35 placebo subjects in PATENT-1. Routine ECG recording was conducted on all Phase III trial participants.

Study 13796 found that using a positive control of moxifloxacin 400 mg, the study setting was sensitive to detect a LS mean difference (moxifloxacin versus placebo) in QTcF of 15 msec and in QTcB of 16 msec. In the Thorough QT subset of PATENT-1, the mean change from baseline in QTcB was 2 msec and 4 msec in the riociguat 1.0 to 2.5 mg and placebo groups, respectively. In the overall PATENT-1 population (193, 43 and 84 subjects in the riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups, respectively) where single ECGs were collected, the mean QTcF was between 420 and 435 msec with no mean change from baseline of >7 msec at any visit. There were no cases of QT interval increase of 60 msec during the treatment phase (although there was one case at the safety follow up visit) and no reports of QT prolongation associated events. There was also no indication of QT prolongation in the overall Phase III population.

> Comment: The evaluator concludes that it is possible that riociguat may result in small changes to the QT interval although any prolongation appears small and from the provided data did not appear to result in any adverse clinical effects.

10.10.2. Bone toxicity

The exploratory biomarkers dihydroxy vitamin D, type I collagen C-telopeptides (CTX) and osteopontin, as well as calcium and phosphate, were evaluated to assess possible change in bone metabolism. This was due to nonclinical findings of skeletal effects, in particular at the growth plate, in juvenile and adolescent rats and mice.

In the pivotal trials, there were no relevant changes in mean serum calcium or phosphate nor relevant differences compared to placebo. The change from baseline to end of the primary study in 1,25-dihydroxy vitamin D was also unremarkable. There were small increases from baseline in mean CTX and mean osteopontin levels in the two pivotal Phase II trials which appeared similar to placebo.

> Comment: The clinical implication of these findings is uncertain.

The rate of musculoskeletal and connective tissue disorders was similar between riociguat and placebo in the CTEPH (19.7 versus 21.6%) and PAH patients (15.7%, 15.9% 15.9% in the riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups, respectively). The most frequent events were back pain, pain in extremity and arthralgia. All events were mild or moderate in severity. In the extension studies the rate of musculoskeletal disorders was 27.3% in PATENT-2 and 29.9 % in CHEST-2, and there were no SAEs in this SOC.

10.10.3. Other safety issues

There was no evidence of liver toxicity, serious skin reactions or unwanted immunological events. The changes on haemoglobin were also not felt to represent haematological toxicity.

10.11. Other safety issues

10.11.1. Safety in special populations

Gender: When treated with riociguat, data from Pool 1 found that women had a higher rate than men of hypotension (10.3% versus 4.2%).

Age: There were only small numbers of subjects aged over 75 years in the Phase III program. As expected, there was an increase rate of events in older subjects which was also seen in the placebo group.

Renal Impairment: In Pool 1 the rate of mild and moderate renal impairment was approximately 35% and 20%, respectively. Creatinine clearance <30 mL/min was an exclusion criteria however 4 such subjects were included. PK data found that subjects with renal

impairment had an increased exposure to riociguat that was not proportional the decrease in renal function. In the Pool 1, the risk of hypotension increased with decreasing renal function (4.7% with eGFR ≥90 mL/min, 14.9% with eGFR 30-60 mL/min). There was also an increased rate of SAEs with decreasing renal function 11.0%, 15.3%, 19.8%, 50.0% in subjects with eGFR ≥90, 60-<90, 30-<60 and <30 mL/min, respectively.

Hepatic impairment: Patients with significant liver disease were excluded from the trials and as such there are no available data on this population. Increased exposure was found in subjects with moderate hepatic impairment in the PK studies.

Pregnancy and lactation: Reproductive toxicity has been noted on nonclinical studies and riociguat is secreted in breast milk. Pregnant women and breast feeding women were excluded from the development program. There were however 3 pregnancies recorded, two had documented first trimester exposure and the outcomes were elective abortion, spontaneous abortion and salpingectomy (for an ectopic). It is recommended that riociguat should be contraindicated in both pregnancy and lactation and that a risk minimisation program be implemented.

Pre-treatment: In the pooled controlled study population (n=490) treated with riociguat, 138 (28.2%) had been pretreated with an ERA, 22 (4.5%) with a PCA, 2 (0.4%) with ERA and PCA, and 328 (66.9%) were therapy-naive. Overall the profile of TEAEs was similar between groups. The rates of severe TEAEs and SAEs were similar between pretreatment groups. The rate of TEAEs leading to discontinuation of riociguat was 3.0% and 2.2% in therapy-naïve and ERA pretreated subjects, respectively. A higher rate in subjects pretreated with an ERA than in therapy-naive subjects was seen for anaemia (7.2% versus 4.3%), palpitations (9.4% versus 4.9%) and gastrointestinal disorders (63.0% versus 50.0%).

Left heart failure: There are no data on this population from the PAH or CTEPH studies. However data are available from the Phase II Study 14308 in 201 subjects with PH associated with left ventricle systolic dysfunction (ejection fraction ≤40%). In this study there were 67 subjects treated with riociguat 2.0 mg TDS. Overall, the safety profile was in line with the PAH and CTEPH studies except for an increased risk of SAEs of atrial fibrillation (4.5% versus 0%) and cardiac failure (10.4% versus 4.3%).

10.12. Safety related to drug-drug interactions and other interactions

In Pool 1 riociguat-treated subjects, the use of at least one concomitant ERA was reported in 29.0%. The rate of SAEs was similar between riociguat subjects who used or did not use concomitant ERA. The rate of peripheral oedema was higher in riociguat-treated subjects using a concomitant ERA than without an ERA (20.9% versus 15.7%).

Study 15096, which examined concomitant treatment with the PDE-5 inhibitor sildenafil, found that over the long term extension phase (mean exposure of 10 months) there was an unacceptably high rate of death (3/17, 17.6%) and discontinuations due to TEAEs (5/17, 29%). Co-administration with PDE-5 inhibitors must therefore be avoided.

Pharmacokinetic data showed that antacids and the proton pump inhibitor omeprazole decrease riociguat exposure. The rate of use of drugs increasing the gastric pH was high (46% in the controlled Phase III studies and 49% in the extension studies). There was a higher SAE rate in subjects using gastric pH increasing medications compared to non-users but this was also seen in the placebo group (SAEs: 18.1% versus 9.7% for riociguat and 20.9% versus 12.2% for placebo). The sponsor proposes that this may reflect more underlying disease in users.

In Pool 1 riociguat treated subjects, the rate of concomitant CYP3A4 inhibitor use was 13.3% and of concomitant CYP3A4 inducer use was 21.2%. Co-administration with CYP inhibitors increases exposure and so will need to be avoided.

Smoking may induce CYP1A1 and so may increase riociguat clearance which could affect efficacy rather than safety. In the Phase III program the rate of smoking was low at 6% and therefore the population too small to draw conclusions.

Phase I data indicated a strong interaction with nitroglycerine resulting in considerable hypotension. The concomitant use should be contraindicated.

10.13. Evaluator's overall conclusions on clinical safety

In the Phase III clinical program there were 490 subjects treated with riociguat, 317 with PAH and 173 with CTEPH. The mean treatment duration in the PAH controlled study was 81 days, 80 days and 78 days in the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups, respectively and in the CTEPH controlled study was 108 days and 110 days in the riociguat 1.0 to 2.5 mg and placebo groups, respectively. In the PAH population there were 221 subjects who received treatment for 48 weeks and 52 subjects for 108 weeks. The total exposure was 435.7 person years. In the CTEPH population, there were 97 subjects who received treatment for 48 weeks and 39 subjects for 96 weeks. The total exposure was 206.2 person years.

The rate of death in both pivotal trials was lower in the riociguat than placebo groups (PAH: 0.8%, 2.4% and 1.6% in the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups, respectively. CTEPH: 1.2% versus 3.4% riociguat versus placebo). Four of the five deaths in CHEST-1 were cardiopulmonary related events. There was one death from renal failure. There were 3 deaths in PATENT-1, one RV failure with PAH, one sepsis and one haemoptysis.

SAE rates were no higher with riociguat than placebo in PATENT-1 (11-18% riociguat versus 18% placebo) and slightly higher in CHEST-1 (20% riociguat versus 16% placebo). The most frequent SAEs were syncope and right ventricular failure with the addition of PAH, PH, cardiac catheterisation and pneumonia in the long term extension studies.

Discontinuation rates due to TEAEs were similar to or lower than placebo in both studies (2.9% riociguat versus 2.3% placebo in CHEST-1 and 1.6-3.1% riociguat versus 7.1% placebo in PATENT-1). Discontinuation due TEAEs was low in the extension studies (1.5% in CHEST-2 and 7.7% in PATENT-2).

Most TEAEs were mild or moderate with severe events occurring in 9-11% of riociguat treated subjects in both controlled studies which was similar or lower to the rate in the placebo groups. The most frequently involved SOCs were gastrointestinal and nervous system. Events more frequent with riociguat were headache, dyspepsia, peripheral oedema, dizziness, hypotension, anaemia, diarrhoea and vomiting.

The sponsor stated that *'headache can be attributed to riociguat-induced vasodilation, whereas dyspepsia and gastro-oesophageal reflux disease can be attributed to riociguat-induced relaxation of smooth muscle cells of the lower oesophageal sphincter'*.

The rate of syncope was no greater with riociguat. Hypotension was the most notable adverse event (10.2%, 3.2%, 4.8% in the in the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups, respectively in PATENT-1, and 11.5% riociguat versus 4.5% placebo in CHEST-1). There was evidence of dose response effect on hypotension as measured by rates of TEAE and proportion of subjects with low SBP (<95 mmHg) 2-3 hours post dose. Serious hypotension was not frequent and was reported in 0.4% (versus 0% placebo) in pooled analysis of the pivotal trials. Hypotension TEAEs occurred in 8% and 6% of the subjects in the long term studies PATENT-2 and CHEST-2, respectively.

Severe bleeding events were more frequent with riociguat (1.6-3.2% versus 0% in PATENT-1, 3.5% versus 0% in CHEST-1). The most frequently reported serious bleeding event was haemoptysis and these SAEs occurred at a higher rate with riociguat (5 cases, 1.0% versus 0 cases in the placebo group).

Data also indicated a risk of anaemia with a higher rate of TEAEs in the PAH population (8.3%, 2.4%, 1.6% in the respective PATENT-1 groups). This was not seen in the CTEPH population. The mean change from baseline in haemoglobin was not clinically relevant.

While there were variable findings on laboratory assessment of renal function, there was a signal of renal failure with a higher rate of serious TEAEs of renal failure in pooled data (Pool 3: 1.3% versus 0.3%) with two unresolved and one fatal case.

There were no notable findings on liver function. Vital sign assessments, including arterial blood gases, were unremarkable except for the effects on blood pressure. There was an overall shift to lower mean SBP and DBP with riociguat consistent with it mechanism of action. ECG findings were unremarkable and there was no evidence of QTc prolongation in the subset of subjects assessed in PATENT-1.

Long term safety data were not controlled so definitive conclusions cannot be drawn. Nonetheless, the profile and rates of events were consistent with the primary studies.

Bone toxicity findings in nonclinical studies have been noted. While there were exploratory biomarkers (CTX and osteoponin) assessed, the clinical implications of the findings are uncertain. In assessment of TEAEs, there were no signals evident in the musculoskeletal and connective tissue SOC.

Data from Study 15096 found that efficacy was not improved by the combined use of riociguat and PDE inhibitors and that there was a high risk of treatment discontinuation and death in the extension study. Therefore, PDE inhibitors should not be used with riociguat.

Safety findings in subgroups showed a higher rate of hypotension in females, limited number of elderly subjects and increased risk of hypotension and of SAEs with decreasing renal function.

There were no safety data in pregnant or lactating women, children or subjects with severe renal impairment (creatinine clearance < 30 mL/min), on dialysis or with significant hepatic disease. It is noted that subjects with hepatic and renal impairment have increased exposure to riociguat. Due to the reproductive toxicity and breast milk secretion riociguat must be avoided in pregnancy and lactation.

Subjects with low SBP (<95 mmHg) at baseline or with a history of atrial fibrillation or left heart failure were excluded from the pivotal trials and consequently safety data in these potentially at risk groups are unavailable in the PAH or CTEPH population. The Phase II Study 14308 in patients with PH associated with LV systolic dysfunction (ejection fraction ≤40%) found an increased risk of atrial fibrillation and cardiac failure with riociguat 2.0 mg.

Drug interactions with CYP inhibitors result in increased exposure and consequently safety risks and will need to be avoided. The severe risk of hypotension with concomitant nitroglycerine and the safety risks found in the clinical trial with sildenafil mean that nitrates must be contraindicated and PDE-5 inhibitors avoided.

11. First round benefit-risk assessment

11.1. First round assessment of benefits

The benefits of riociguat in the proposed usage are:

- Robust efficacy data from two pivotal trials, one in each population of PAH and CTEPH which were supported by secondary endpoints of WHO functional class and haemodynamic parameters.

- Clinically meaningful efficacy data (improvement in 6MWD of 36 m in PAH and 46 m in CTEPH) in rare, potentially fatal conditions where there are limited treatment options and an evident unmet medical need.
- Clinically meaningful efficacy was also demonstrated across subgroups (inoperable and postoperative CTEPH, therapy naïve and ERA pretreatment PAH, idiopathic PAH and connective tissue disease PAH).
- Maintenance of efficacy up to 18 months, albeit in an uncontrolled study.
- No evident negative impact on mortality in either pivotal trial.
- An acceptable safety profile where the rates of SAEs and discontinuations due to AEs were low and in line with placebo.
- Adequate long term safety data, with 376 patients treated for at least 48 weeks and 173 for at least 96 weeks (Pool 3).

11.2. First round assessment of risks

The risks of riociguat in the proposed usage are:

- Hypotension, with an increased risk in patients ≥65 years and those with renal impairment. The risk appeared manageable as the rate of serious or severe hypotension or that resulted in discontinuation was low.
- Serious haemoptysis and pulmonary haemorrhage which could be fatal. A risk of other bleeding events and anaemia was also seen.
- Renal failure which could be via a hypotensive effect or perhaps direct action.
- Unmasking of pulmonary venous occlusive disease with resultant pulmonary oedema.
- Common adverse events included headache, dizziness, dyspepsia, peripheral oedema, nausea, diarrhoea and vomiting.
- Gastrointestinal effects of abdominal pains, abdominal distension, constipation, dysphagia, gastroesophageal reflux, gastritis and gastroenteritis. These were generally mild or moderate in severity.
- Long term safety and efficacy data not fully characterised with controlled data.
- Populations at risk included patients with hypotension, hepatic impairment and severe renal impairment.
- Drug interactions including with nitrates, PDE-5 inhibitors and inhibitors or inducers of hepatic cytochromes.
- Reproductive toxicity with potential risks in pregnant or lactating women and the paediatric population.
- Vasodilatory action results in risks to certain patient groups such as those with hypovolaemia or LV outflow obstruction.
- Lack of safety data in patients with significant cardiovascular or cerebrovascular disease.
- Potential for off-label use in other types of pulmonary hypertension.

11.3. First round assessment of benefit-risk balance

Pulmonary hypertension is group of diseases characterised by a progressive increase in PVR leading to right heart failure and premature death. Riociguat is a new chemical entity which acts

by stimulating the soluble guanylate ecyclase (sGC), the enzyme that catalyses the formation of cGMP. This elevation of cGMP in smooth muscle causes relaxation and consequent pulmonary and systemic vasodilation. Riociguat has been developed in two PH patient populations: PAH (WHO Group 1) and CTEPH (Group 4). This application covers both indications which have been granted Orphan designation.

Overall, the submitted dossier was very well compiled and comprehensive. The clinical development program was based on two Phase III randomised, placebo controlled efficacy studies in which the primary endpoint was the change from baseline in the 6 minute walk distance. This improvement in exercise capacity, using the 6MWD, is the EMA recommended endpoint for PH trials provided there is no negative impact on survival (EMA 2009).[18]

These pivotal trials, PATENT-1 and CHEST-1, both met their primary endpoint with statistically significant and clinically meaningful improvement compared to placebo in the 6MWD. Exploratory responder analysis also found that approximately half the patients in both populations improved at least 40 m on the 6MWD (compared to 20-30% of placebo-treated subjects). The trials were well conducted and the data were considered robust as results were concordant between trials, consistent across analysis populations and subgroups, there were relatively low levels of missing data and sensitivity analyses using different assumptions for dealing with missing data were also consistent with the primary analysis.

The sponsor has proposed a complex indication which included a number of subgroups of PAH and CTEPH. Efficacy was demonstrated across the PAH groups of idiopathic and connective tissue disease as well in those using riociguat as monotherapy or in combination in an ERA or PCA. For the CTEPH population, efficacy was also seen in those with inoperable CTEPH. For those with persistent postoperative disease CTEPH efficacy was as at a lower level (27 m versus 54 m) and the confidence intervals crossed zero. The sample size in this subgroup was much smaller (52 riociguat treated compared to 121 with inoperable CTEPH) which is likely to have contributed to the wide confidence interval. Given the consistency of effect across all subgroups, the evaluator believes that it is acceptable to include these specified subgroups in the indication.

ERAs and prostanoids are being recommended for inclusion in the indication but there were no PK interaction studies conducted. Nonetheless concomitant use occurred in the pivotal studies with acceptable results and the variety of products used was broad. Therefore the evaluator believes it is acceptable for their inclusion in the proposed indication.

The indication specifies that the efficacy in PAH predominantly included patients with WHO functional class II-III. This was also the case in the CTEPH study but this information has not been included in the indication. As the vast majority of patients in both studies were in WHO functional class II or III and there are minimal data from other functional classes, the evaluator recommends that the indicated population be limited to WHO functional class II and III (for example, *for the treatment of adult patients with PAH/CTEPH classified as WHO functional class II and III*...). Similar wording is used in the indications for tadalafil and sildenfil.

The primary efficacy endpoint was supported by improvement in WHO functional class in both trials and positive haemodynamic effects. The time to clinical worsening, a composite endpoint of death, non-planned PH hospitalisation and PH related deterioration (as recommended in the EMA guidelines) was significantly improved in the larger trial in PAH but not in the CTEPH population. The proposed indication also includes secondary efficacy endpoints in addition to improvement in exercise capacity. Even though the selected secondary endpoints of (WHO functional class in both populations and delay in clinical worsening in PAH) were found to be statistically significant, the evaluator does not believe the indication should be based on

[18] EMA (2009). Committee for medicinal products for human Use (CHMP). Guideline on the clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. EMEA/CHMP/EWP/356954/2008.

secondary endpoints. In addition, the EMA guidelines clearly state that while studies using improvement in exercise testing may vary between 3 and 6 months *a minimum of 6 months is usually necessary to demonstrate an improvement in time to clinical worsening*. The two pivotal studies were of shorter duration. Consequently, the indication needs to be reworded using only the primary endpoint "*to improve exercise capacity*". The effect on other endpoints has been included in the Clinical Trials Section of the PI. This recommendation is also in line with the indication of other PH treatments (for example, tadalafil). In addition, the evaluator noted in the RMP the proposed indication for both conditions in the EU is only "*to improve exercise capacity*".

The dosing regimen is an individual titration regimen with a starting dose of 1.0 mg TDS and an increase each 2 weeks based on patient's peripheral SBP to a maximum of 2.5 mg TDS. A lower dose of 0.5 mg is also proposed should down titration be necessary. This regimen was used in both pivotal studies and at the end of the controlled period (12 to 16 weeks) approximately 90% of subjects were tolerating 2.5 mg or 2.0 mg. In the PAH population of PATENT-1, there were very similar results on the primary efficacy outcome for subjects treated with the proposed dosage regimen (to 2.5 mg TID) and those treated with a capped regimen up to 1.5 mg TDS. Also it is interesting to note that while riociguat plasma concentrations were significantly correlated with reductions in haemodynamic parameters and increases in cardiac index, there was no correlation between change in 6MWD and riociguat AUC. It was also found that the rate of hypotension, a major adverse effect of riociguat, was dose dependent. This leads to questioning whether there may be no additional benefit in titrating beyond 1.5 mg TDS. Unfortunately, the capped regimen was an exploratory arm with a small sample size and no formal statistical comparisons were undertaken between dose groups. Therefore, a definite conclusion regarding efficacy of one regimen over another is not possible. Given that the proposed dosage is based on an individual's haemodynamic response and the safety profile of the 2.5 mg regimen was acceptable, the evaluator believes it may be reasonable to allow dosage up to 2.5 mg with strong wording on hypotension risks and when not to continue dose escalation or when to down titrate. Nevertheless, the sponsor has been asked to discuss the rationale for the decision not to pursue the lower maximum dose.

A question has also been raised regarding the timing of hypotension events to assess the risk during titration compared to during maintenance therapy. Given the results of this enquiry, further wording regarding hypotension risk may need to be included in the PI. In addition, the sponsor has also been asked to justify the 1.0 mg starting dose for titration. Given the known variability in SBP measurement, it could be prudent to start all patients at lower dose of 0.5 mg TDS and then titrate slowly.

Overall, the safety profile of riociguat was acceptable. The number of subjects with long term data are sufficient particularly given the condition's rarity; 376 for at least 48 weeks which included 221 with PAH and 97 with CTEPH from the two pivotal trials. These data will still need to be supplemented by ongoing active surveillance as outlined in the RMP. There was no formal assessment of survival nonetheless it was encouraging to see lower rates of death in the riociguat treated patients in both Phase III trials. In addition, the rates of SAEs and adverse event related treatment discontinuation were low and not notably greater than in the placebo groups.

Hypotension was a significant adverse event and is a direct consequence of riociguat's mode of action. Most events were not serious, did not result in treatment discontinuation. Furthermore, there was no increased risk of syncope. Nevertheless, this major risk of hypotension needs to be made more prominent in the PI and the evaluator recommends severe hypotension (SBP <90 mmHg) is added as a contraindication. In addition, due to the lack of clinical data in patients with severe proven or suspected coronary artery disease and the contraindication nitrates due to the drug interaction, the evaluator recommends that the use of riociguat in patients with coronary artery disease who require nitrates also be specified as a contraindication.

Haemoptysis and pulmonary haemorrhage were identified major risks and the precaution in the product information clearly states that the treating physician *should regularly assess the benefit–risk with each individual patient*. The sponsor has also adequately outlined the risk of unmasking pulmonary venous occlusive disease with discontinuation of treatment if the diagnosis is considered.

The data also indicated a signal for renal failure, with a higher risk of SAEs of renal failure, whether it be from hypotensive effects or perhaps a direct renal effect. Monitoring of renal function is recommended and this has been requested to be included in the PI. Likewise due to the risk of bleeding events and the signal of higher anaemia rates in the riociguat treated patients, monitoring of haemoglobin is also recommended for inclusion in PI.

Patients with hepatic and renal impairment are at risk of adverse effects due to the increased exposure. The precautions in patients with severe renal impairment or on dialysis, as well as in those with severe hepatic impairment, need to be made more prominent in the PI. Furthermore, the statements regarding similar exposure between healthy controls and subjects with mild hepatic impairment in the PI are incorrect and need altering together with dosage instructions for this population. Dosage instructions for patients with renal impairment are adequate.

Pharmacokinetic studies showed a number of drug interactions which have been adequately outlined in the proposed PI. A major interaction with nitrates was seen during the interaction study with nitroglycerine and so this combination is contraindicated. The small study assessing coadministration with the phosphodiesterase-5 inhibitors (sildenafil 20 mg TDS) found no efficacy benefit and a higher risk of treatment discontinuation and death in the extension study. Therefore, PDE inhibitors should not be used with riociguat and the evaluator recommends this be added as a contraindication.

Reproductive toxicity has been noted in nonclinical studies and riociguat is also secreted in breast milk. Currently the PI only contraindicates riociguat in pregnancy and the evaluator recommends that lactation should be added to the contraindications. Importantly, it is recommended to implement an active risk miminsation strategy to ensure there is no foetal exposure in women taking riociguat. This should include pregnancy testing prior to treatment initiation and at regular intervals in women of child-bearing potential.

The potential paediatric risk due to the nonclinical bone findings has been stated in the PI and the risk management plan should monitor any potential off-label paediatric use as well as any skeletal defects. The labelling is clear on the indicated population however the evaluator recommends close monitoring of off-label use in other PH populations as part of the RMP. It is noted that the RMP proposes a registry for all PH patients treated with riociguat and this should allow close safety surveillance.

In summary, pulmonary hypertension is a rare, progressive and ultimately fatal disease although rate of progression may be variable. For patients with PAH there are few treatment options, while for patients with CTEPH many may not be surgical candidates or have persistent PH postsurgery. These are conditions in which there is an evident unmet medical need. The development program for riociguat found a safety profile with some significant risks (such as haemoptysis and hypotension), nonetheless these risks were outweighed by the robust and clinically meaningful efficacy results and the high need for further treatments in this potentially fatal condition. Given this, the evaluator finds the benefit-risk balance of riociguat given the proposed usage, is favourable. This is subject to the sponsor addressing the recommended changes to the PI, the questions (see below) and adoption of the proposed changes to the indication.

11.4. First round recommendation regarding authorisation

The evaluator finds the benefit-risk balance of riociguat in the treatment of PAH and CTEPH to be positive and recommends authorisation subject to:

- Alteration of the indication (see below).
- Adoption of changes to the draft PI and CMI.
- Satisfactory responses to the questions (see below).
- Inclusion in the RMP of the additional risks for postmarketing surveillance.

A proposed revised indication is:

Chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4):

Adempas is indicated for the treatment of adult patients with

- *inoperable CTEPH,*
- *persistent or recurrent CTEPH after surgical treatment*

classified as WHO functional class II and III to improve exercise capacity.

Pulmonary arterial hypertension (PAH, WHO Group 1):

Adempas is indicated for the treatment of adult patients with PAH classified as WHO functional class II and III to improve exercise capacity.

Efficacy in PAH was shown in patients on riociguat monotherapy or in combination with endothelin receptor antagonists or prostanoids.

Studies establishing effectiveness in PAH predominately included patients with aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

12. Clinical questions

12.1. Pharmacokinetics

Nil.

12.2. Pharmacodynamics

Nil.

12.3. Efficacy

1. The efficacy of the capped dose regimen (1.0 to 1.5 mg) appeared to be comparable to the proposed regimen for registration (1.0 to 2.5 mg) in the PATENT-1 study. In line with good therapeutic practice of prescribing the lowest efficacious dose, discuss why this lower dose has not been examined further and any benefits of using the higher dose over the lower dose.

12.4. Safety

2. In the Phase III program, describe when the hypotension events occur in relation to treatment commencement or titration and during maintenance therapy. Describe any risk of hypotension events in subjects who have already tolerated a given dose. Given these data, discuss if any specific warnings should be included in the product information which

would alert physicians to the risk of hypotension at any time rather than just during dose titration.

3. Was there a greater risk of hypotension in patients with lower SBP at commencement of treatment? Should this be included in the product information? Discuss.
4. Given the known variability in SBP measurement, it could be prudent to start dose titration for all patients at the lower dose of 0.5 mg TDS and titrate slowly. Discuss this proposal and justify the choice of 1.0 mg over 0.5 mg as a starting dose for titration.
5. Given the results from Study 15096, discuss why concomitant use of PDE-5 inhibitors is listed as a precaution and not a contraindication. Does the sponsor believer there is a clinical place for concomitant administration of riociguat with a PDE-5 inhibitor?

13. Second round evaluation of clinical data submitted in response to questions

The sponsor submitted a response to the questions posed (dated 29 October 2013). The questions and a summary of the sponsor's responses and the evaluator's comments on the sponsor's responses are discussed below.

13.1. Efficacy

1. The efficacy of the capped dose regimen (1.0 to 1.5 mg) appeared to be comparable to the proposed regimen for registration (1.0 to 2.5 mg) in the PATENT-1 study. In line with good therapeutic practice of prescribing the lowest efficacious dose, discuss why this lower dose has not been examined further and any benefits of using the higher dose over the lower dose.

13.1.1. Sponsor's response

Based on data from CHEST and PATENT studies, riociguat is safe and efficacious using the individual dose titration (IDT) to 2.5 mg TDS. The sponsor acknowledges that the capped titration (CT) arm (to 1.5 mg TDS) was comparable to IDT on the 6MWD but *considers that no definitive judgment on the efficacy of the CT arm can be made due its exploratory nature and relatively small sample size*. The capped dose group was included at FDA request but the study was not designed to assess the benefit risk of this regimen.

With the similar results on the 6MWD in PATENT-1 between IDT and CT groups, the FDA and EMA requested post-hoc comparisons of the riociguat capped titration versus placebo. The sponsor stated that *nominally statistically significant differences favouring 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).* The mean change from baseline in PVR was -8.9, -223.3, and -167.8 dyn*second*cm-5 and for CO was -0.01, 0.93, and0.42 L/min in the placebo, riociguat IDT, and riociguat CT groups, respectively. It was concluded that these haemodynamic data on PVR and CO *suggest a benefit from the increased dose in the riociguat IDT treatment group when compared to the riociguat CT.*

The data based on a post-hoc analysis from the added exploratory CT treatment arm with limited patient numbers support that 1.5 mg TID is already an effective and safe dose in patients with PAH. If approved, there will be patients who would benefit from this dose. However, patients who can tolerate higher doses of riociguat may have an additional clinical benefit.

The sponsor also stated that based on the primary endpoint 6MWD, at least 5 populations of PAH patients have been identified in the PATENT-1 study who may have benefited from the IDT

regimen as compared to the CT regimen within the 12 weeks of double-blinded treatment (patients with connective tissue disease associated PAH, patients pretreated with ERAs, smokers, patients with a creatinine clearance ≥80 mL/min, and patients with a baseline 6 MWD ≥380 m) (Figure 14). The latter 4 groups were associated with lower riociguat exposure (Figure 15).

Figure 14. Subgroup analyses for 6MWD by riociguat treatment–Study 12934 (PATENT-1)

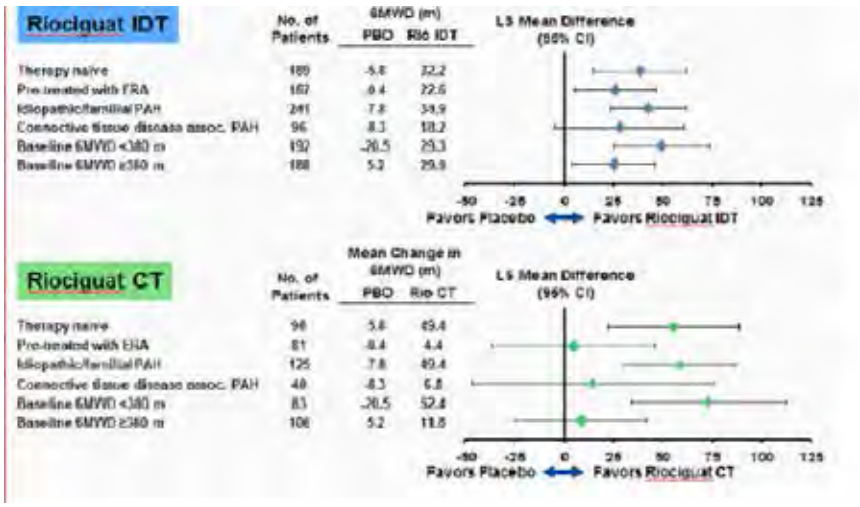
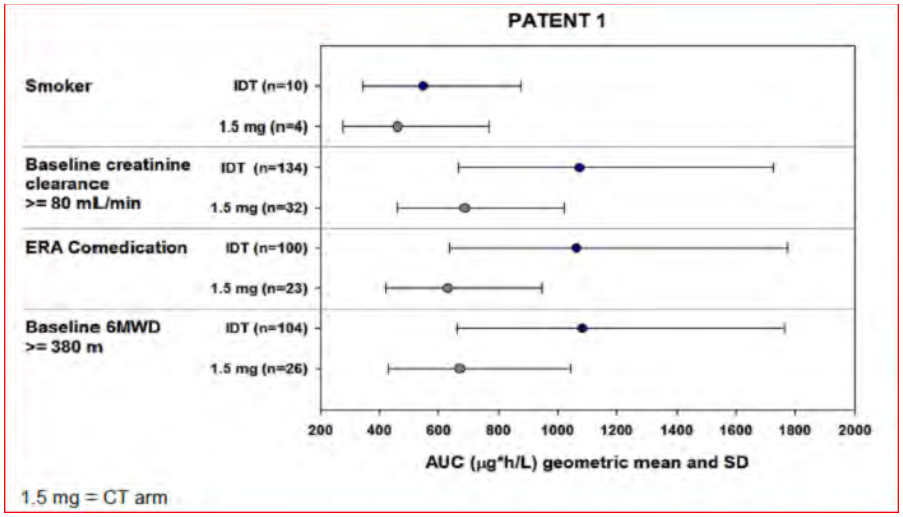


Figure 15. Comparison of riociguat exposure following CT and IDT administration in subgroups identified to have lower exposure – Study 12934 (PATENT-1)



The sponsor also states that longer term data are available with the IDT regimen while only 12 week data are available from PAH patients in PATENT-1 study with the 1.5 mg capped regimen. The dose escalation to 2.5 mg was well tolerated and *does not appear to be associated with incremental safety concerns. In the Sponsor's opinion, the robustness of the efficacy results for the CT dose arm is limited due to the small sample size and, in that light, should be seen as indicative of the riociguat 1.5 mg TID dose being already effective.*

13.1.2. Evaluator's comments:

The evaluator agrees that the data are *indicative of the riociguat 1.5 mg TID dose being already effective* and acknowledges that there are possible benefits of the IDT regimen over the CT in some patient subgroups and on haemodynamic data for PVR and CO. Data on the CT regimen are limited by sample size, short treatment duration and exploratory post hoc analyses and as such cannot form the basis for dosing recommendations. Given that the proposed dosage is an

individual titration regimen and is based on haemodynamic tolerability, the evaluator concludes that a regimen up to 2.5 mg is acceptable.

13.2. Safety

2. In the Phase III program, describe when the hypotension events occur in relation to treatment commencement or titration and during maintenance therapy. Describe any risk of hypotension events in subjects who have already tolerated a given dose. Given these data, discuss if any specific warnings should be included in the product information which would alert physicians to the risk of hypotension at any time rather than just during dose titration.

13.2.1. Sponsor's response:

Hypotension data were presented for hypotension reported as an adverse event (AE), hypotension as recorded by blood pressure measurements (that is, SBP <90 mmHg), and hypotension as combined for both.

Overall, treatment-emergent hypotension adverse events were reported in 10.0% (49/490) of patients in the riociguat group and 3.7% (8/214) in the placebo group during the double-blind phase of the phase 3 studies CHEST-1 and PATENT-1. The sponsor claims that during the double-blind phase of the Phase III studies CHEST-1 and PATENT-1, most hypotension AEs occurred during the titration phase in both treatment groups (visits 1-4, maintenance dose from visit 5) (Table 20).

Table 20. Number and incidences of subject with treatment emergent hypotension (documented as AE) by dose level and time interval in the main studies. All pivotal studies (safety analysis set)

Number and incidence of subject with treatment-emergent hypotension (documented as AE) - by dose level and time interval in main studies - all pivotal studies (safety analysis set)

Visit Interval / Dose	Visit 1 - Visit 2	Visit 2 - Visit 3	Visit 3 - Visit 4	Visit 4 - Visit 5	Visit 5 - Visit 6	Visit 6 - Visit 7
0.5 mg		0/ 9 (0.0%)	0/ 7 (0.0%)	0/ 4 (0.0%)	0/ 4 (0.0%)	0/ 1 (0.0%)
1.0 mg	17/ 490 (3.5%)	0/ 41 (0.0%)	0/ 22 (0.0%)	0/ 15 (0.0%)	1/ 16 (6.3%)	0/ 6 (0.0%)
1.5 mg		9/ 428 (2.1%)	2/ 95 (2.1%)	0/ 80 (0.0%)	0/ 78 (0.0%)	0/ 11 (0.0%)
2.0 mg			7/ 349 (2.0%)	1/ 44 (2.3%)	0/ 55 (0.0%)	0/ 20 (0.0%)
2.5 mg				4/ 323 (1.2%)	10/ 307 (3.3%)	1/ 123 (0.8%)
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%)
Total Verum	17/ 490 (3.5%)	9/ 478 (1.9%)	9/ 473 (1.9%)	5/ 466 (1.1%)	11/ 460 (2.4%)	1/ 161 (0.6%)

Note: Events were identified by Project Bayer MedDRA Query 'Hypotension'.
Note: The time of the first dose of the new visit was relevant for the assignment of adverse events to the visit interval and dose group
Note: Interval visit 6 - visit 7 exists in study chest 1 only
/by-sasp/patdb/ia/632521/stat/2013/04_ae_dose_time/pgms/t-adae-visit.sas ae01 evzrx 08MAY2013 14:30
End of table

Comment: The evaluator has noted that the rate of hypotension AEs in all riociguat-treated patients during the titration periods ranged from 3.5% at visit 1-2 to 1.1% at visit 4-5. At the visit 5-6 period (post-titration), the hypotension rate was still 2.4% overall and the rates by dose level were 3.3% in the 2.5 mg, 6.3% in the 1.0 mg and 0% in the other groups.

In the double blind part of the CHEST-1 and PATENT-1 studies, the rate of treatment emergent hypotension was 42.7 versus 14.9 per 100 person-years in the riociguat and placebo groups, respectively and decreased to 7.1 events in the long term extension studies.

The rate of SBP <90 mmHg was 17.8% (87/490) and 9.8% (21/214) in the riociguat and placebo groups, respectively, in the Phase III studies CHEST-1 and PATENT-1. It was more frequent between visit 1 and 2 (7.3%) but still occurred at subsequent periods (2.9% to 6.3%) (Table 21). The rate during double blind treatment (124.0 versus 71.0 events per 100 p-y) decreased during the long term extension studies (49.5 events per 100 p-y). The combined rate of hypotension AEs and low SBP was 138 versus 80 events per 100 p-y in the riociguat and placebo groups, respectively and 53.5 events per 100 p-y in the long term studies.

Table 21. Number and incidences of subject with treatment emergent hypotension (SBP <90 mmHg) by dose level and time interval in the main studies. All pivotal studies (safety analysis set)

Visit Interval / Dose	Visit 1 - Visit 2	Visit 2 - Visit 3	Visit 3 - Visit 4	Visit 4 - Visit 5	Visit 5 - Visit 6	Visit 6 - Visit 7
0.5 mg		0/ 9 (0.0%)	0/ 7 (0.0%)	0/ 4 (0.0%)	0/ 4 (0.0%)	0/ 1 (0.0%)
1.0 mg	36/ 490 (7.3%)	3/ 41 (7.3%)	7/ 22 (31.8%)	2/ 15 (13.3%)	3/ 16 (18.8%)	1/ 6 (16.7%)
1.5 mg		11/ 428 (2.6%)	3/ 95 (3.2%)	1/ 80 (1.3%)	3/ 78 (3.8%)	1/ 11 (9.1%)
2.0 mg			12/ 349 (3.4%)	4/ 44 (9.1%)	5/ 55 (9.1%)	1/ 20 (5.0%)
2.5 mg				12/ 323 (3.7%)	18/ 307 (5.9%)	4/ 123 (3.3%)
Placebo	8/ 214 (3.7%)	4/ 208 (1.9%)	4/ 204 (2.0%)	8/ 201 (4.0%)	5/ 200 (2.5%)	2/ 84 (2.4%)
Total Verum	36/ 490 (7.3%)	14/ 478 (2.9%)	22/ 473 (4.7%)	19/ 466 (4.1%)	29/ 460 (6.3%)	7/ 161 (4.3%)

Note: Events were identified by low systolic blood pressure (<90 mmHg).
Note: The time of the first dose of the new visit was relevant for the assignment of adverse events to the visit interval and dose group
Note: Interval visit 6 - visit 7 exists in study chest 1 only
/by-sasp/patdb/ia/632521/stat/2013/04_ae_dose_time/pgms/t-adae-visit.sas ae02 evzrx 08MAY2013 14:30
End of table

Kaplan Meier plots for the time to first hypotension event (AE or SBP <90 mmHg) in the pivotal studies show fewer events in the maintenance period (Figures 16 and 17).

Figure 16. Kaplan Meier plot for time to first hypotension after start of study drug (Adverse event or systolic blood pressure <90 mmHg) in pooled CHEST-1 and PATENT-1 (Main phase, Safety analysis set)

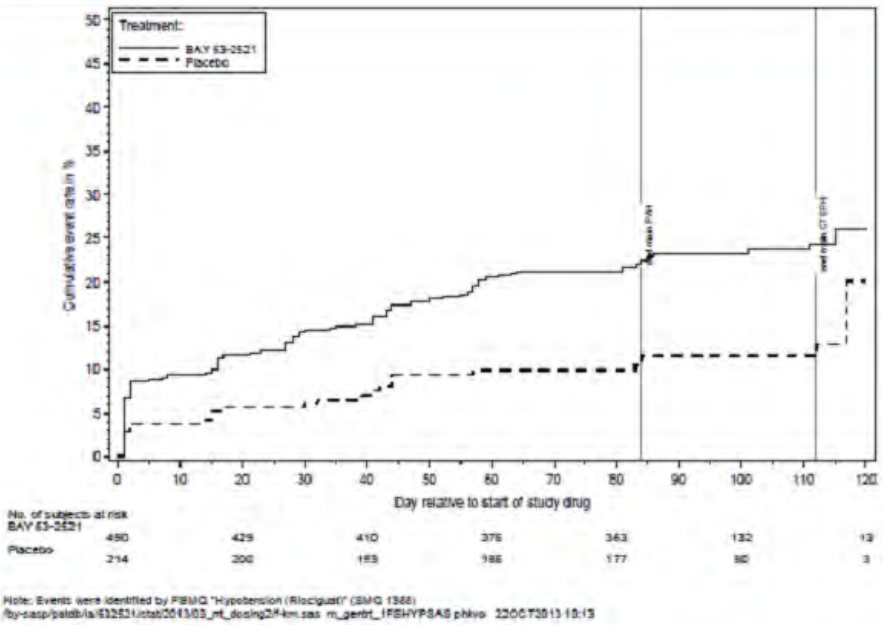


Figure Note: The end of double blind treatment is indicated by the vertical lines

Figure 17. Kaplan Meier plot for time to first hypotension after start of study drug (Adverse event or systolic blood pressure <90 mmHg) in pooled CHEST-1 and PATENT-1 (Main and Extension phases, Safety analysis set)

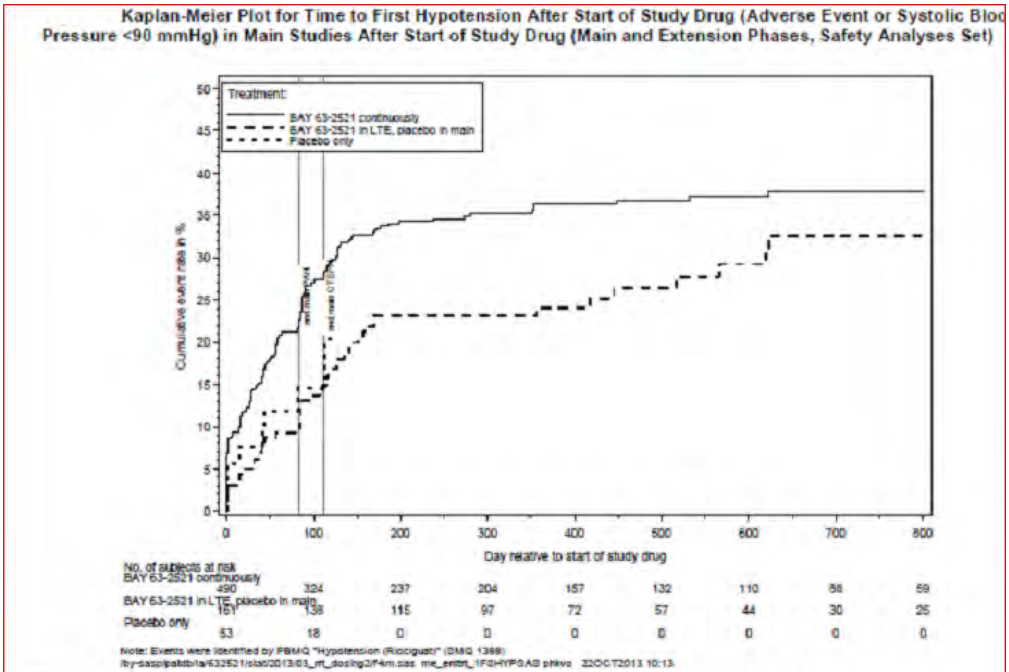


Figure Note: The end of double blind treatment is indicated by the vertical lines.

The sponsor concludes that the *low incidence of hypotension after the titration period (including the blinded sham titration of 8 weeks in PATENT-2 and CHEST-2) demonstrates the good long term tolerability that has been also observed in patients in phase 2 (Study 12166) covering treatment periods of more than 4 years. Based on the study data no other specific warnings for hypotension need to be included at any time other than just during dose titration*.

13.2.2. Evaluator's comments

The evaluator agrees that the risk of hypotension is greater during titration than during maintenance therapy but does not agree that the risk is such that it does not warrant warning physicians. It is recommended that specific wording is included in the *Precaution* section relating to hypotension to state that while the risk of hypotension is greater during titration it may occur during maintenance therapy. It should also state that physicians should consider a dose reduction if patient develops signs or symptoms of hypotension.

3. Was there a greater risk of hypotension in patients with lower SBP at commencement of treatment? Should this be included in the product information? Discuss.

13.2.3. Sponsor's response

The analysis of hypotension events by baseline systolic blood pressure showed an increased risk of hypotension with lower levels of baseline systolic blood pressure. Patients with a systolic blood pressure of <95 mmHg at baseline should have been excluded from the study according to the protocol (Table 22). The sponsor states that *the design of the study led to an increased rate of reported events of hypotension. The vast majority of hypotension events were not assessed as SAEs, did not lead to discontinuation of treatment, were transient and most events occurred at initiation of therapy or at titration. Thus, the Applicant is of the opinion that this information does not need to be included in the product information.*

Table 22. Number of subjects with treatment emergent hypotension (documented as AE or SBP <90 mmHg) by systolic blood pressure at baseline (categories) by primary system organ class. All pivotal studies (safety analysis set)

MedDRA primary system organ class	All riociguat (double-blind studies) n (%)	All placebo (double-blind studies) n (%)	All riociguat (long-term extende treatment) n (%)
	Systolic blood pressure at baseline: <95 mmHg		
	N=2 (100%)	N=0 (100%)	N=2 (100%)
Any Event	2 (100%)	0	1 (50%)
Investigations	2 (100%)	0	1 (50%)
Vascular	0	0	0
	Systolic blood pressure at baseline: 95 to < 105 mmHg		
	N=113 (100%)	N=42 (100%)	N=127 (100%)
Any Event	43 (38.1%)	12 (28.6%)	54 (42.5%)
Investigations	32 (28.3%)	11 (26.2%)	49 (38.6%)
Vascular	14 (12.4%)	1 (2.4%)	12 (9.4%)
	Systolic blood pressure at baseline: 105 to < 115 mmHg		
	N=145 (100%)	N=63 (100%)	N=171 (100%)
Any Event	30 (20.7%)	7 (11.1%)	53 (31.0%)
Investigations	22 (15.2%)	5 (7.9%)	44 (25.7%)
Vascular	9 (6.2%)	3 (4.8%)	13 (7.6%)
	Systolic blood pressure at baseline: 115 to < 125 mmHg		
	N=102 (100%)	N=42 (100%)	N=114 (100%)
Any Event	15 (14.7%)	6 (14.3%)	18 (15.8%)
Investigations	7 (6.9%)	4 (9.5%)	16 (14.0%)
Vascular	8 (7.8%)	2 (4.8%)	3 (2.6%)
	Systolic blood pressure at baseline: ≥125 mmHg		
	N=128 (100%)	N=87 (100%)	N=143 (100%)
Any Event	24 (18.8%)	1 (1.5%)	14 (9.8%)
Investigations	13 (10.2%)	1 (1.5%)	4 (2.8%)
Vascular	13 (10.2%)	0	11 (7.7%)

13.2.4. Evaluator's comments:

Hypotension risk is greater in those with low SBP (95-115 mmHg) at baseline (Table 22). For this reason the evaluator recommends including wording in the *Dosage and Administration* section of the PI along the lines of that included in the US label: *For patients who may not tolerate the hypotensive effect of Adempas, consider a starting dose of 0.5 mg taken three times a day.*

4. Given the known variability in SBP measurement, it could be prudent to start dose titration for all patients at the lower dose of 0.5 mg TDS and titrate slowly. Discuss this proposal and justify the choice of 1.0 mg over 0.5 mg as a starting dose for titration.

13.2.5. Sponsor's response

The sponsor stated *that the clinical study program did not test the 0.5 mg TID dose of riociguat. In the phase 3 studies, only four patients received a reduced the dose to 0.5 mg riociguat TID after starting with 1.0 mg riociguat TID…. Data from the phase 3 studies by titration step show that most events of hypotension (reported as AE) are more linked to onset of new treatment and dose change rather than to the actual received dose. As the Applicant has no data using a starting dose of 0.5 mg riociguat TID in patients with CTEPH or PAH, the Applicant cannot make a recommendation for the lower dose and there are only hypothetical reasons that might suggest to start with a lower dose*.

13.2.6. Evaluator's comments

The evaluator accepts the development program was structured around a starting dose of 1.0 mg. Nevertheless, as a safety precaution it is recommended that a lower starting dose is considered for those who may be at risk of hypotension. The following wording is suggested for inclusion in the *Dosage and Administration* section of the PI (as per the US label):

For patients who may not tolerate the hypotensive effect of Adempas, consider a starting dose of 0.5 mg taken three times a day.

5. Given the results from Study 15096, discuss why concomitant use of PDE-5 inhibitors is listed as a precaution and not a contraindication. Does the Sponsor believer there is a clinical place for concomitant administration of riociguat with a PDE-5 inhibitor?

13.2.7. Sponsor's response

The sponsor has proposed to change the product information and contraindicate concomitant use with PDE-5 inhibitors. The details of these changes are beyond the scope of this AusPAR.

13.2.8. Evaluator's comments

These changes are acceptable.

14. Second round benefit-risk assessment

14.1. Second round assessment of benefits

After evaluation of the data provided in response to the first round of evaluation, the assessment of benefits of riociguat in the proposed usage remain unchanged.

14.2. Second round assessment of risks

After evaluation of the data provided in response to the first round of evaluation, the assessment of risks of riociguat in the proposed usage remain unchanged.

14.3. Second round assessment of benefit-risk balance

In the second round evaluation, clinical data in relation to dosage and hypotensive effects were reviewed. In particular, assessment of the capped titration regimen (to 1.5 mg TDS) over the individual dose titration regimen (to 2.5 mg TDS) was undertaken. These data on the capped regimen indicated an efficacy effect, however were limited by the small sample size and exploratory nature of the assessment which resulted in an inability to formally draw conclusions. As the dosage regimen proposed is tailored to the individual's response, the evaluator concludes that it is acceptable for this regimen up to 2.5 mg TDS to be used.

Data on hypotension risks during maintenance therapy, while less prominent than during dose titration, demonstrated an ongoing risk. Therefore, it is recommended specific wording on this is added to the *Precaution* section of the PI relating to hypotension. The risk of hypotension was higher in those with lower SBP at baseline and a lower starting dose could be considered in this group or any patient the physician may feel is at risk of hypotension. Relevant changes to the *Dosage and Administration* section have been proposed which are along the lines of that approved in the US.

The sponsor did not provide any situations where it believed there would be a clinical place for concomitant use of riociguat with a PDE-5 inhibitor and given the notable safety risks has agreed to make such concomitant use a contraindication rather than a precaution.

In summary, after the second round of evaluation of data submitted in response to questions, the evaluator finds that the benefit-risk balance of riociguat given the proposed usage remains favourable. This is subject to the sponsor addressing the recommended changes to the PI and adoption of the proposed changes to the indication.

14.4. Second round recommendation regarding authorisation

The evaluator finds the benefit-risk balance of riociguat in the treatment of PAH and CTEPH to be positive and recommends authorisation subject to:

- Alteration of the indication (see below).
- Adoption of changes to the draft PI and CMI.
- Inclusion in the RMP of the additional risks for postmarketing surveillance.

A proposed revised indication is:

Chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4):

Adempas is indicated for the treatment of adult patients with

- *inoperable CTEPH,*
- *persistent or recurrent CTEPH after surgical treatment*

classified as WHO functional class II and III to improve exercise capacity.

Pulmonary arterial hypertension (PAH, WHO Group 1):

Adempas is indicated for the treatment of adult patients with PAH classified as WHO functional class II and III to improve exercise capacity.

Efficacy in PAH was shown in patients on riociguat monotherapy or in combination with endothelin receptor antagonists or prostanoids.

Studies establishing effectiveness in PAH predominately included patients with aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

15. References

EMA (2009). Committee for medicinal products for human Use (CHMP). Guideline on the clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. EMEA/CHMP/EWP/356954/2008.

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