EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2014

EMA/CHMP/734750/2013

Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Adempas

International non-proprietary name: riociguat

Procedure No. EMEA/H/C/002737/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Adempas
Applicant:	Bayer Pharma AG Muellerstrasse 178 13353 Berlin GERMANY
Active substance:	riociguat
International Nonproprietary Name:	riociguat
Pharmaco-therapeutic group (ATC Code):	C02KX05
Therapeutic indication:	Chronic thromboembolic pulmonary hypertension (CTEPH) Adempas is indicated for the treatment of adult patients with WHO functional class II to III with • inoperable CTEPH, • persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity (see section 5.1). Pulmonary arterial hypertension (PAH) Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO functional class (FC) II to III to improve exercise capacity. Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease (see section 5.1).
Pharmaceutical form:	Film-coated tablet
Strengths:	0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg
Route of administration:	Oral use
Packaging:	blister (PP/Alu)
Package sizes:	42 tablets, 84 tablets and 90 tablets

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List of abbreviations

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
ALP	Alkaline phosphatase
ALT	(SGPT) alanine aminotransferase
ANCOVA	analysis of covariance
APAH	associated with pulmonary arterial hypertension
ASA	acetylsalicylic acid
AST	aspartate aminotransferase (also known as SGOT, qv)
ATC	Anatomic Therapeutic Chemical Classification System
AUC	area under the concentration vs. time curve from zero to infinity after single (first) dose
Bay 63-2521	Riociguat
Bay 60-4552	Main metabolite M-1, pharmacologically active
Bay 38-9456	Vardenafil
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
BSEP	Bile salt export pump (human)
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
cGMP	cyclic guanosine monophosphate
CLCR	Creatinine clearance
CLR	Clearance of riociguat
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
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
CNP-pGCcGMP	C-type natriuretic peptide - particulate guanylate cyclase - cyclic guanosine monophosphate

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
d	day
DBP	diastolic blood pressure
dyn	dyne [1 dyn = 1 g*cm*s^{-2} = 10^{-5} N (Newton)]
ECG	electrocardiogram
EMA	European Medicines Agency
EQ-5D	European quality of life 5-dimensions instrument
ERA	endothelin receptor antagonist
EU	European Union
F	Female
Fabs	absolute bioavailability
FC	functional class
FDA	Food & Drug Administration
FPAH	familial pulmonary arterial hypertension
fu	unbound fraction
GFR	glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
gSD	geometric standard deviation
h	hour (s)
hERG	Human ether-a-go-go related gene
HPAH	heritable pulmonary arterial hypertension
HIV	human immunodeficiency virus
HR	heart rate
IC50	inhibitory concentration (50% inhibition)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDT	individual dose titration
ILD	interstitial lung disease
INR	international normalised ratio (prothrombin time)
IPAH	iidiopathic pulmonary arterial hypertension
IR	immediate release
ITT	intention to treat

Ki	inhibition constant
IVRS	interactive voice response system
LC-MS/MS	High-pressure liquid chromatography with tandem mass spectrometric detection
LFT	liver function test
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
LPH	Living with Pulmonary Hypertension
LS	mean last square mean
LTE	long term extension
M	male
MAP	mean arterial pressure
MDR-1	multi-drug resistance protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important clinical different
MRHD	maximum recommended human dose
mRNA	messenger ribonucleic acid
MTD	maximal tolerated dose
6MWD	6 minute walking distance
6MWT	6 minute walking test
n	number
N/A	not applicable
NDS	new drug submission
NIH	National Institutes of Health (US)
NO	nitric oxide
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NONMEM	non-linear mixed effect model
NTCP	sodium-dependent taurocholate co-transporting polypeptide (human)
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NTX	N-terminal cross-linking telopeptides of type I collagen
NYHA	New York Heart Association
OATP	organic anion-transporting polypeptide (human)
P450	cytochrome P450 enzyme
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
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
POOL-1 DB	Double-blind study phase in studies 11348 (CHEST-1) and 12934 (PATENT-1)

POOL-1 LTE	Long-term extension phase in studies 11349 (CHEST-2) and 12935 (PATENT-2)
PP	per protocol
PPH	primary pulmonary hypertension
PPHN	primary pulmonary hypertension of the newborn
PT	preferred term
PT	prothrombin time, when referred to laboratory sections
PT INR	prothrombin time – international normalised ratio
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
QbD	Quality by Design
RAP	right atrial pressure
RHC	right heart catheter
RMP	risk management plan
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 guanylatl 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 (three times daily)
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)
VKA	vitamin K antagonist
Vss	apparent volume of distribution at steady state
VTE	venous thromboembolism
WHO	World Health Organisation
WHO FC	World Health Organisation functional class

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer Pharma AG submitted on 5 February 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Adempas, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 April 2012.

Adempas was designated as an orphan medicinal product EU/3/07/518 on 20 December 2007. Adempas was designated as an orphan medicinal product in the following indication: Treatment of pulmonary arterial hypertension including treatment of chronic thromboembolic pulmonary hypertension.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Adempas as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found here.

The applicant applied for the following indication:

Chronic thromboembolic pulmonary hypertension (CTEPH)

Treatment of adult patients with

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

to improve exercise capacity. Studies establishing effectiveness included predominately patients with WHO functional class II – III.

Pulmonary arterial hypertension (PAH)

Treatment of adult patients with PAH to improve exercise capacity. Efficacy was shown in patients on riociguat monotherapy or in combination with endothelin receptor antagonists or prostanoids.

Studies establishing effectiveness included predominately patients with WHO functional class II – III and aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that riociguat was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0254/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance riociguat contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 January 2007 and 23 October 2008. The Scientific Advice pertained to, among others, the use of clinical samples for phase II studies in phase III, the use of systolic blood pressure as a surrogate for the dose titration endpoint and the design of the pivotal CTEPH and PAH clinical trials.

Licensing status

Adempas has been given a Marketing Authorisation in Canada (23 Sep 2013), USA (08 Oct 2013), Switzerland (22 Nov 2013), Chile (27 Dec 2013) and Japan (17 Jan 2014).

1.2. Manufacturers

Manufacturer responsible for batch release

Bayer Pharma AG
51368 Leverkusen
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff

Co-Rapporteur: Martina Weise

- The application was received by the EMA on 5 February 2013.
- The procedure started on 27 February 2013.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 20 May 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 May 2013.
- The PRAC Rapporteur Risk Management Plan (RMP) Assessment Report was endorsed by PRAC on 13 June 2013.
- During the meeting on 27 June 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 01 July 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 September 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 October 2013.
- During the CHMP meeting on 21 November 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 28 November 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 31 December 2013 (Annex 7). This assessment report included an additional list of Outstanding Issues to be addressed by the applicant.
- The PRAC RMP Advice and Assessment Overview was adopted on 09 January 2014.
- The applicant submitted the responses to the CHMP second List of Outstanding Issues on 10 January 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the additional Outstanding Issues to all CHMP members on 16 January 2014.
- The CHMP adopted a report on similarity of Adempas with Volibris, Revatio, Ventavis and Opsumit on 23 January 2014.
- During the meeting on 23 January 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Adempas.

2. Scientific discussion

2.1. Introduction

Both, chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) are rare and life-threatening forms of pulmonary hypertension (PH). Both conditions share similar pathological features, and are characterised by pulmonary arterial micro

vascular remodelling, deregulation 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.

CTEPH is a chronic, debilitating disease characterised clinically by dyspnoea, fatigue, chest pain, dizziness, peripheral oedema, coughing, haemoptysis, and, in advanced disease, fainting and syncope. It most often results from obstruction of the pulmonary vascular bed by non-resolving thromboemboli.

CTEPH can arise in patients after acute or recurrent pulmonary emboli or deep venous thrombosis. Increased pulmonary vascular resistance (PVR) subsequently leads to progressive pulmonary hypertension and right heart failure. In the non-occluded areas, a pulmonary arteriopathy indistinguishable from that of PAH can develop and contribute to disease progression. The incidence of CTEPH is not known, but recent studies suggest that 1% to 3.8% of patients develop the condition within two years of acute pulmonary embolism. Without intervention, the prognosis of patients with CTEPH is poor and depends on the haemodynamic severity of pulmonary hypertension. The only potentially curative treatment is surgical removal of the obstructive material by pulmonary endarterectomy (PEA). However, a substantial percentage of patients with CTEPH are not operable, and 10% to 15% of operated patients suffer from persistent pulmonary hypertension. Currently, there are no approved medicines for patients with inoperable CTEPH and persistent or recurrent PH following PEA and, therefore, the unmet medical need is high. To-date, there is only one multi-centre, randomised, placebo-controlled clinical study in patients with CTEPH that showed an effect of bosentan over placebo for PVR but not for the 6-minute walking test (6MWT) or time to clinical worsening (TTCW). Thus, the trial was positive for one of the pre-defined independent co-primary endpoints (PVR) and not supported by the other (6MWD). Several uncontrolled studies have shown moderate benefit of PAH-specific medicines in patients with CTEPH. Additionally, CTEPH registry data indicate that PAH specific therapies – including endothelin receptor antagonists (ERA) and phosphodiesterase-5 (PDE5) inhibitors – are frequently used "off-label" in patients with CTEPH, despite there being no compelling evidence to support this approach.

PAH is characterised by vasculopathy with extensive remodelling of the pulmonary circulation that results in narrowing of the arterial lumen and impaired flow-mediated vasodilatation. The consequent increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) limits the ability of the right ventricle to pump blood through the lungs, causing shortness of breath and reduced physical performance. PAH is a progressive disease, and ultimately leads to right heart failure and death. The pathophysiology of PAH is not fully understood, but is thought to involve abnormal interactions between endothelial and smooth muscle cells, leading to vasoconstriction, vascular smooth muscle cell proliferation, vascular endothelial proliferation, and in situ thrombosis. An up-regulated Endothelin-1 system, defective prostacyclin synthase activity, and abnormalities of the nitric oxide (NO) pathway are considered important mediators of these pathological changes, and form the therapeutic targets for currently available PAH-specific therapies [Chin 2008, McGoon 2009].

Available pharmacological therapies for PAH address the three target pathways mentioned above as probably implicated in the pathogenesis of the disorder:

ERAs, by inhibiting the effects of elevated Endothelin-1 levels, reduce vasoconstriction, smooth muscle cell proliferation and pulmonary vessel fibrosis.

Prostacyclin analogues relax and reduce proliferation of vascular smooth muscle cells.

PDE5 inhibitors potentiate the anti-platelet, antiproliferative, and vasodilatory effects of NO.

There is significant need to develop data that support the emerging practice of combination therapy (combinations of PAH-specific medicines targeting different, complementary pathways). While combination therapy has mechanistic and biological plausibility, there remains paucity of data to support this and in fact several studies have failed to show the benefit of dual oral therapy. To-date, only one product has been authorised for use in combination therapy.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing riociguat as active substance. Other ingredients are: cellulose microcrystalline, crospovidone, hypromellose, magnesium stearate, lactose monohydrate, sodium lauryl sulfate, hydroxypropylcellulose, propylene glycol and titanium dioxide.
The product is available in PP/Aluminium foil blister packs as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The chemical name of riociguat is methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazo-lo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate and has the following structure:

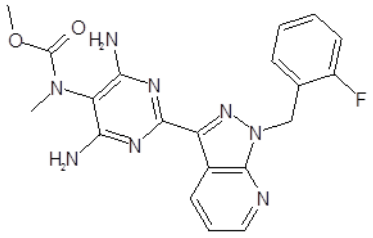


Figure 1: Chemical structure of riociguat.

Riociguat is a white to yellowish crystalline powder, not hygroscopic. It is practically insoluble in water and shows a strong pH-dependent solubility in aqueous media with a maximum around pH 2, slightly soluble in acetone and methanol and freely soluble in dimethylsulfoxide and dimethylformamide.

Riociguat has a non-chiral molecular structure. Polymorphism has been observed for the active substance. Riociguat exists in two modifications, i.e. modification I and modification II. Modification I is the thermodynamically stable form at room temperature. There are also three pseudo-polymorphous solvate forms. The manufacturing process consistently produces the same

polymorphic form, modification I. The polymorphic form is controlled in the specification of riociguat micronized drug substance by XRPD analysis.

The structure of riociguat is derived from the route of synthesis, from experimental analysis and spectral data: IR, Raman, UV VIS, ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry. In addition, elementary analysis and x-ray structural analysis were performed. Full characterization of the produced solid state form has been performed. Modifications I and II as well as the pseudo-polymorphs and the amorphous form are distinguishable.

Manufacture

Micronised riociguat manufacturing process consists of three synthetic steps, two crystallisation and one milling step using well defined starting materials with acceptable specifications.

Due to the low water solubility of riociguat, the milling step of the manufacture of the active substance is also a critical step. Therefore, the particle size distribution of the active substance is a critical quality attribute controlled in the specification for the active substance. The manufacturing process has been developed using elements of Quality by Design (QbD) such as risk-assessment, OVAT (One Variable At a Time) experiments and design of experiments. The results of these studies were used to define proven acceptable ranges (PARs) for the different steps of the riociguat manufacturing process.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Impurities presented at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for: appearance (visual examination), identity (IR, HPLC and X-ray Powder Diffractometry), assay (HPLC), impurities (HPLC), residual solvents (GC), heavy metals (ICP-MS) and particle size distribution (Ph. Eur.).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Batch analysis data on four commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The active substance specifications are based on the active substance critical quality attributes (CQA). The CQA identified were assay, identity, appearance, particle size distribution, polymorphous form, palladium, organic purity, residual solvents and genotoxic impurities.

Stability

Stability data on six pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package 36 months under long term conditions at 25 ºC / 60% RH and for up to 12 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Photostability testing following ICH guideline Q1B was performed on one batch. The results showed that solid riociguat is not sensitive to light since

there was no discolorations of the solid, no decrease in the assay and no increase of any degradation products. Based on the results obtained, no special protection from light is necessary in the production or handling of the solid crystalline active substance. Results on stress conditions (thermal, hydrolytic, and oxidative stress conditions) were also provide on one batch. The results showed that riociguat is extremely stable under thermal stress conditions in solid state and not hygroscopic. In addition, the results showed sufficient stability with regard to hydrolytic stress in solution under acidic, neutral and moderate basic conditions in the pH-range of pH 7 to pH 9. Only under severe stress test conditions at elevated temperature of 70 °C for 24 hours at pH 1 some minor degradation was observed. The possible formation of a potentially genotoxic impurity under simulated gastric conditions has been specifically investigated. Results confirm that the potential formation under the tested conditions would not lead to a daily intake of more than 0.5 µg (TTC). Riociguat was less stable under basic conditions. The observed degradation is pH-dependent. Under stress test conditions at a pH of 13 (0.1 N NaOH) and elevated temperature up to 70°C for 24 hours or time dependent for up to 1 week stored at 25°C a complete degradation of Riociguat was observed. Riociguat is sufficiently stable related to oxidative stress. Under normal oxidative stress conditions at 25°C/24 hours in presence of 3 % H_2O_2 no degradation was observed.The following parameters were tested*:* appearance, impurities and assay.

The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the drug substance manufactured by the proposed manufacturer is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective of the pharmaceutical development was to provide an oral formulation containing riociguat micronized with high convenience and patient compliance. Immediate release tablet formulations of small size have been selected as dosage form. The different dose strengths were all based on the same basic qualitative composition (with differences only in pigment composition of film-coating) and manufacturing process. All dose strengths have been formulated to same tablet weight (85 mg plus 2.5 mg film coat) and same size (6 mm diameter). Riociguat tablets are film-coated to facilitate swallowing and a colour code design was used to distinguish between the different dose strength and to facilitate tablet identification.

The physicochemical characteristics relevant to the performance of the finished product are particle size and dissolution. To facilitate drug dissolution riociguat is micronized by air-jet milling. Fast and complete in vitro dissolution has been demonstrated for tablets manufactured with micronized riociguat within the specified limits of particle size distribution, whereas tablets manufactured with riociguat particle size outside the specified limits showed slower and incomplete drug dissolution.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of ferric oxide yellow and red which comply with Directive 2008/128/EC. The excipients have been chosen based on preliminary formulation development experience and excipient compatibility studies. Lactose monohydrate and microcrystalline cellulose are used as fillers, crospovidone as disintegrant, hypromellose as binder, magnesium

stearate as lubricant and colloidal silicon dioxide as glidant. Sodium lauryl sulfate improves wetting of the active substance and therefore facilitates the granulation process. There are no novel excipients used in the finished product formulation.

The pharmaceutical development of the finished product contains QbD elements.

The quality target product profile (QTPP) was defined as an immediate release dosage form, which can be swallowed easily, allows flexible dose adjustments for patients, can be distinguished between the different dose strength, that meets compendial and other relevant quality standards.

A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical quality attributes (CQAs) identified were assay, uniformity of content and appearance. Critical process parameters (CPPs) have also been adequately identified.

In addition, it has been demonstrated that a change of the polymorphic form under the established manufacturing conditions and during storage under climate zone I-IV was not expected.

The dissolution method has been adequately developed and its discriminating capability demonstrated. The discriminatory power of the method was monitored using product batches manufactured from drug substance with different particle size. The use of surfactant and the dissolution medium was justified.

The formulation development from Phase I to Phase III clinical trials has been adequately described. The tablet composition and manufacturing principles were not changed with only one exception regarding the colour of the film-coat: the tablets used in clinical studies phase I and II were coated in red (titanium dioxide and ferric oxide red as pigment) and in clinical phase III studies the colour was changed to pale orange (titanium dioxide, ferric oxide yellow and ferric oxide red as pigment). The dissolution profiles obtained for the batches used in the Phase I and II and those used in the phase III, using the proposed dissolution method, are comparable.

The primary packaging is PP/Aluminium foil blister as stated in the SmPC. The material complies with Ph.Eur.and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Manufacture of the product

The manufacturing process consists of seven main steps: (1) blending, (2) wet-granulation, (3) drying, (4) post-blending, (5) compression, (6) coating and (7) packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Proven acceptable ranges have been defined for all steps of the medicinal product. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

Product specification

The finished product release specifications include tests for appearance (visual examination), identification of riociguat (HPLC and NIR or TLC), assay (HPLC), impurities (HPLC), uniformity of dosage unit (HPLC), dissolution (HPLC) and microbial purity (Ph.Eur.).

Batch analysis results are provided for six pilot scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 3 pilot scale batches of each strength of the finished product stored under long term conditions for 36 months at 25 ºC / 60% RH, under intermediate conditions for 36 months at 30 ºC / 75% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of riociguat are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, impurities, assay, microbial purity and dissolution. The analytical methods used are stability indicating.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results showed that the product is stable to light.

Based on available stability data, the shelf-life as stated in the SmPC is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant has applied Quality by Design (QbD) principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance or finished product. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Riociguat (BAY 63-2521) is a soluble guanylate cyclase (sGC) stimulator, a key enzyme in the NO-sGC-cGMP pathway. sGC activation increases cellular cGMP concentration which in turn activates specific downstream effectors including kinases, phosphodiesterases and ion channels, resulting e.g. in vasorelaxation, inhibition of smooth muscle cell proliferation and migration.

Primary pharmacodynamic studies

In multiple *in vitro* studies it was shown that riociguat is a potent stimulator of sGC (as measured increase in the cellular cGMP concentration) in the nM to low µM concentrations. Further increases in cellular cGMP can be induced by combination of riociguat with a NO donor. Riociguat also has vasorelaxing effect on isolated vessels (including nitrate tolerant vessels), various tissues and perfused heart. Relatively large variations in inhibitory concentration (50% inhibition) (IC50) values are seen between studies, however in most studies IC50 values ranged between high nM, sub-µM concentrations. Available data suggests that the main action of riociguat is through reversible stimulation of the α1/β1 subunit of sGC with a smaller contribution by the α2/β1 isoform. It appears that disease state of the tissue does not lead to a reduction in in sGCα1/β1 expression, and may even increase sGCα1/β1 expression, and thus will not negatively affect the potential beneficial effect of riociguat on the disease

The *in vivo* hemodynamic effects of riociguat have been investigated in healthy animals, spontaneous hypertensive rats (SHR) and three models of progressive pulmonary arterial hypertension, (i.e. the hypoxia-induced PAH in mice, monocrotaline injection in rats and combined hypoxia and VEGF receptor inhibition in rats (SUHx model)). In healthy rats, dogs and spontaneous hypertensive rats, riociguat-mediated effects were dose-dependent reduction in systemic blood pressure and a compensatory increase in heart rate. In dog more parameters were evaluated and the additional treatment-related effects were: reduced left ventricle pressure and pulmonary pressure and increases in cardiac output, coronary blood flow, oxygen saturation and contractility. In all three animal models of progressive PAH disease, decreased progression or full inhibition of disease progression was observed, but no improvement of disease parameters to levels seen in healthy controls. Compared to untreated disease-controls riociguat-treatment resulted in a decrease in pulmonary vascular resistance, right ventricular systolic pressure and right heart hypertrophy. In all three models, riociguat had no effect on systemic blood pressure.

Hemodynamic effects of riociguat (e.g. systemic blood pressure lowering, cardiac output increase, reduction in peripheral resistance, heart rate increase) are expected in all different disease models of PAH. Such effects were shown in the model of "PH induced by hypoxia and SU5416" and U46619-induced PH. The hemodynamic assessment was performed 24h after the last oral administration of riociguat (at trough levels) and not continuously during the course of the study. This might explain the missing data on the decrease in systemic blood pressure in the experimental PAH models under riociguat treatment.

In the animal model that most closely mimics the human PAH pathology (SUHx), a reduction in disease-related pulmonary remodelling (vascular muscularization, occlusive lesions, medial wall thickening) was observed following riociguat treatment. Of note, the dose commonly used in the disease model was 10 mg/kg/day, which is relatively high based on effects seen in healthy animals. This result, taken together the pharmacodynamic effect seen in the *in vivo* studies with riociguat, is consistent with its mechanism of action, i.e. stimulation of the NO-sGC-cGMP pathway, leading to vasodilatation.

The pharmacodynamic effects of the main metabolite (M-1, or BAY 60-4552) have also been investigated in *in vitro* and *in vivo* studies, and have also been investigated in clinical development. The data indicate that M1 has the same pharmacodynamics effects as the parent albeit somewhat less potent (pharmacological activity: 1/10th to 1/3rd of riociguat).

Secondary pharmacodynamic studies

As part of the secondary pharmacology studies, specificity studies have been performed for riociguat and its metabolite M1. Data indicate that riociguat and M1 are specific for sGC, do not interfere with other enzymes of the NO-sGC-cGMP pathway, and do not stimulate membrane-bound guanylate cyclase receptors at to concentrations up to 10 µM.

Signalling through sGC has been implicated in other physiological processes such as antiaggregation and neuronal signalling. Indeed, activation of the sGC-cGMP pathway by riociguat in human and rat platelets has been demonstrated *in vitro*.

Furthermore, *in vivo* studies indicate that riociguat can prolong bleeding time and reduce clot formation. *In vitro*, riociguat shows effects on platelet function at high, *in vivo* non-relevant concentrations. Thus, the slight effects on rat tail transection bleeding time is considered not to be related to the cGMP-related effects on platelets, but rather a consequence of the strong vasodilative effects of riociguat. Furthermore, investigation of platelet aggregation, bleeding time and interaction of riociguat and warfarin in healthy human volunteers did not show any anti-platelet effects as seen in preclinical investigation. Therefore, it is considered highly unlikely that the observed bleeding events in riociguat-treated patients are caused by an anti-platelet effect of riociguat.

It is known that sGC signalling also plays a role in neuronal signalling. No attempt to test the effect of riociguat in neurological models functions has been made. Based on the results in the safety pharmacology studies, it appears that riociguat does not have an immediate detrimental effect on CNS. Furthermore, no behaviour effects were noted in the repeated dose toxicity studies. Therefore, based on the assessment of the current data, riociguat does not have a significant biological effect on neuronal signalling.

It has been suggested that the NO-sCG-cGMP signalling pathway is also involved in migration of smooth muscle cells, and riociguat –inhibited the migration of human coronary artery vascular smooth muscle cells *in vitro*.

As may be expected based on the mechanism of action, riociguat was found to have an effect on the erectile response in rabbits. Riociguat treatment reduced the atherosclerotic plaque formation in Apo E-deficient mice. Furthermore, riociguat reduced blood pressure in several animal models of hypertension and decreased hypertension-related tissue damage or tissue remodelling in the used animal models.

Safety pharmacology programme

The effect of riociguat and its main metabolite M-1 on vital organs (cardiovascular system including electrocardiogram (ECG), respiratory system and central nervous system) as well as on supplemental organ functions (gastrointestinal function, renal function, metabolism (glucose, lipids) and blood) was investigated in several *in vitro* and single dose *in vivo* studies.

In vitro studies (hERG assay and a rabbit cardiac Purkinje fibre action potential assay) do not indicate potential adverse effect at clinical relevant concentrations.

In i*n vivo* studies in dogs, shortening of QT was seen due to increased heart rate. Correction of the QT interval for the increased heart rate was performed using several formulae. QT interval was corrected for heart rate (QTc) using Bazett's (QTcB), Fridericia's (QTcF) and van de Water's (QTcV) formula. A small but significant increase in QTcB and QTcF was seen but not QTcV. Thus, the interpretation of the potential of riociguat to prolong QT interval in dogs depends on the used formula. While overall the data suggest that the QTc prolongation potential is not high, the dog data do not unambiguously show a lack of potential for QTc prolongation.

However, in humans no increased risk of QT prolongation was observed, but the data set was quite limited.

No substantial effects on respiration and lung mechanics or CNS parameters were seen. Riociguat treatment did reduce gastric motility *in vivo* and ilial contraction *in vitro*. A slight increase in blood glucose and a clear decrease in urine volume were noted immediately following a single dose of riociguat.

Pharmacodynamic drug interactions

Several in vivo studies have been performed on the effects on hemodynamic parameters of the combination of riociguat with a PDE5 inhibitor (vardenafil or sildenafil). In general, co-administration of riociguat with vardenafil/sildenafil resulted in additive effects on haemodynamics. In an acute model of PAH, sildenafil appeared more selective in reducing pulmonary arterial hypertension vs. systemic blood pressure than riociguat, and the combination of sildenafil with riociguat appeared to have an even improved pulmonary selectivity. In dogs it was found that glycerol trinitrate maintains its acute blood pressure lowering effect in presence of riociguat.

Riociguat further increased the acetylsalicylic acid-associated prolonged bleeding time, but did not further prolong the bleeding time when combined with rivaroxaban, clopidogrel or iloprost.

2.3.3. Pharmacokinetics

Absorption

Absorption of riociguat is rapid and around 60-65% in rat and about 80% in dog. The bioavailability is high in humans (94%) and lower in dogs (approximately 50-70%) and rats (approximately 35-65%). At comparable doses, exposure to riociguat is higher in dog than in rat.

Pharmacokinetics of riociguat are linear with dose in dog over the dose range 0.03 to 2 mg/kg and less than dose-proportional in the dose range 2 to 6 mg/kg. In rats, more than dose-proportional kinetics are seen over the dose range 0.3 to 3 mg/kg, and linear kinetics up to 40 mg/kg. Regarding the metabolite M-1, exposure in rats increases proportionally with dose in the dose range 2.5 to 40 mg/kg. In dogs the exposure increases proportionally in the dose range 0.3 to 1 mg/kg. Less than dose-proportional increases are seen in dogs up to 3 mg/kg. Generally, a slight or moderate accumulation in riociguat and M-1 exposure after repeated dosing is observed in rat and dog.

Distribution

Plasma clearance is moderate in rat and dog and accompanied by a moderate volume of distribution, indicating distribution into tissues. The plasma half-lives are short in both rat and dog with ~1-2 hours. The half-life of the pharmacologically active metabolite M-1 (pharmacological activity $1/10^{th}$ to $1/3^{rd}$ of parent) is determined in dog and amounts to ~5 hours. The terminal half-life of the total radioactivity is much longer (90 hours in dog and 9 to 17 hours in rat) indicating the presence of metabolites with longer half-lives.

The free fraction of riociguat in plasma is moderate to low with an unbound fraction (f_u) in rat, dog and mouse of 15-20% and of 4-5% in human and rabbit. The plasma protein binding is pH and NEFAs-presence dependent; it increases with decreasing pH and decreases with NEFAs. In addition, when co-administered with salicylic acid, riociguat free fraction increases 1.5-fold. In rat and dog, riociguat was almost equally distributed between plasma and erythrocytes. In humans on the other hand, the plasma to blood ratio of riociguat indicates the presence of more riociguat in plasma compared to the erythrocytes.

Riociguat is rapidly and widely distributed to tissues, except in seminal vesicles and testes revealing a delayed uptake of radioactivity. Organs with the highest radioactivity 24 hours after administration were organs/tissues involved in riociguat and its related radioactivity elimination. Accumulation in human skin and eye could occur. Repeated versus single dosing revealed an increase in radioactivity for most organs, with a possible risk for accumulation after repeated dosing in adrenal tissue, kidney, liver, lung, skin, spleen, thyroid, bone marrow, testes, and aorta wall. The blood-to-brain and blood-to-testes penetration of radioactivity was low. Riociguat-related radioactivity is able to cross the placenta in rats.

Metabolism

Riociguat is metabolised to various metabolites *in vitro* and *in vivo*. The major metabolites in human plasma are M-1 (N-demethylation of riociguat) and M-4 (N-glucuronide of M-1).

In vitro experiments using clinically relevant concentrations of riociguat showed that 4 CYP isoforms are involved in the biotransformation of riociguat to M-1, namely CYP1A1, 2J2, 3A4 and 3A5. CYP1A1 is the major enzyme involved in the M-1 formation. A high inter-individual

variability in the plasma concentration-time curves of riociguat was observed in man. This could be explained by the involvement of the highly inducible CYP1A1. In section 4.4 of the SmPC, it is stated that "concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-gp/ breast cancer resistance protein (BCRP) inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure. These drugs should be used with caution. Blood pressure should be monitored and dose reduction of riociguat be considered (see SmPC sections 4.5 and 5.2)". In individuals without or with a low CYP1A1 activity, the same kinetics of riociguat can be observed as in individuals with normal CYP1A1 activity that also use strong CYP1A1 inhibitors.

The ratio between the active metabolite M-1 and parent compound differs largely across the non-clinical species.

Excretion

Drugs inhibiting UGT1A1 and UGT1A9 may lead to significant changes in the elimination pathways of M-1, , and as a consequence in the pharmacology. Drug-drug interactions via UGTs can therefore not be excluded. The inhibitory potency of potential co-medications including mefenamic acid, diflunisal and atazanavir on the glucuronidation of M-1 was determined and IC50 values amounted to 47 µM, 24 µM and >10 µM. DDI potential was assessed by using Cmax,u/IC50 ratios. These values are not reassuring, since IC50 values should be compared to 50 × $C_{max,unbound}$ as is stated in the EMA guideline on drug-drug interactions. In the absence of further data, the applicant has added a warning to section 4.5 of the SmPC stating the possibility of interactions with drugs that are inhibitors of UGT1A1 and/or 1A9.

Noticeable differences in excretion and metabolic profile in the excreta were observed between the species. Riociguat is primarily excreted via the faecal/biliary route (approx.70-80%) in rat and dog, mainly as parent compound in rat and as M-1 and M-4 in dog. The renal route accounted for approx. 10-20%, and active secretion of parent and metabolites by gastrointestinal mucosa is another possible route of excretion observed in rats. Enterohepatic recirculation cannot be ruled out. Riociguat is also secreted in rat milk. In humans, excretion of riociguat occurred almost equally via the renal (approx. 30-45%) and faecal/biliary (approx. 45-60%) route, mainly as parent compound or as M-1. This ratio and the metabolic profile vary per individual subject and are dependent on the biotransformation rate.

Riociguat is a substrate for P-glycoprotein, BCRP and OCT2 but not a substrate for OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT3 at the investigated concentrations. M-1 is a substrate for P-glycoprotein and BCRP but not a substrate for OCT1, OCT2 and OCT3 at the investigated concentrations.

The applicant indicated that riociguat and M-1 are not substrates for OAT1 and OAT3 at concentrations of 0.3 µM and 3 µM. For riociguat, this is in line with the fact that the renal clearance of riociguat in humans was approximately the normal glomerular filtration rate (when considering a fraction unbound of 5% in human plasma). Thus, riociguat is not actively secreted via the kidneys. The applicant has agreed to determine the substrate characteristics towards OAT1 and OAT3 at the lowest feasible concentration using 3H-labelled compound, under the prerequisite that the synthesis of 3H-labeled compound is successful. In addition, the applicant agrees to determine the substrate characteristics towards OCT1, OCT3 (riociguat and M-1) and OCT2 (M-1) at the lowest feasible concentrations. Based on current results, lowest achievable

test concentrations are in the range of 150 nM, but lower concentrations might be feasible when 3H labelled compound is available. The reports are expected to be available by end of 2014. According to the EMA Drug-Drug-Interaction (DDI) guideline the provision of the studies for M1 is imperative. The outcome of the study directly relates to predicting DDI in clinical practice and is relevant for warnings in the SmPC. The applicant has included this study as a category 3 study in the RMP (see also the Obligation to complete post-authorisation measures in the Recommendations section of this report).

The concentrations used to test the inhibitory potential of M-1 covered the clinically relevant plasma concentration range. No inhibition of the OAT1, OAT3, OATP1B1 and OATP1B3 transporters at these clinically relevant concentrations by M-1 was observed. At clinical relevant concentrations of riociguat and M-1 no significant inhibition of BSEP is expected.

The applicant will provide a study to determine the inhibitory potential of M-1 towards MATE1 and MATE2 in overexpressing cells. The report will be available in May 2014. The applicant further agrees that if this study indicates that riociguat and M-1 are inhibitors of one of these transporters, the SmPC will be changed accordingly. According to the EMA Drug-Drug-Interaction guideline the provision of this study is imperative. The study outcome directly relates to predicting DDI in clinical practice and is relevant for warnings in the SmPC. The applicant has therefore included this study as a category 3 study in the RMP (see also the Obligation to complete post-authorisation measures in the Recommendations section of this report).

Riociguat and M-1 are no inhibitors of UGTs and SULT at clinically relevant concentrations.

2.3.4. Toxicology

Single dose toxicity

After intravenous administration, mortality occurred at 30 mg/kg in mice. After oral administration, the acute toxicity in mice and rats was low. Lethality occurred at 2000 mg/kg, whereas 300 mg/kg was the highest non-lethal dose. Overt symptoms, which preceded mortality, were piloerection, remotility, uncoordinated gait, hunched posture, laboured breathing, narrowed palpebral fissure, closed eyelids, diarrhoea and reduced body weight gain. Necropsy revealed no specific cause of death, but pathology findings in rats (gas-filled stomach; dark-red discolorations of lung and adrenal glands) suggest that smooth muscle cell relaxation and exaggerated haemodynamic effects of riociguat have also contributed to the high-dose mortality.

Repeat dose toxicity

Repeat-dose toxicity studies by oral gavage were conducted up to 26 weeks in rats and in dogs up to 52 weeks at exposures of riociguat up to 10-fold and 2.5-fold, respectively, when compared to human exposure at the MRHD. In addition, in rats and mice, dose-range findings studies up to 13 weeks were performed to support dose selection for the carcinogenicity studies. Diet admixture was chosen in these studies to obtain constant plasma levels. In addition, for M-1 metabolite, a complete set of oral repeat-dose toxicity studies up to 13 weeks in mice, 26 weeks in rats and 39 weeks in dogs was performed.

In mice, the dose-limiting effect was reduced gastro-intestinal tract mobility. Overt symptoms (distended abdomen, increased girth and reduced general conditions) indicated that the mode of

action is related to exaggerated pharmacodynamic effects of riociguat, i.e. smooth muscle relaxation in the gastro-intestinal tract. Motility disturbances in the intestine, accompanied by diarrhoea, dysbiosis and by the prominent presence of vacuolated Paneth cells (which produce antimicrobial products) along the gastro-intestinal mucosa, led to chronic erosive and ulcerative typhlitis and colitis with regenerative mucosal hyperplasia in the jejunum, ileum and caecum. In the high dose range, effects were observed in the liver (centrilobular hypertrophy, dilated gall bladder), bone marrow (increased myelopoiesis), hematopoietic system (slight anaemia), leading to increased haematopoiesis in the liver and spleen, adrenal glands (reduced vacuolation of de zona fasciculate), thymus (atrophy), testes (slightly increased apoptosis), ovaries (less corpora lutea) and uterus (atrophy). The number of thrombocytes was not increased, or only moderately increased. Coagulation times were not measured, but thrombotic events were not reported. In the 13-week study, the NOAEL was established at 16 ppm (≈6 mg/kg/day) for females and at 80 ppm (≈24 mg/kg/day) for males. At these NOAELs, the exposure of riociguat is in the same range as compared with that in human at the maximum recommended human dose (MRHD), based on AUC.

In rats, the NOAEL was established at 10 mg/kg/day for females and at 2.5 mg/kg/day for males, based on the results of the 26-week study. At these NOAELs, the exposure of riociguat is in the same range as compared with that in human at the MRHD, based on AUC. At higher exposures, the observed effects were essentially the same as those in mice. Pharmacodynamic effects related to smooth muscle relaxation included overt symptoms (penile erection, reddening of the ears and extremities), increased girth, reduced gastrointestinal mobility, accompanied by Paneth cell hypertrophy, dilated intestine and vasodilatation of the mesenteric veins. There were no inflammatory reactions. Other effects included effects on the adrenals (increased zona glomerulosa), thymus (variability in weight), prostate (slightly decreased weight), and seminal vesicles (slightly decreased weight). Other findings, not seen in mice, included bile duct hyperplasia and periportal inflammation in the liver. Haematological investigation showed slightly increased counts of leucocytes and lymphocytes. The spleen showed slightly increased haematopoiesis, but blood cell parameters and blood coagulation were without toxicologically relevant changes. Other target organs than those in mice included the heart (swelling of the arterial media of the left ventricle) and kidney (increased weight, pigmented proximal tubules, tubular casts). Rats also showed hypertrophy of the parathyroid gland, leading to increased calcium levels in plasma. Other findings included bone (diaphysal) remodelling and hyperosteosis in growing adolescent rats upon repeated administration of riociguat or M-1. In addition, hyperplasia of the parathyroid glands was observed in the rat carcinogenicity study. Although parathyroid hormone levels have not been measured, the findings could not be no correlated with changes in calcium and phosphate levels plasma. These data do not suggest that treatment with riociguat could lead to demineralization of bone. A risk of osteoporosis in human by treatment with riociguat is not expected. However, the implications of the adverse effects on bone encountered in growing rats on paediatric patients in whom the epiphysis is not yet closed are not clear. Therefore, based on the assessment of the current data, the use of riociguat in children and in growing adolescents should be avoided (see sections 4.2, 4.4 and 5.3 of the SmPC).

In rats the thyroid is one of the organs that show accumulation of riociguat and/or its metabolites. In a 26-week mechanistic study addressing the effect of riociguat on bone morphology and bone mineral density, there were slight, but significant effects on the thyroid at

the mid dose and higher, including decreased thyroid weight and decreased T3 levels in plasma. Reduced T3 relative to the control group was also reported in the rat 26 week study and the dog 52 week study. In 13 and 28-weeks repeated dose toxicity in rats focussed on the metabolite M1, decreases in T3 were often accompanied by increased T4 and TSH levels in plasma. There was no histological correlate for these findings.

Adverse effects on thyroid function are not expected in the clinical setting, as the feedback/control of thyroid hormone works quite well in human. Rats are particularly sensitive to changes in T3 and T4, as in the blood of this species contains no thyroxin binding globulin, in contrast to most other mammals, including humans. Thyroxin binding globulin binds more than 90% of the thyroid hormone in the blood and in this way form a buffer against large fluctuations in the T3 and T4 production. With this knowledge, the lack of relevant changes in plasma T3 and T4 in the dog studies could be explained.

In dogs, the toxicology profile was dominated by the exaggerated hemodynamic effects of vasodilation. These effects started at human therapeutic exposure levels. The gastro-intestinal system and the cardiovascular system were the most sensitive. The effects on the gastro-intestinal system included vomiting and diarrhoea. Effects on the cardiovascular system included reduced blood pressure and reflex tachycardia, accompanied by morphological changes in the myocardium (oedema, endocarditis) and coronary arteries (vascular hypertrophy). Although considered to be adverse, the effects on cardiovascular system are considered to be the result of exaggerated pharmacodynamic effect of blood pressure reduction in healthy animals. Dogs are particularly sensitive to hemodynamic changes and related coronary vascular and myocardial effects. In patients with pulmonary hypertension consequent pathology in the heart and vasculature would not arise by riociguat, since riociguat is intended to correct pulmonary vascular resistance, systolic blood pressure and cardiac output.

The adrenal hypertrophy of the zona glomerulosa may be the result of the vasodilatory properties of riociguat through activation of the renin-angiotensin-aldosterone system, a reflex response to a prolonged reduction in blood pressure. In the 13- and 26-weeks study, there was a slight QT prolongation after correction for heart rate. Considering that in vitro and in vivo safety pharmacology investigations did not reveal evidence for a cardiovascular risk, the slight QT prolongation is considered to reflect an incomplete correction for the reflex tachycardia. There were no relevant changes in red and white blood cell parameters and in blood coagulation. At the high dose, there was a transient decrease in T4 (week 6) which returned to normal later on, whereas T3 levels, being significantly low in week 13, stayed low for the males, but returned to normal for females. The relevance of this finding for human is not clear. Based on the results of the 52-week study, the NOAEL in dogs was established at 0.5 mg/kg/day in males and females. At these NOAELs, the exposure of riociguat is in the same range as compared with that in human at the MRHD, based on AUC.

Genotoxicity

Riociguat is considered not to be genotoxic. It was non-mutagenic in in-vitro mutation tests in bacteria (Ames test). It did not induce chromosomal aberrations in mammalian cells in vitro (Chinese hamster V9 cells) and in vivo in a bone marrow micronucleus test and a bone marrow cytogenetic assay, both in mice. The major metabolite of riociguat (=M1) was not mutagenic in

bacteria (Ames test) and not clastogenic in mammalian cells in vitro (Chinese hamster V9 cells) and an in vivo micronucleus test in mice.

Carcinogenicity

The carcinogenic potential of riociguat was tested in 2-year oral studies in mice and rats by diet administration.

Mice showed low gastro-intestinal tract tolerability. Due to the mode of action-related smooth muscle cell relaxation, reduction in motility, dysbiosis and subsequent chronic inflammation as well as mucosal degeneration and regenerative hyperplasia developed. These changes resulted in an increased intercurrent mortality in high dose males as well as large bowel adenocarcinomas in two females at the mid dose (two times human exposure at MRHD) and in one male at the high dose (three times human exposure at MRHD). The tumours were localized in the caecum (females) or in the colon infiltrating the caecum (males). Considering that the underlying gastrointestinal lesions were mouse-specific, these tumours are not relevant for human. Other major reasons for non-treatment-related intercurrent mortality and evenly distributed throughout all groups were fatal amyloidosis in several organs and systemic tumours as common background. In testes, the low incidence of benign Leydig cell tumours was covered by data from historical controls.

In rats, gastrointestinal inflammation and reactive hyperplasia were not observed and, consequently, gastro-intestinal tumours were not found. Neoplastic and hyperplastic lesions were randomly distributed among all groups, including the controls. However, as in mice, low incidence of benign Leydig cell tumours was covered by data from historical controls.

There was a slight increase in the number of benign tumours in the adrenal medulla. Since this increase was statistically not significant, this finding is not considered to be relevant for human.

The most common causes of death were chronic progressive nephropathy, tumours (benign and malignant), inflammation and thrombosis (heart, kidneys and other organs). In the decedent animals, there was an increased incidence of cardiac enlargement and atrial thrombosis in the high-dose males as compared to data from historical controls. The cause of the atrial thrombotic events is not clear. There were no relevant changes in blood cell parameters and blood coagulation, but there was an association with cardiac enlargement. Patients with pulmonary hypertension generally have generally an enlarged heart. An enlarged atrium is susceptible to thrombosis, if atrial fibrillation occurs.

Available data on safety pharmacology do not point to a proarrhythmic potential of riociguat. At three different functional levels, e.g. by in-vitro hERG assay, ex vivo Langendorf assays in rat hearts and in vivo in anesthetized telemetry as well as conscious telemetered dogs, there was no proarrhythmic potential of riociguat and/or the metabolite M1 at clinical relevant concentrations

Atrial fibrosis is one of the common motives seen with clinical atrial fibrillation is, often in association with aging. In the 26-week repeated-dose toxicity in rats, ventricular fibrosis has been seen, but at a low incidence and only in the high-dose males (1 out 20 animals at 40 mg/kg/day). In the rat carcinogenicity study, focal fibrosis in the heart was observed at low incidences in mid- and high-dose males and females, but without a clear dose relationship (1 out 50 males at 10 mg/kg/day and 20 mg/kg/day; 1 out 50 females at 10 mg/kg/day and 2 out 50 females at 20 mg/kg/day).

Based on these nonclinical data, there is no clear basis to conclude that the small increase in number deaths by atrial thrombosis in the rat carcinogenicity is study is related to atrial thrombosis. The CHMP and PRAC agreed that atrial fibrillation is not an identified risk, but did classify it as a potential risk which has been included in the in the Risk Management Plan.

Pharmacokinetics show higher concentrations of riociguat and/or its metabolites in the kidney. This can be explained by the excretory function of the kidney. However, the possibility cannot be excluded that the enrichment of [14C]riociguat-induced radioactivity in the kidneys of rats represents a substance accumulation in the kidneys. The effects of riociguat have been investigated in various experimental models of kidney disease. These data show that riociguat has renoprotective, but not renotoxic, effects in animals. Metabolite M-1 demonstrated kidney toxicity only at high doses in rats, but not in mice or dogs. Overall, the preclinical data give no indication for a nephrotoxic effect of riociguat at therapeutically relevant doses.

Reproduction Toxicity

In Segment I studies in rats, there were no effects on male and female fertility. At the high dose, the time to insemination was prolonged; absolute testes weights were slightly decreased, whereas relative testes weight was unaffected.

In Segment II studies in rats and rabbits, the profile of riociguat was mainly related to the haemodynamic effects of riociguat. In rats, at dose levels showing clear-cut maternal toxicity due to blood pressure reduction, an increase in cardiac malformations (ventricular septal defects) and an increase in the overall percentage of foetuses with skeletal malformations per group were observed. Placental hypoperfusion and obstruction may cause a reduced supply of nutrients to the embryonic tissues, which can affect development and growth of embryonic structures or result in tissue loss. The increase in cardiac malformations in the rat is therefore considered to be an impact of exaggerated pharmacodynamics rather than a separate teratogenic potential of the molecule itself.

In rabbits, increased placental weights and a higher incidence of partly necrotic placentas were seen. In addition, abortion and total resorption were observed. The low safety margin at the NOAEL's (AUC unbound 1.7-fold in the rat and 1.2-fold in the rabbit of the human MRHD) can be accepted as riociguat is contraindicated in pregnancy (see sections 4.3, 4.6 and 5.3 of the SmPC).

Riociguat may be secreted into rat milk. However, the absolute amount is low, i.e. in the range of a few % of the dose. In the absence of human data, due to the potential for serious adverse reactions in nursing infants riociguat should not be used during breast-feeding (see section 4.6 of the SmPC).

Juvenile toxicity

The exposure to neonatal rats to riociguat and the metabolite M-1 was clearly higher compared to juvenile and adult rats.

In juvenile rats, riociguat-related effects on bone morphology were observed. In juvenile rats treated at doses of $\geq$ 10 mg/kg/day with riociguat treatment starting at postnatal day (PND) 6 over a treatment period of about 3 weeks, thickening of trabecular bone and hypercellularity consisting of activated osteoblasts and osteoclasts were observed, and in addition hyperostosis

and remodelling in the metaphyseal and diaphyseal bone was found. In contrast, in juvenile rats treated for 14 weeks starting at PND 6 with riociguat doses of up to 3 mg/kg/day, no histopathological observations were made in the femur. The effects on bone metabolism and morphology in juvenile rats seem to be due to the sGC stimulating effects of Riociguat. In studies on endothelial NO synthase gene-deficient mice, it has been demonstrated that eNOS is involved in the postnatal regulation of bone mass, and lack of the eNOS gene results in reduced bone formation and volume which is related to impaired osteoblast function (Aguirre et al. 2001). Furthermore, cGMP is involved in chondrocyte differentiation via activation of protein kinase G II (PKGII). The PKGII knockout mice are dwarfs that develop short bones due to a defect in endochondral ossification at the endochondral plate of bones during development (Pfeifer et al. 1996). Additionally, PKGII-deficient rats exhibited an expanded growth plate, impaired bone healing, and an accumulation of postmitotic but nonhypertrophic cells (Chikuda H. et al 2004). Until more is known about the implications of these findings, the use of riociguat should be avoided in children and in adolescents that are still growing. This is reflected in sections 4.2, 4.4 and 5.3 of the SmPC.

Phototoxicity

Riociguat shows light absorption in the range of 290 to 720 nm and it reaches the skin. The outcome of the 3T3 NRU (Neutral Red Uptake) Phototoxicity Assay was equivocal, but, based on the negative outcome of the LLNA test in mice, riociguat is not considered to be phototoxic *in vivo*.

Immunotoxicity

No specific immunotoxicity studies were performed, since repeat-dose toxicity studies did not reveal any specific concerns. Antigenicity has also not been studied.

Metabolites

The toxicological profile of metabolite M-1 was comparable to the profile of riociguat, except that the M-1 showed a higher nephrotoxic potential as compared to riociguat.

The renal toxicity of M-1 was restricted to very high exposure levels in rats and consisted of tubular degeneration and regeneration followed by tubular hyperplasia affecting predominantly the collecting ducts. In dogs metabolite M-1 did not induce renal toxicity. In the mouse and rat carcinogenicity studies performed with metabolite M-1 and terminated preterm, no evidence of treatment-related effects on the kidneys was seen.

In conclusion, metabolite M-1 demonstrated kidney toxicity only at high doses in rats, but not in mice or dogs. Overall, the preclinical data give no indication for a nephrotoxic effect of riociguat at therapeutically relevant doses.

Impurities

All unspecified impurities are below the limit of quantitation (0.05%) and all specified impurities are below or equal to 0.1%. The specified impurities were evaluated for genotoxic concern by in-silico QSAR analyses for genotoxic alerts. The results of these analyses showed no concerns.

2.3.5. Ecotoxicity/environmental risk assessment

Riociguat (Mw 422.42 g/mole) is an organic molecule containing ionisable N atoms, with a reported (single) pKa value of 4.34. The molecule is predominantly neutral at pH values of ≥ 7 and positively charged at lower pH values. Water solubility (Sw) at 25° C: 4 mg/L in water and in pH 6 buffer. At pH 7, 8 and 9, Sw is 3 mg/L, while at lower pH, Sw increases, up to 980 mg/L at pH 2. Riociguat is hydrolytically stable at pH 4, 7 and 9 (50°C); the hydrolysis half-life at 25°C is estimated to be >1 year. Its log Dow at pH 4 is 1.77 and log Kow is 2.30 at pH 9 and 2.30 at pH 7. This is below the B screening criterion, hence riociguat is neither PBT nor vPvB.

For refinement of Fpen, prevalence data from the Orphan designation were used. Summed prevalence for CTEPH and PAH for the EU is 19.2 per million, resulting in a PECsw of 0.075 ng/L, which is below the EMA action limit. Further studies were nevertheless submitted, results of which are summarised in the following. Riociguat is not readily biodegradable. In a water/sediment simulation study (OECD 308) at 20°C, riociguat showed no degradation during the 100 d test period, no metabolites were detected in water and sediment. At day 100, 9 and 15% bound residue was determined in two sediments, while 93-96% of the substance was present in sediment and 3.3-3.8% in water. Riociguat is very persistent. The organic carbon normalized partition coefficient (Koc) determined in an OECD 121 screening assay, is 380 L/kg. The toxicity to algae (D. subspicatus; effect on growth rate) resulted in a 72 h NOEC of 0.96 mg/L, EC10 of 3.8 mg/L and an EC50>4.8 mg/L. Chronic toxicity to Daphnia magna resulted in a NOEC reproduction of 0.073 mg/L (EC10 0.28 mg/L). NOEC for the endpoints mortality, nr. of broods and time to 1st brood were all ≥ 0.57 µg/L. Larvae and adults of the sediment dwelling midge Chironomus riparius were not affected in development rate and emergence; NOEC ≥ 350 mg/kg d.w. (normalized to 10% organic carbon and corrected for extractable fraction) for both endpoints.

Table NC1: Environmental endpoints (Summary of main study results)

Substance (INN/Invented Name): riociguat			
CAS-number (if available): 625115-55-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	shake flask	log D_{ow} 1.77 at pH 4 log K_{ow} 2.37 at pH 7 log K_{ow} 2.30 at pH 9	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.30 to 2.37	not B
Persistence	ready biodegradability	not readily biodegradable	
	$DT50_{sediment}$	>>100 d	vP
Toxicity	$NOEC_{algae}$	0.96 mg/L	
	$NOEC_{crustacea}$	0.037 mg/L	
	$NOEC_{fish}$	PM	T
	NOEC or CMR	not investigated	
PBT-statement	riociguat is considered not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.038	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	carbamate		
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**

Adsorption-Desorption	OECD 121	K_{oc} = 380 L/kg			OECD 121
Ready Biodegradability Test	OECD 301F	not readily biodegradable			
	DT50 hydrolysis	Stable. t½ >1 y at 25°C			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 3.5 and 6 d $DT_{50, sediment}$ = >100 d $DT_{50, whole system}$ = >100 d % shifting to sediment = 50-70% at day 7-8, ~95% at day 100			Values valid for 20°C. Not degradation was observed. Riociguat is vP.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *Desmodesmus subspicatus*	OECD 201	NOEC EC10 EC50	0.96 3.8 >4.8	mg/L mg/L mg/L	growth rate growth rate growth rate
Daphnia magna. Reproduction Test	OECD 211	NOEC EC10	0.037 0.28	mg/L mg/L	reproduction reproduction
Fish, Early Life Stage Toxicity Test / *Pimephales promelas*	OECD 210	PM	PM		
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥6.3	mg/L	
Phase IIb Studies					
Sediment dwelling organism / *Chironomus riparius*	OECD 218	NOEC	≥417	mg/kg_{dw}	normalised to 10% o.c.

2.3.6. Conclusion on the non-clinical aspects

The CHMP concluded that the non-clinical data presented by the applicant support the use of the product, and therefore recommend the approval of Adempas. The CHMP however considered that the following measures were necessary to address the outstanding non-clinical issues regarding potential drug-drug interactions:

- The Applicant will test if synthesis of 3H-labelled compound is feasible. If feasible, the Applicant will investigate at clinically relevant concentrations a) whether riociguat is a substrate for OAT1, OAT3, OCT1, and OCT3 and b) whether M-1 is a substrate for OAT1, OAT3, OCT1, OCT2 and OCT3. The reports are expected by December 2014.
- The study reports on the inhibition potential of M-1 towards MATE1 and MATE2 have to be submitted by the Applicant by May 2014. In addition, if these studies indicate that riociguat and M-1 are inhibitors of one of these transporters, the Applicant is requested to change the SmPC accordingly.

The SmPC appropriately reflects the non-clinical data submitted with riociguat.

2.4. Clinical aspects

The clinical pharmacology program for riociguat is comprised of 32 studies, including 768 healthy subjects or patient-volunteers (with renal or hepatic impairment, respectively), and 26 PH patients.

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

An overview about the Audit findings and the inspection reports from the FDA was reviewed during the procedure. Overall the number and the nature of the findings did not raise concerns with regard to overall adherence to GCP and the validity of the pivotal studies.

2.4.2. Pharmacokinetics

Introduction

Pharmacokinetics of riociguat were investigated in 8 phase I bioavailability studies, 2 phase I bioequivalence studies (with Japanese subjects), 27 studies pertinent to pharmacokinetics using biomaterials and 11 clinical phase I pharmacokinetics studies. Additional pharmacokinetic data originate from 9 clinical phase I and II pharmacokinetics / pharmacodynamics studies.

Methods

The analytical methods used for the determination of riociguat and metabolite M-1 were acceptable and sufficiently validated. A cross validation was performed for the method performed at the different analytical sites. The methods for pharmacokinetic data analysis and statistical methods are acceptable. The POP-PK methods are acceptable and sufficiently described and validated for their purposes as these are exploratory only.

Absorption

Riociguat is rapidly absorbed with maximum concentrations (C_{max}) appearing 1-1.5 hours after tablet intake. The absolute bioavailability of riociguat is high, approximately 94%. Absorption of riociguat is dependent on the site of drug release in the gastrointestinal tract. Bioavailability of riociguat decreased when administered to the deeper parts of the gastrointestinal tract.

The Applicant performed several bioavailability/bioequivalence studies with IR tablets and oral suspensions including paediatric formulations. No major differences were found between oral IR formulations and suspension formulations of riociguat. The proposed commercial formulation is identical to the clinical phase III formulations, only the ratio of the pigments was varied. This change in pigments was expected not to influence bioavailability, as was confirmed by two Japanese studies. The manufacturing process was comparable throughout the clinical development and for the commercial formulations. Additionally, it was shown that the 0.5, 1.0, 1.5, 2.0, and 2.5 mg phase III tablets demonstrate dose proportional pharmacokinetic parameters.

There is no food effect on the extent of exposure of riociguat, however, there is a food effect on the rate of absorption as it demonstrates a postponed t_{max} and a reduced C_{max} (minus 35%).

Distribution

The volume of distribution at steady-state (V_{ss}) was determined to be approximately 30 L for riociguat, indicating its low affinity to tissues which is in agreement with animal data.

The fraction not bound to plasma proteins (f_u) of riociguat was approximately 3-5% in human plasma, with no concentration dependency. Riociguat was mainly bound to serum albumin and

α1-acidic glycoprotein in human plasma. There was low binding to LDL, gamma-globulin, and alpha-globulin.

The free fraction of metabolite M-1 in human plasma was comparable with riociguat (3.6%), with no concentration dependency. The main binding protein for M-1 in human plasma was serum albumin. The plasma to blood ratio (Cp/ Cb) of riociguat was approximately 1.5. Riociguat penetrated the placental barrier to a moderate extent in pregnant rat and the blood/ brain barrier to a low extent.

Elimination and metabolism

Elimination half-life is about 7 hours in healthy subjects and about 12 hours in patients.

Combined excretion of the parent compound riociguat and metabolites is both renal (33 to 45%) and biliary/faecal (48 to 59%). Unchanged riociguat was excreted with (passive) glomerular filtration in the kidneys by approximately 4 to 19% of the administered dose and via biliary/ faecal routes by about 9 to 44%. The metabolite M-1 was found in the urine by 7 to 23% and faeces by 15 to 43%. Riociguat and metabolite M-1 are excreted both by renal and biliary/faecal routes.

Pharmacokinetics of metabolites

Metabolite M-1 is the major metabolite of importance. M-1 demonstrates pharmacological activity at one tenth to one third the activity of riociguat. As shown in pre-clinical studies, M-1 is linked with renal toxicity at exposure levels more than 10-fold of human exposure in terms of unbound AUC. The enzymes CYP2C8, CYP2J2, CYP3A4, and CYP1A1 play a role in the formation of this metabolite. CYP1A1 is of particular importance as smoking increases activity of this enzyme, and two- to threefold higher riociguat clearance has been observed in smokers. In light of this, patients are advised to stop smoking when starting treatment due to the risk of a lower response (see section 4.2 and 4.5 of the SmPC).

In general, the pharmacokinetic parameters of the main metabolite M-1 have adequately been assessed in the studies and data of M-1 are provided alongside riociguat throughout the report. The metabolite M-1 demonstrates on average a Cmax of 25%, a longer tmax, a similar AUC and a longer half-life than the parent compound. No pharmacokinetics of the other metabolites is provided except for the mass balance study, which is acceptable.

Genetic polymorphisms were investigated in the light of pharmacokinetic variability. There were no genetic polymorphisms identified by the Applicant to contribute to the variability.

Other pharmacokinetic properties

Dose linearity was demonstrated over the therapeutic range of 0.5 (1.0) and 2.5 mg.

The compound riociguat demonstrated dose linearity with only minor accumulation after 10 days of 3 times daily dosing (up to 157%). Accumulation for metabolite M-1 was 482% to 685%, which is in line with expectations based on $t_{1/2}$ (~14 h) and dosing interval.

Inter-individual variability in riociguat exposure (AUC) across all doses was approximately 60%. The intra-individual variability measured by C_{trough} in PH patients was 35%.

Pharmacokinetics in target population

The elimination phase was prolonged in pulmonary hypertension (PH) patients with approximately 5 hours compared to young healthy subjects, resulting in exposure (AUC) being approximately threefold higher at steady state compared to healthy subjects.

Special populations

Mean dose- and weight- normalised area under the curve (AUC) of riociguat in non-smoking individuals was 53% higher in subjects with mild renal impairment, 139% higher in subjects with moderate renal impairment and 54% higher in subjects with severe renal impairment compared to subjects with normal renal function. Smokers had a higher metabolic clearance of riociguat.

Hepatic impairment affects riociguat hepato-biliary clearance resulting in clinically relevant increases in exposure for non-smoking subjects with moderate hepatic insufficiency (Child Pugh B) by 50% (total) to 70% (unbound). There are no data in patients with severe hepatic impairment (Child Pugh C), therefore use of riociguat is contraindicated in this population (see sections 4.2 and 4.3 of the SmPC).

The CHMP agreed with the applicant that there are no clinically significant changes in riociguat pharmacokinetics due to race or age to be expected in patients as presented in the data. The changes in riociguat pharmacokinetics due to gender or body weight are not clinically relevant (see section 4.2 of the SmPC).

Interactions

In vitro

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

No clinically relevant drug-drug interactions due to inhibition of transporters such as P-gp or BCRP, or BSEP, or organic anion transporting polypeptides OATP1B1, OATP1B3, or organic anion transporters OAT1, OAT3, or organic cation transporters OCTs by riociguat are expected. Furthermore, metabolite M-1 is not an inhibitor of P-gp, BCRP, BSEP, OATPs, OATs and OCTs at relevant therapeutic concentrations.

Riociguat and M-1 revealed an inhibitory potency on CYP1A1 in vitro with an inhibition constant (Ki) value of 0.6 µM, each.

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

- N-demethylation, i.e. metabolite M-1 formation in human liver microsomes was considerably inhibited by protease inhibitors (ritonavir, atazanavir > indinavir and antifungal azoles (ketoconazole > clotrimazole, miconazole).
- Pronounced inhibition of recombinant human CYP1A1 – an important CYP isoenzyme in riociguat metabolism, especially in smokers – was observed by the antifungal azoles

ketoconazole, clotrimazole and miconazole as well as carvedilol, ebastine, quercetin and tyrosine kinase inhibitors like erlotinib, gefitinib, imatinib, sorafenib and sunitinib.

In Vivo

Pre- and co-treatment with 40 mg omeprazole led to a decrease in riociguat bioavailability with a mean C_{max} decrease of approximately 35% and a mean AUC decrease of 26%.

The data indicate a PK interaction between Maalox and riociguat by reducing its extent and rate of absorption from the gastro-intestinal tract. With reduced riociguat C_{max} by 56%, bioavailability (AUC) of riociguat and consecutively exposure to M-1 were reduced by 34% and by 33% in comparison to administration of riociguat alone.

Pre- and co-treatment with the multi-pathway CYP and P-gp/BCRP inhibitor ketoconazole led to an increase in riociguat exposure with a mean C_{max} increase by 46% and a mean AUC increase by 150%, indicating a relevant PK interaction.

A four-day pre-treatment and subsequent co-administration of clarithromycin resulted in an altered riociguat exposure with an increase in mean AUC by 41% but no significant change in mean C_{max}. Similarly, for M-1 a mean AUC increase by 19% but no significant change in mean C_{max} was observed. While riociguat renal clearance remained almost unaffected, a small decrease for M-1 mean renal clearance by 18% was observed.

The pharmacokinetics of midazolam are not altered by concomitant administration of riociguat.

There were no relevant PK interactions between riociguat and the oral anti-coagulant warfarin (Coumadin), Aspirin, nitroglycerin or sildenafil.

The above interactions are adequately reflected in section 4.5 of the SmPC.

2.4.3. Pharmacodynamics

The pharmacodynamics of riociguat were evaluated in several of the clinical pharmacology studies in a) healthy subjects (studies 11258, 11260) b) healthy Japanese and Chinese subjects (studies 14361, 12640, 12639) and c) patients with PAH (study 11874).

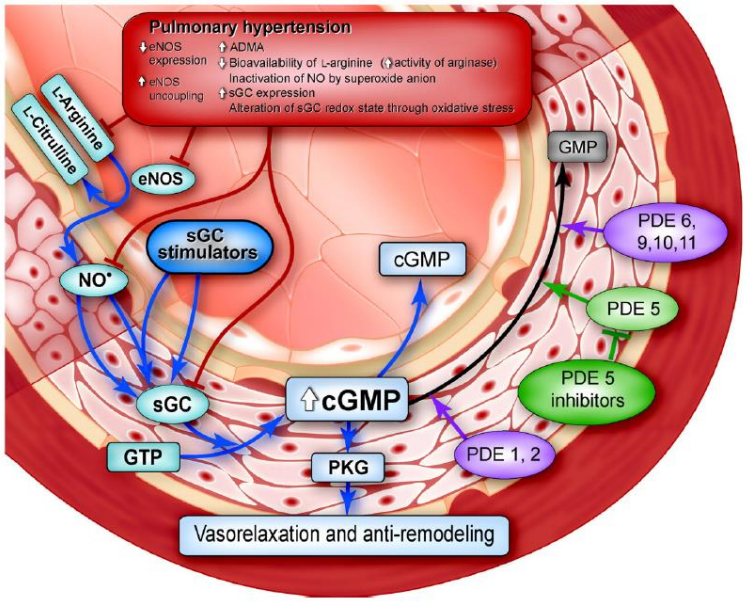
Mechanism of action

A wide body of literature suggests that chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) are associated with impaired NO-sGC-cGMP signalling in the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. Inhibitors of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), the enzyme that is responsible for degradation of cGMP, have been utilised in PAH. Riociguat is evaluated as the first member of a novel class of compounds, the sGC stimulators.

sGC is a key enzyme in the cardiopulmonary system and the receptor for NO. It catalyses the generation of the signalling molecule cGMP that plays a pivotal role in regulating cellular processes, such as vascular tone, proliferation, fibrosis, and inflammation. With its dual mode of action riociguat directly stimulates sGC and synergises with NO, this way restoring the NO-sGC-

cGMP pathway. Riociguat exerts its biological effects independently of NO, which is present in low levels in some patients with CTEPH and PAH (figure PD1).

Figure PD-1: Pharmacological targets in the nitric oxide (NO) / soluble guanylate cyclase (sGC) / cyclic guanosine monophosphate (cGMP) signalling pathway in pulmonary hypertension.



Stasch et al., Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. Circulation. 2011 May 24;123(20):2263-73

Primary pharmacology

Repeat-dose studies in healthy volunteers show that riociguat administration is associated with a systemic blood pressure lowering effect. On the diastolic blood pressure, this is dose dependant and increases after repeated dosing. A less pronounced effect is seen on the systolic blood pressure after a single dose. There are compensatory mechanisms like increased heart rate (HR) and renin secretion, but these are attenuated by time. The cGMP increases further over time, which probably contributes to the durability of the effect.

Study 11874 was the proof of concept study to investigate safety, tolerability, pharmacokinetics of riociguat and its impact on pulmonary- and systemic haemodynamic and gas exchange in patients with pulmonary hypertension (PAH, CTEPH or interstitial lung disease (ILD)) in a non-randomised, non-blinded design. The vast majority of patients suffered from PAH or CTEPH. Only one subject with ILD was included. Therefore, the study population is considered sufficiently representative for the target population. The study investigated escalating (part A) and fixed doses (part B) of riociguat. Administering riociguat 1 mg and 2.5 mg, resulted in reduction of both pulmonary and systemic pressures; the dose response is more obvious in the systemic pressure measurements. However, the numbers are small, precluding robust results (n=15) (table PD1).

Importantly, an effect on the pulmonary haemodynamics comparable to NO was demonstrated (table PD2). The haemodynamic effects observed in this study lasted for more than five hours supporting the proposed 6- to 8-hour dosing interval corresponding to a three times a day (t.i.d.) dosing regimen (Figure PD2).

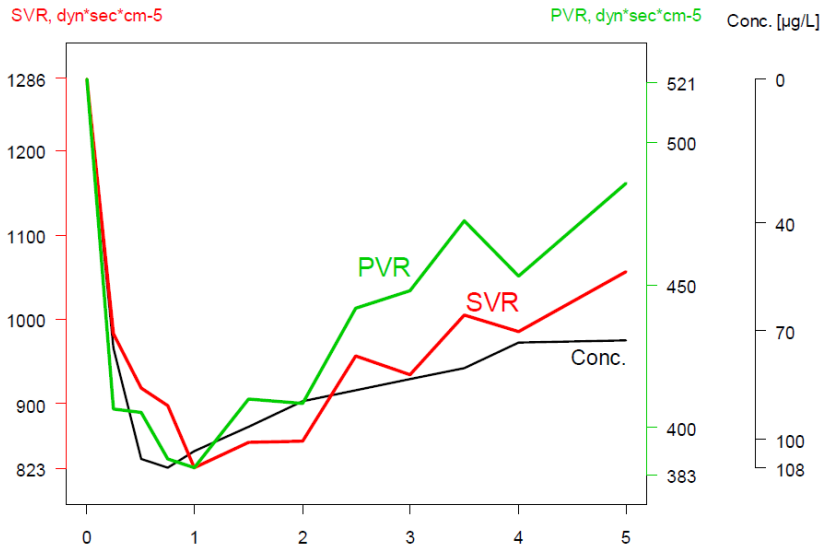
Table PD1: Point estimates (LS-means) for peak effects on PAPmean, systemic SBP, PVR, SVR, and cardiac index following a single oral solution dose of 2.5 mg and 1 mg riociguat (subjects valid for PD in Part B; n=15) (Study 11874)

Parameter	Unit	Point estimator (LS-mean)	95% confidence interval	*P* value of F statistic
2.5 mg riociguat (n=10)				
Mean pulmonary arterial pressure	mmHg	-5.10	[-7.12; -3.08]	0.0001
Systolic systemic blood pressure	mmHg	-28.60	[-36.21; -20.99]	<0.0001
Pulmonary vascular resistance	dyn*s*cm^{-5}	-168.12	[-273.87; -62.36]	0.0046
Systemic vascular resistance	dyn*s*cm^{-5}	-545.90	[-724.19; -367.62]	<0.0001
Cardiac index	L/min/m^2	0.95	[0.72; 1.18]	<0.0001
1 mg riociguat (n=5)				
Mean pulmonary arterial pressure	mmHg	-6.80	[-9.66; -3.94]	0.0001
Systolic systemic blood pressure	mmHg	-24.00	[-34.76; -13.24]	0.0003
Pulmonary vascular resistance	dyn*s*cm^{-5}	-296.45	[-463.67; -129.23]	0.0022
Systemic vascular resistance	dyn*s*cm^{-5}	-689.95	[-942.08; -437.82]	0.0001
Cardiac index	L/min/m^2	0.65	[0.33; 0.98]	0.0008

Table PD2: Point estimates (LS-means) for the difference between riociguat and NO in peak effects on PAPmean, systemic SBP, PVR, SVR, and CI following a single oral solution dose of 2.5 mg and 1 mg riociguat (subjects valid for PD in Part B; n=15) (Study 11874)

Parameter	Unit	Point estimator (LS-mean)	95% confidence interval	*P* value of F statistic
2.5 mg riociguat				
Mean pulmonary arterial pressure	mmHg	-3.10	[-6.27; 0.07]	0.0546
Systolic systemic blood pressure	mmHg	-25.70	[-34.26; -17.14]	<0.0001
Pulmonary vascular resistance	dyn*s*cm^{-5}	-132.85	[-242.95; -22.75]	0.0220
Systemic vascular resistance	dyn*s*cm^{-5}	-541.49	[-698.20; -384.78]	<0.0001
Cardiac index	L/min/m^2	0.89	[0.71; 1.07]	<0.0001
1 mg riociguat				
Mean pulmonary arterial pressure	mmHg	-4.40	[-8.88; 0.08]	0.0539
Systolic systemic blood pressure	mmHg	-18.60	[-30.71; -6.49]	0.0055
Pulmonary vascular resistance	dyn*s*cm^{-5}	-242.33	[-416.41; -68.24]	0.0104
Systemic vascular resistance	dyn*s*cm^{-5}	-589.26	[-810.88; -367.64]	0.0001
Cardiac index	L/min/m^2	0.64	[0.39; 0.89]	0.0001

Figure PD2: Mean PVR, SVR and riociguat plasma concentration over time (subjects valid for PK & PD in Part B, 2.5 mg dose group; n=10) (Study 11874)



Secondary pharmacology

Influence of Riociguat on Bone Metabolism, and laboratory findings

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

Study 13790 was a randomised, double-blind, placebo-controlled, 2-fold crossover study to investigate the effects of multiple-dose riociguat (2.5 mg t.i.d. over 14 days) on bone resorption and formation markers in sixteen healthy male non-smoking subjects. The main results are shown in table PD3.

Table PD3: Summary of the main factor "treatment" of the ANCOVA on pharmacodynamic parameters (all subjects valid for PD; n=16) (Study 13790)

Parameter (unit)	LS means of ""riociguat minus placebo"			
	Estimated difference	95% confidence interval limits Lower	Upper	*P* value
CTX (µg/24 hours) in urine	**237.06**	**150.68**	**323.45**	**<0.0001**
CTX_{norm} (µg*min/mL*24 hours)	0.56	-1.35	2.46	0.5402
CTX (µg/L) in serum	0.01	-0.01	0.03	0.2469
NTX (nmol/24 hours) in urine	15.96	-31.49	63.42	0.4844
NTX_{norm} (nmol*min/mL*24 hours)	-0.58	-1.33	0.17	0.1196
PINP (ng/mL) in serum	-4.19	-6.57	-1.82	0.0019
bAP (µg/L) in serum	-1.13	-1.41	-0.85	<0.0001
Osteocalcin (µg/L) in serum	-1.12	-1.46	-0.77	<0.0001
PTH (pmol/l) in serum	0.19	0.04	0.34	0.0167
Amount of calcium (mmol) in urine	0.97	0.86	1.09	<0.0001
$Calcium_{norm}$ (mmol*min/mL)	5.45	3.62	7.28	<0.0001
Calcium (mmol/L) in serum	-0.03	-0.04	-0.01	0.0007
Amount of sodium (mmol) in urine	-2.18	-7.74	3.38	0.4161
Amount of potassium (mmol) in urine	0.51	-1.45	2.47	0.5857
Amount of creatinine (µmol) in urine	195.36	1.19	389.53	0.0488
Creatinine (µmol/L) in serum	-5.05	-5.95	-4.15	<0.0001
Urine volume (mL)	-46.00	-106.97	14.98	0.1280
Creatinine clearance (mL/min)	7.89	5.48	10.30	<0.0001
Renin (ng/mL/h) in plasma	0.20	-0.02	0.42	0.0675
cGMP (µmol) in urine	1.09	1.00	1.17	<0.0001
cGMP (nmol/L) in plasma	2.75	2.41	3.10	<0.0001

Results show increased bone resorption parameters in urine, which the Applicant explained by the increased GFR due to vasodilatation. This applies also to calcium excretion. However, there is an associated decrease in bone formation parameters such as N-terminal propeptide of type I collagen (PINP), bone-specific alkaline phosphatase (bAP), and osteocalcin. The long-term risk of bone changes and fractures are listed as a potential risk in the RMP.

Red blood cell count (0.15 10^9/mL, 3.17%), haematocrit (0.01, 3.57%), and haemoglobin (5g/L, 3.56%) decreased significantly in this study. This was associated with a significant increase in reticulocyte count after 6-7 days. Further analysis of the Phase III data showed that haemodilution caused by an increase in intravascular volume due to vasodilating effect of riociguat is likely the cause of the observed anaemia. The submitted data does not indicate that the anaemia represents a clinically relevant risk for the outcome of the patients treated chronically with riociguat. Anaemia is listed as a common TEAE in the SmPC.

The small observed increase in GFR (3.2%) in all pivotal phase 3 studies after 12/13 weeks is unlikely to affect plasma electrolyte concentrations in a clinically relevant fashion.

Effect on Cardiac depolarisation

Due to the drug exposure being higher in patients than in healthy subjects, a thorough QT study according to pertinent guidelines could not be conducted in healthy subjects. The influence of riociguat on ECG parameter was investigated within the phase III trials (see the Clinical safety section of this report).

Pharmacodynamic interactions with other medicinal products or substances

Riociguat has the potential to interact with other vasodilators acting on the NO-cGMP pathway. Thus, an additive effect on pulmonary and systemic circulation might have been expected. This was investigated with nitroglycerin and sildenafil. Based on the results of a phase I study showing significant hypotensive effects and syncope, a contraindication regarding the co-administration of riociguat with nitrates or NO- donors (such as amyl nitrite) in any form is implemented in the SmPC (see section 4.3 and 4.5 of SmPC).

The Applicant investigated the co-administration of riociguat with sildenafil in PAH patients in two studies (11917 and 15096).

Study 11917 was an open-label, non-controlled study in 7 subjects (3 men and 4 women) with PAH, stable for the last 6 weeks and treated with 20 mg sildenafil t.i.d. The study investigated safety, tolerability, PK of sildenafil, riociguat and M1, and the impact on pulmonary and systemic haemodynamics of single doses of 0.5 mg riociguat (administered 3 hours after 20 mg sildenafil) and 1 mg of riociguat (administered after another 2 hours to the same subjects).

Study 15096 was an interaction study to evaluate changes in blood pressure following 1, 1.5,2, and 2.5 mg riociguat t.i.d (dose titration) compared to placebo treatment on the background of stable sildenafil pre-treatment in subjects with symptomatic pulmonary arterial hypertension.

Both studies showed additive systemic hypotensive action. Study 15096 deserves attention considering that it is comparable to clinical practice. This study investigated patients on stable and authorised doses of sildenafil (20 mg t.i.d.), and then allowed co-administration of riociguat for 12 weeks. The study recruited few patients (n=18). The baseline values of blood pressure in both groups were largely discrepant, confounding the results. The addition of riociguat on top of stable doses of sildenafil led to further reduction in blood pressure in the first weeks compared to the placebo group, but on the long term the values were comparable. However, the safety issues encountered are worth mentioning. The discontinuation rate in the long-term extension (LTE) was high (6/17), clearly pointing to a tolerability issue; probably the associated hypotension. These additive haemodynamic effects on the systemic circulation might culminate in single patients leading to a clinically relevant event. Importantly, during the LTE phase (cut-off date 18 December 2012) three death cases had been reported. In one case a 67-year-old female subject experienced fatal 'cardiac arrest', which was assessed by the investigator and company as not related to riociguat. In the second case a 46-year-old female died following acute 'decompensation of chronic right heart failure'. The investigator and the sponsor assessed the event as not related to riociguat. In the third case a 53-year-old white female experienced 'fall' and 'subdural haematoma' leading to death. As a causal involvement of riociguat in the fall, via a decrease in blood pressure, could not be excluded with certainty the causal relationship was assessed as related to riociguat. The EMA was notified on 19 December 2012 by the Applicant about their intention to stop the LTE phase of the study. This decision was endorsed. This interaction is implemented as a contraindication in the proposed SmPC (see section 4.3 and 4.5; and section 2.6.4 of this report, Adverse events of special).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Absorption of riociguat is dependent on the site of drug release in the gastrointestinal tract. Bioavailability of riociguat decreased when administered to the deeper parts of the gastrointestinal tract, which is probably due to limited solubility at neutral pH. Influence of P-gp and BCRP substrate characteristics is less likely due to the dose proportionality of riociguat. Dose linearity is demonstrated from 0.5 to 2.5 mg in single and multidose studies in respect to C_{max} and AUC.

Food effect

There is no food effect on the extent of exposure of riociguat, however, there is a food effect on the rate of absorption which is demonstrated by a postponed t_{max} and a reduced C_{max} (minus 35%). This is reflected in the SmPC section 5.2. Metabolite M-1 is the major metabolite of importance. M-1 demonstrates pharmacological activity at one tenth to one third the activity of riociguat. As shown in pre-clinical studies, M-1 is linked with renal toxicity. The enzymes CYP2C8, CYP2J2, CYP3A4, and CYP1A1 play a role in the formation of this metabolite. CYP1A1 is of particular importance as it is the main M-1 forming enzyme and smoking increases activity of this enzyme; two- to threefold higher riociguat clearance has been observed in smokers.

Special population (smokers)

In the phase III trial all included patients who are smokers were up-titrated to the 2 highest strengths t.i.d.

Renal impairment

Mean renal clearance of both riociguat and the metabolite M1 decreased with decreasing renal function compared to results in healthy controls. Although exposures observed in subjects with renal impairment were highly variable, it can be concluded that riociguat exposure increased in all groups of renal impairment, but did not increase proportionally to decreasing renal function. Mean dose- and weight-normalised AUC of riociguat in non-smoking individuals was 53% higher in subjects with mild renal impairment, 139% higher in subjects with moderate renal impairment and 54% higher in subjects with severe renal impairment compared to subjects with normal renal function. Smokers had a higher metabolic clearance of riociguat to M-1 due CYP1A1 induction and therefore lower exposure to riociguat than non-smokers. Smokers with severe renal impairment (n=2) showed low AUC_{norm} comparable to healthy controls. The Applicant concluded that, the influences of renal impairment on riociguat PK to be expected in PH patients were clinically relevant, however, did not merit any dose adjustment beyond the individual dose titration. Based on the lack of clinical data in severe renal impaired patients with creatinine clearance below 30 mL/min or being on dialysis, Adempas is not recommended in these patients.

Hepatic impairment

Hepatic impairment affects riociguat hepato-biliary clearance resulting in clinically relevant increases in exposure for patients with moderate hepatic insufficiency (Child Pugh B) by 51% (total) to 70% (unbound). The influences of hepatic impairment on riociguat PK to be expected in PH patients were moderate and do not merit any dose adjustment beyond the individual dose

titration. Based on the lack of clinical data in Child Pugh C patients, there is a contraindication for therapeutic use in this special group of patients at risk (see section 4.3 of the SmPC).

Interactions

Pre- and co-treatment with the multi-pathway CYP and P-gp/BCRP inhibitor ketoconazole led to an increase in riociguat exposure with a mean C_{max} increase by 46% and a mean AUC increase by 150%, indicating a relevant PK interaction. The interaction was markedly more pronounced in those subjects exhibiting per se a higher clearance for riociguat (i.e. shorter half-life, lower AUC), reflecting the strong inhibitory potential of ketoconazole towards CYP1A1. The exposure of M-1 decreased with regard to mean C_{max} by approximately 49% and mean AUC by 24%. A single dose of riociguat did not affect the bioavailability of ketoconazole (see section 4.5 of the SmPC).

A four day pre-treatment and subsequent co-administration of clarithromycin resulted in an altered riociguat exposure with an increase in mean AUC by 41% but no significant change in mean C_{max}. Similarly, for M-1 a mean AUC increase by 19% but no significant change in mean Cmax was observed. While riociguat renal clearance remained almost unaffected, a small decrease for M-1 mean renal clearance by 18% was observed. The data indicate a moderate PK interaction between clarithromycin, a strong inhibitor of CYP3A4 and weak-to-moderate inhibitor of P gp, and riociguat. As riociguat renal clearance remained almost unaffected, an inhibition of the CYP3A4-mediated part of the riociguat metabolic clearance by clarithromycin pre- and co-administration is most probable. The unexpected increase in M1 exposure following CYP3A4 inhibition is probably a result of the multi-pathway biotransformation. These results were not considered to have any clinically relevant consequences.

The pharmacokinetics of midazolam are not altered by concomitant administration of riociguat. Midazolam is a recommended sensitive probe substrate when investigating in vivo any CYP3A4 interaction potential of investigational drugs. The midazolam PK are known to be markedly altered by the co-administration of CYP3A4 inhibitors. Thus, based on this study the CHMP agreed with the Applicant that riociguat does not affect the activity of CYP3A4.

Pharmacodynamics

Riociguat is the first member of a novel class of compounds, the sGC stimulators which act by directly stimulating the synthesis of cGMP and enhancing the action of NO. Like other vasodilators used in PAH, riociguat administration is associated with a systemic blood pressure lowering effect; 5 mg riociguat is not well tolerated due to the associated drop in blood pressure. Riociguat 1 mg and 2.5 mg, resulted in reduction in both pulmonary and systemic pressure measurements; with comparable effects to NO on the pulmonary haemodynamics. Administration of riociguat for 14 days to healthy volunteers resulted in general vasodilatation and haemodilution that can explain some observed changes. However, there is a decrease in bone formation parameters such as N-terminal propeptide of type I collagen (PINP), bone-specific alkaline phosphatase (bAP), and osteocalcin. It is generally accepted that the NO-sGC-cGMP and the natriuretic peptide- particulate (membrane-bound) guanylate cyclase (pGC)-cGMP pathway play an important role in regulation of bone and cartilage homeostasis. The long-term consequences of these changes are unknown; this is reflected in the RMP.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of riociguat are well described by the Applicant. Metabolism and excretion of riociguat is complex. Riociguat is cleared by a wide range of enzymes, and substrate for various transporters. Main intrinsic factors: smoking, renal impairment (increase up to 100%), hepatic impairment and weight (40% higher exposure in subjects <60kg compared to subjects 60-90 kg). Subjects with impaired renal and hepatic function and subjects weighing <60 kg showed a higher exposure to riociguat and are more at risk for hypotension. Particular care should be exercised during individual dose titration.

Pharmacodynamics

Riociguat causes vasodilatation through a new mechanism of action. Dose titration is an important step and the achieved dose appears to be mainly determined by the ensuing hypotension. Vasodilatation is accompanied by haemodilution and a reduction in some serum chemistry parameters. The co-administration with PDE5 inhibitors was considered a plausible pharmacological option to augment the effect on the NO-GC pathway; however, this was associated with an unfavourable safety profile, such that a contraindication is implemented in section 4.3 of the SmPC.

2.5. Clinical efficacy

This application is based on the results of efficacy data obtained from the clinical study program conducted until 03 May 2012, and comprises data from the following studies (table E1):

- 2 Phase II studies: study 12166 and its long-term extension study 12166 LTE.
- 4 Phase III studies: study 11348 (CHEST-1) and its long-term extension study 11349 (CHEST-2) to support the CTEPH indication; and study 12934 (PATENT-1) and its long-term extension study 12935 (PATENT-2) to support the PAH indication.

Table E1: Overview of the phase II and III studies

Phase II studies

Study number Primary indication	Study Design	Riociguat regimen and treatment duration	Comparator	ITT population	Riociguat dosage: number of subjects
Phase II trials PAH and CTEPH					
12166 (report PH-35772) Treatment of PAH and CTEPH	Multicenter, non-randomized, non-blinded, non-controlled, dose-titration	12 weeks 0.5, 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration	None	N = 72 [e]	IDT at end of study 3.0 mg [a]: 1 2.5 mg: 51 2.0 mg: 7 1.5 mg: 8 1.0 mg: 4 0.5 mg: 1
12166 (report A61224) Long-term extension study in treatment of PAH and CTEPH	Multicenter, non-randomized, non-blinded, non-controlled, dose-titration	Interim analysis after up to 4.5 years of treatment 0.5 , 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration	None	N = 68 [f]	IDT up to 2.5 mg IDT [b] 7.5 mg TID [c]: 51 6.0 mg TID: 4 4.5 mg TID: 7 3.0 mg TID: 6

Phase III studies

Study number Primary indication	Study Design	Riociguat regimen and treatment duration	Comparator	ITT population	Riociguat dosage: number of subjects
Phase III trials CTEPH					
11348 (report A62508) Treatment of CTEPH	Multicenter, double-blind, randomized, placebo-controlled	16 weeks 0.5 , 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration	Placebo	N = 261	Arm 1 IDT up to 2.5 mg TID: 173 Arm 2 Placebo: 88
11349 (report A62509) Long-term extension study in treatment of CTEPH	Multicenter, multinational, open label, one-arm extension	8 weeks titration, following main study until drug approval 0.5 , 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration	None	N = 194 [f] (cut-off date 03 May 2012)	IDT up to 2.5 mg TID: 194 (Former riociguat = 129 subjects Former placebo = 65 subjects)
Phase III trials PAH					
12934 (report A62510) Treatment of PAH	Multicenter, double-blind, random ized, placebo-controlled, 3-arms, dose-titration	12 weeks 0.5 , 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration 1.0 to 1.5 mg capped dose titration	Placebo	N = 443	Arm 1 IDT up to 2.5 mg TID: 254 Arm 2 1.5 mg TID (capped) [d]: 63 Arm 3 Placebo: 126
12935 (report A62511) Long-term extension study in treatment of PAH	Multicenter, multinational, open label, one-arm extension	8 weeks titration, following main study until drug approval 0.5 , 1.0, 1.5, 2.0 or 2.5 mg TID Individual dose titration	None	N = 363 [f] (cut-off date 16 Apr 2012)	IDT up to 2.5 mg TID: 363 (Former riociguat 1.5 mg = 52 Former riociguat IDT = 215 Former placebo = 96)

2.5.1. Dose response studies

The choice of the dose range of 1.0 mg to 2.5 mg t.i.d to be further investigated in phase II/III studies is based on the results shown in healthy subjects and the proof of concept study.

Study 12166

Design

This phase II study was an open-label, multi-centre, non-randomised, non-blinded, non-controlled study of 12-week t.i.d. dosing of riociguat in patients with PH due to either PAH or CTEPH. The primary study objective was to investigate the safety, tolerability and feasibility of individual dose titration (IDT) of riociguat according to peripheral systolic blood pressure.

Methods

An individualised dose titration scheme is employed based on the systolic blood pressure (SBP) response. The patient is initially administered 1 mg t.i.d and depending on the SBP the dose is adapted every two weeks if necessary, for a period of eight weeks.

Results

Most of the patients (68%) could tolerate the highest dose of 2.5 mg tid, which is reassuring. Adverse events (AE) related to hypotension were reported, but none led to discontinuation of the medication. Blood pressures normalised in all but two cases without a change in drug regimen. In these two cases, a lower dose of riociguat was started and tolerated. The results show that indeed this individual dose titration (IDT) appears to adapt the systemic haemodynamics to the vasodilatory effect of riociguat.

With regard to the practical feasibility of this dose-titration scheme, there appears to be no delay in attaining efficacy although the effect is not maximal in some patients. The time course of the effect on 6MWD in the Phase-III trials confirms this: In PATENT (PAH), after 4 weeks the change from baseline was 25.6 and 12.6 m in the IDT and placebo arms respectively; In CHEST (CTEPH), after 4 weeks the change from baseline was 27.2 and 12.5 m in the IDT and placebo arms respectively.

It is agreed that the proposed dose titration is sufficiently justified by inter-individual differences in PK/PD and susceptibility. In addition to a visit after 4 weeks (as in the ESC guideline), the titration scheme requires 2 additional visits, after week 2 and after week 6. This may be cumbersome if the riociguat treatment is overseen by a referral centre which is far away; however, this is left to the perceived benefit risk assessment of riociguat.

In general, the vasodilatory effect appears to be more pronounced in PAH patients than CTEPH patients, on both the systemic and pulmonary blood pressure (table E4) and eventually on the 6MWT (table E5). These differences are attributed to the different baseline characteristics; PAH subjects presenting a sicker study population compared to CTEPH subjects. Study 12166 included an adequate number of subjects with PAH or CTEPH to achieve the study objectives of this proof-of-concept study. The 2 subgroups were however too small to demonstrate subgroup-specific effects of riociguat. Additionally, differences in pathophysiology between CTEPH and PAH may be important. So far, experience with the therapeutic response in CTEPH is limited; some agents that were effective in PAH were not effective in CTEPH suggesting that CTEPH may be less sensitive to vasodilatation.

Table E4: Swan-Ganz haemodynamics – point estimators (LS-mean) and 95% confidence intervals for changes on 84 days from baseline (all subjects with available Swan-Ganz haemodynamic measurements at Day 84; n=50)

Primary diagnosis	Parameter	Unit	n	Point estimator (LS-mean)	Lower 95% confidence limit	Upper 95% confidence limit	*P* value of F-statistic
PAH	RAP_m	mmHg	20	0.6500	-2.3111	3.6111	0.6511
	PAP_{syst}	mmHg	19	-6.7368	-14.5166	1.0430	0.0855
	PAP_{diast}	mmHg	19	-8.6316	-14.7540	-2.5091	**0.0083**
	PAP_{mean}	mmHg	20	-6.8500	-12.1456	-1.5544	**0.0139**
	PCWP	mmHg	20	1.9000	-0.4173	4.2173	0.1024
	HR	BPM	19	3.3158	-2.7406	9.3722	0.2651
	SBP	mmHg	18	-8.3333	-16.0278	-0.6388	**0.0354**
	DBP	mmHg	18	-4.6667	-11.2263	1.8930	0.1517
	MAP	mmHg	16	-7.7250	-13.3160	-2.1340	**0.0100**
	CO	L/min	19	0.9289	0.2972	1.5607	**0.0063**
	PVR	$dyn*s*cm^{-5}$	19	-323.4148	-461.0064	-185.8231	**0.0001**
	PVRI	$dyn*s*cm^{-5}m^2$	19	-587.5743	-838.4763	-336.6722	**0.0001**
	SVR	$dyn*s*cm^{-5}$	16	-486.0385	-864.3035	-107.7736	**0.0152**
	SVRI	$dyn*s*cm^{-5}m^2$	16	-846.1325	-1588.141	-104.1239	**0.0280**
	CI	$L/min/m^2$	19	0.5068	0.1854	0.8282	**0.0038**
	PVR/SVR	%	16	-8.0684	-15.1164	-1.0204	**0.0275**
CTEPH	RAP_m	mmHg	30	0.0333	-1.6437	1.7104	0.9678
	PAP_{syst}	mmHg	29	-7.7241	-12.5889	-2.8594	**0.0029**
	PAP_{diast}	mmHg	29	-2.3448	-4.0976	-0.5920	**0.0105**
	PAP_{mean}	mmHg	30	-4.3333	-6.6317	-2.0350	**0.0005**
	PCWP	mmHg	30	0.6667	-0.8183	2.1517	0.3661
	HR	BPM	30	-0.6667	-4.8493	3.5160	0.7467
	SBP	mmHg	29	-7.0000	-14.6028	0.6028	0.0697
	DBP	mmHg	29	-8.7586	-14.3745	-3.1427	**0.0034**
	MAP	mmHg	29	-3.8862	-11.7600	3.9876	0.3206
	CO	L/min	29	0.8479	0.5756	1.1203	**<0.0001**
	PVR	$dyn*s*cm^{-5}$	29	-207.1200	-254.3771	-159.8630	**<0.0001**
	PVRI	$dyn*s*cm^{-5}m^2$	29	-386.9251	-478.6733	-295.1769	**<0.0001**
	SVR	$dyn*s*cm^{-5}$	28	-349.3060	-548.9612	-149.6507	**0.0012**
	SVRI	$dyn*s*cm^{-5}m^2$	28	-673.4052	-1046.401	-300.4094	**0.0009**
	CI	$L/min/m^2$	29	0.4563	0.3100	0.6025	**<0.0001**
	PVR/SVR	%	28	-5.1856	-11.0917	0.7205	0.0828

Table E5: 6-minute walk test – point estimators (LS-mean) and 95% confidence intervals for changes on D84 from baseline

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

Safety results of phase II study 12166 and its on-going long-term extension are discussed under the safety section of this report.

Conclusion

The dose range between 1.0 mg and 2.5 mg covers the range from the minimum effective dose to the maximum tolerated dose in healthy volunteers based on the effects seen for heart rate, blood pressure and plasma renin activity. Therefore, 1.0 mg was selected as the starting dose and 2.5 mg as the maximum dose in the clinical phase II study 12166.

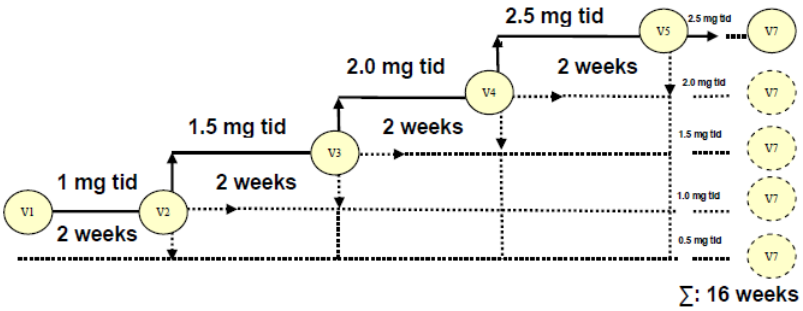
2.5.2. Main studies

2.5.2.1. Study 11348 (CHEST-1)

Methods

This was a Phase III, double-blind, randomised, multi-centre, placebo-controlled study of the efficacy and safety of oral riociguat in subjects with **CTEPH** (Figure E1).

Figure E1: Trial Design and dose titration.



Study Participants

To be eligible for inclusion, subjects had to have a diagnosis of inoperable or postoperative CTEPH and an eligibility and baseline 6MWD test between 150 m and 450 m. Subjects with inoperable CTEPH had to have a PVR >300 dyn·s·cm^{-5} measured at least 90 days after start of full anticoagulation and a PAP_{mean} >25 mmHg; inoperability was diagnosed by an experienced surgeon or a central adjudication committee. Criteria to define inoperability can vary per centre, which may have implications for a global trial. The criteria of inoperability were established by an experienced surgeon, the definition of whom is acceptable. The inoperability assessment focused on the assessment of the technical operability under consideration of surgical accessibility of the organised thrombi and concordance between surgical accessible vascular obstruction and PVR. This is plausible. In CHEST-1, subjects with postoperative CTEPH (persisting or recurrent PH after pulmonary endarterectomy) had to have a PVR >300 dyn·s·cm^{-5} measured at least 180 days after surgery. There is no consensus on the definition of post-operative CTEPH, but the used definition in CHEST-1 is defendable.

Treatments

After a pre-treatment phase of approximately four weeks, eligible subjects were randomised in a 2:1 ratio to receive riociguat TID as an individual dose titration (IDT, between 1.0 mg and 2.5 mg TID) or placebo TID in an 8-week titration phase (from Visit 1 to Visit 5) (fig E1). The SBP was measured at trough before intake of the morning dose under consideration of the following algorithm:

- If trough SBP ≥95 mmHg, increase dose (+0.5 mg TID)

- If trough SBP 90 – 94 mmHg, maintain dose
- If trough SBP <90 mmHg without symptoms of hypotension, reduce dose (-0.5 mg TID)
- 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 TID).

The titration phase was followed by an 8-week main study phase (from Visit 5 to Visit 7). The titration scheme follows that employed in study 12166, but with more relaxed cut-off values to indicate hypotension: trough SBP ≥95 mmHg allowed increasing the dose, instead of 100 mmHg (study 12166). In CHEST-1 and PATENT-1 the rate of syncope was slightly lower on treatment as compared to placebo, whereas the rate of presyncope was slightly higher. Albeit riociguat has major effects on systolic blood pressure, the treatment algorithm of the pivotal trials including the target blood pressures did not raise concerns.

Objectives

To assess the efficacy and safety of oral riociguat in subjects with inoperable CTEPH or recurrent or persisting PH after surgical treatment.

Outcomes/endpoints

The primary efficacy variable was change from baseline in 6MWD after 16 weeks. Secondary efficacy endpoints included:

- Change from baseline in PVR after 16 weeks
- Change from baseline in NT-proBNP after 16 weeks
- Change from baseline in WHO functional class after 16 weeks
- Time to clinical worsening (TTCW: the first occurrence of death, heart/lung transplantation, rescue PEA due to persistent worsening of PH, hospitalisation due to persistent worsening of PH, start of new PH-specific treatment, persistent decrease of more than 15% from baseline or more than 30% compared to the last study-related measurement in 6MWD, persistent worsening of functional class)

This design is generally acceptable for a claim of improvement in exercise capacity in an indication where no other medicinal product is registered. As the relevant CHMP guideline (EMEA/CHMP/EWP/356954/2008) does not specifically address CTEPH, developing a clinical program in line with that recommended for PAH products is acceptable due to the disease similarities. In this guideline, hard endpoints measuring clinical outcomes are favoured over investigating improvements in exercise capacity. This was already communicated to the Applicant in the scientific advice (EMEA/H/SA/814/1/FU/1/2008/P A/II). During the assessment the 6MWT was still considered a valid endpoint, however, investigations of clinical outcomes would have been more relevant and TTCW should have been the preferred choice as primary or key secondary endpoint.

The investigated secondary endpoints are relevant; however the importance of measuring time to clinical worsening could have been emphasized more, for instance by placing it higher in the hierarchical testing

The components defining clinical worsening are not all equally robust. For example, the criteria for heart and lung transplantation vary per country and may be subjective in a global trial. Likewise, the criteria to justify the need for an additional PH therapy are not clearly shown. The endpoint is also not adjudicated which should have been done in this trial.

Sample size

The primary efficacy outcome was defined as the change in 6MWD from baseline to week 16 (last observation until week 16).

Assuming an SD of 70 m, it was calculated that 261 subjects valid for ITT (174 in the riociguat 1.0-2.5 mg group, 87 in the placebo group, 2:1 randomization) would be required to detect a placebo-adjusted difference of 30 m in 6MWD with a power of 90% and a two-sided significance level of 5%.

Allowing for an invalidity rate of 3%, a total of 270 randomized subjects were required

Randomisation

Eligible subjects were randomly allocated to the riociguat 1.0-2.5 mg group (180 subjects planned) or the placebo group (90 subjects planned) using an interactive voice response system (IVRS). Randomization took place at Visit 1 and was done in a 2:1 ratio in accordance with a computer-generated random code. Subjects were randomized in blocks of size 6, reflecting the 2:1 allocation ratio. Separate blocks were used for country groupings within each region

Blinding (masking)

The study was conducted as a double-blind trial. In general, subjects, investigators, and sponsor/contract research personnel remained blinded until the study database was frozen.

Study medication and packaging were identical in appearance for each treatment group. Subjects from the placebo group underwent sham titration from Visit 1 onwards, following the same rules of the individual dose titration scheme. Independently of the investigator's decision to increase, maintain or decrease the dose of study medication, the IVRS always allocated blinded placebo medication.

From Visit 2 onwards, the 6MWD test, Borg Scale assessment, and evaluation of WHO functional class had to be 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.

To allow for ongoing safety monitoring during the conduct of the study, members of the Data Monitoring Committee (DMC) received unblinded safety data. The involvement of an external statistical analysis centre in this process ensured that unblinded information was not available for third parties.

Statistical methods

The primary analysis set for efficacy was the intent-to-treat (ITT) set, which included all randomised subjects who received at least one dose of study medication. The primary efficacy outcome was the analysis of the change in 6MWD from baseline to week 16 (last observation until week 16) in the ITT set. The riociguat IDT and placebo groups were compared using analysis of covariance (ANCOVA), with baseline 6MWD as a covariate and treatment group and region (North America, South America, Europe, China, Asia/Pacific) as main effects. If the Shapiro-Wilk test for normality of residuals was statistically significant, the stratified Wilcoxon test was used as the primary statistical method instead of the ANCOVA. Superiority of the riociguat IDT group over the placebo group was to be declared if the two-sided significance level was less than or equal to 0.05. A per protocol analysis was performed as a supportive analysis.

To minimise bias and include all randomised and treated subjects in the ITT analysis, imputation for missing values was necessary if a subject died, withdrew or had no measurement for some reason at the planned end of the study (week 16). Where a subject died or withdrew due to clinical worsening with no termination visit, the following rules will be used: 6MWD worst possible value (0 m). Death or withdrawal due to clinical worsening were components of time to clinical worsening, so were included as an event by definition. In the case of withdrawal for other reasons with no post-baseline measurements, the baseline was taken. If the subject completed the study as planned, but there is no efficacy measurement at the end of the study, the last post-baseline value was used. To assess the robustness of the results of the primary analysis, a per protocol analysis and several sensitivity analyses were performed.

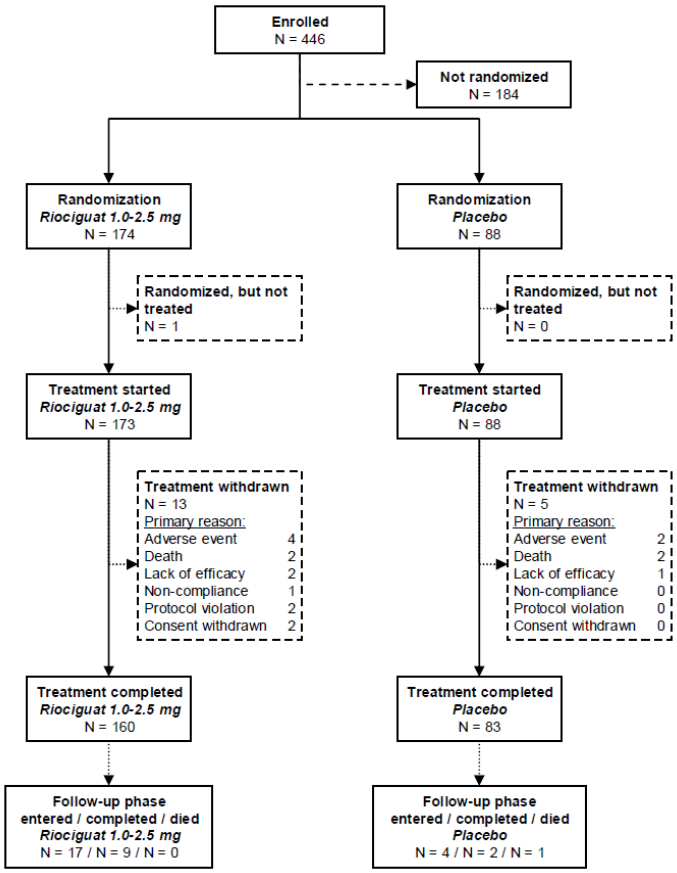
The statistical methods were considered acceptable.

Results

Participant flow

The participant flow in the CHEST-1 study is shown in Figure E2.

Figure E2: Participants flow in CHEST-1



Recruitment

This study enrolled 446 patients in 89 study centres in 26 countries worldwide, of which 262 were randomised.184 patients were not randomised; the most frequent primary reasons for non-randomisation were protocol violation and withdrawal by subject. 18 randomised subjects prematurely discontinued study medication or did not receive the study medication (1 subject). Discontinuation rates are slightly higher in the riociguat group (8%) compared to the placebo group (5.7%). Discontinuations due to AEs (2.3% for each arm) and discontinuations due to death (1.1% vs. 2.3% respectively) were comparable, which is reassuring. There was a difference in the rate of subjects not completing the final 6MWD (riociguat 9, placebo 1). The applicant imputed these data by LOCF, which may not be completely conservative. However, this is not believed to influence the robustness of the trial results.

Conduct of the study

The study was subject to 7 supplier audits and 11 investigator site audits. The reports are not provided but the applicant stated that the study met all local legal and regulatory requirements and was conducted in compliance with the ethical principles of the declaration of Helsinki and

with GCP. The study had a Steering Committee (SC) to supervise the conduct of the study and a Data Monitoring Committee (DMC).

There were 7 protocol amendments, 4 of them were valid for all countries.

Overall the study report did not indicate that there are relevant issues of concern related to the conduct of the study.

Baseline data

Table E6: Main baseline features of recruited patients in CHEST-1

Characteristic	Riociguat 1.0–2.5 mg N=173 (100%)	Placebo N=88 (100%)
Sex		
Male	55 (31.8%)	34 (38.6%)
Female	118 (68.2%)	54 (61.4%)
Race / Ethnicity		
White	120 (69.4%)	65 (73.9%)
Black or African American	7 (4.0%)	1 (1.1%)
Asian	37 (21.4%)	20 (22.7%)
Multiple races	1 (0.6%)	0 –
Hispanic or Latino	8 (4.6%)	2 (2.3%)
Age (years)		
N	173	88
Mean (SD)	59.3 (13.9)	59.2 (12.7)
Median (Min-Max)	62.0 (19-80)	61.0 (26-77)
Age group		
Age <65 years	99 (57.2%)	52 (59.1%)
Age ≥65 years	74 (42.8%)	36 (40.9%)
Weight (kg) at baseline		
N	173	88
Mean (SD)	73.99 (18.47)	76.24 (16.33)
Median (Min-Max)	73.60 (36.0-158)	76.50 (44.0-120)
Body mass index (kg/m^2) at baseline		
N	173	88
Mean (SD)	27.13 (5.75)	27.73 (5.30)
Median (Min-Max)	26.64 (16.9-53.1)	26.52 (17.6-44.0)
WHO functional class		
I	3 (1.7%)	0 –
II	55 (31.8%)	25 (28.4%)
III	107 (61.8%)	60 (68.2%)
IV	8 (4.6%)	2 (2.3%)
Missing	0 –	1 (1.1%)
6MWD category		
<320 m	60 (34.7%)	25 (28.4%)
≥320 m	113 (65.3%)	63 (71.6%)
6MWD category		
<380 m	109 (63.0%)	50 (56.8%)
≥380 m	64 (37.0%)	38 (43.2%)
PVR (dyn*s*cm^{-5})		
N	151	82
Mean (SD)	790.7 (431.6)	779.3 (400.9)
Median (Min-Max)	711.1 195.2-3942.0)	691.4 (258.1-2046.8)
Inoperable CTEPH	121 (69.9%)	68 (77.3%)
Postoperative CTEPH	52 (30.1%)	20 (22.7%)

The main baseline characteristics of the recruited patients are depicted in table E6. The baseline characteristics of the recruited patients generally reflect the known disease distribution and

baseline PVR and 6MWD (Pepke-Zaba, Circulation. 2011;124:1973-1981). There is adequate representation of patients in functional class (FC) II/III, allowing an adequate assessment in these specific FCs. There is also a good representation of both inoperable and operable CTEPH.

There is some reassurance regarding the tolerability of the dose: 77% of subjects were on the highest dose of 2.5 mg, 13% were on 2.0 mg and the rest on lower doses including 1/173 (1%) subject on 0.5 mg. However, it was considered also important to analyse efficacy (primary and secondary endpoints) per dose level to ensure benefit in patients with all dose levels. In this analysis, no obvious dose response differences would be expected as the dose was not randomised but related to an efficacy parameter (blood pressure) and thus to individual PK properties. It is shown the 2.5 mg tid dose is accompanied by the most consistent response regarding the different endpoints measured.

Numbers analysed

The following table provides an overview of analysis set assignments.

Number of subjects in analysis sets

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

Of the 446 subjects enrolled in the study, 262 were randomized and 261 received at least one dose of study medication.

In accordance with the definitions of analysis sets, all 261 treated subjects were valid for safety analysis and for ITT analysis. In this study, the safety analysis set and the ITT analysis set were identical in size. One subject was randomized but not treated.

A total of 43 treated subjects had a major protocol deviation and were not valid for per protocol analysis. Therefore the per protocol analysis set comprised 218 subjects.

Outcomes and estimation

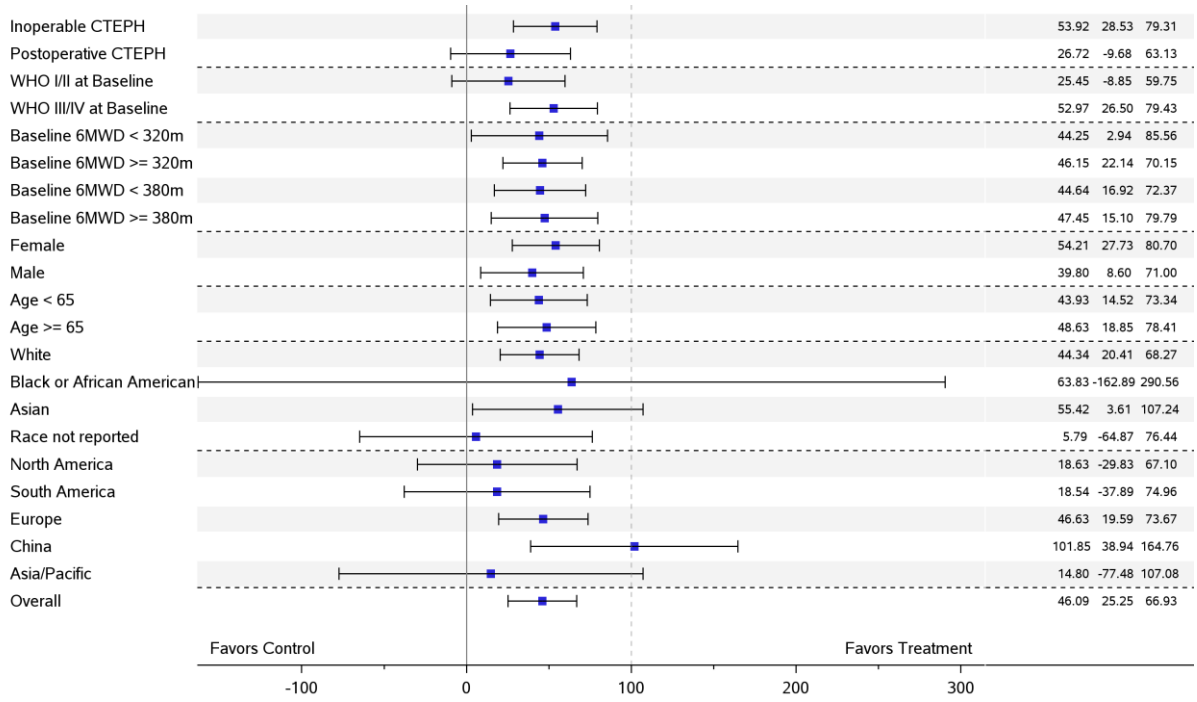
Primary efficacy endpoint

Treatment with riociguat IDT resulted in a significant and clinically relevant improvement in 6MWD from baseline to week 16 (last observation until week 16) as compared to placebo in the ITT analysis set (45.69 m; 95% CI: 24.74 m to 66.63 m; $p<0.0001$). Results of the per protocol analysis showed comparable results (52.24 m (95% CI: 30.53 m to 73.95 m, $p<0.0001$). Further sensitivity analyses confirmed the results of the main analysis.

Subgroup analyses

An improvement of the 6MWD from baseline to last visit was observed for the pre-defined subgroups of types of CTEPH, WHO FC at baseline, baseline 6MWD, age and race as well as other subgroups (Figure E3). Results were not always statistically significant, due to different reasons.

Figure E3: Mean treatment difference in change from baseline to last visit in 6MWD by pre-specified subgroups (ITT analysis set CHEST-1)



Secondary Efficacy Variables

The results of the secondary efficacy variables are shown in Table E7.

Table E7 Secondary efficacy variables: Summary of hierarchical testing - Study 11348 (CHEST-1), 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
6MWD (primary)	<0.0001	0.0001	**<0.0001**	Yes	Yes
PVR	<0.0001	0.0001	**<0.0001**	Yes	Yes
NT-proBNP	0.0293	0.0001	**<0.0001**	Yes	Yes
WHO functional class	–	–	**0.0026**	Yes	Yes
Time to clinical worsening	0.2180 a	–	**0.1724 b**	No	No
Borg CR 10 scale c	–	–	**0.0035**	Yes	No
EQ-5D questionnaire	0.0002	0.0001	**<0.0001**	Yes	No
LPH questionnaire	0.0165	0.0001	**0.1220**	No	No

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

Pulmonary haemodynamics are improved; specifically PVR shows a reduction of around 30%. The results of the postoperative CTEPH are less impressive than inoperable CTEPH (Table E8). The improvement seen for the haemodynamic variable PVR was consistent with other relevant haemodynamic variables, including CO (improvement of 0.9 L/min over placebo (difference of LS means) without a clinically relevant change of heart rate), SVR (reduction of 478 dyn·s·cm^{-5} over placebo), PAPmean (reduction of 5 mmHg over placebo) and mean arterial pressure (reduction of 9 mmHg over placebo).

Table E8: Change in PVR (dyn·s·cm^{-5}) from baseline to last visit by pre-specified subgroups - ITT analysis set

Subgroup Timepoint	Riociguat 1.0–2.5 mg N=173	Placebo N=88
Inoperable CTEPH	n=105	n=63
Baseline	866.5 (471.2)	851.5 (422.7)
Change to last visit	–257.1 (279.4)	33.4 (291.8)
Postoperative CTEPH	n=46	n=19
Baseline	617.5 (252.3)	540.2 (171.6)
Change to last visit	–153.9 (127.3)	–11.0 (204.6)
WHO class I/II at baseline	n=48	n=24
Baseline	794.4 (352.2)	737.2 (468.8)
Change to last visit	–228.8 (225.2)	14.4 (275.2)
WHO class III/IV at baseline	n=103	n=57
Baseline	789.0 (465.5)	798.8 (375.4)
Change to last visit	–224.2 (258.3)	33.0 (273.3)
<320 m 6MWD at baseline	n=52	n=23
Baseline	862.2 (561.4)	913.9 (428.0)
Change to last visit	–258.0 (307.8)	–48.1 (197.7)
≥320 m 6MWD at baseline	n=99	n=59
Baseline	753.1 (341.9)	726.9 (380.8)
Change to last visit	–208.7 (208.9)	50.8 (294.7)

There was also a significant reduction in NT-proBNP. Most of the patients in both treatment arms did not show change in their WHO FC, however, more patients in the riociguat group improved by one (30.6%) or two levels (2.3%) compared to placebo (14.9% and none). Likewise, more patients on placebo deteriorated in FC. There was no significant improvement in TTCW, as expected due to the shortness of the study duration. The results do not indicate a deleterious effect of riociguat on the clinical outcomes of the patients, which is reassuring. The applicant has clarified that the statistical analysis of clinical worsening was based on a first event analysis that excluded some mortality events, but that mortality after a first event was analysed and presented in the respective tables. Additional analyses of TTCW using the CHMP definition corroborate the results of the analyses of the definitions used in CHEST-1. The number of patients experiencing clinical worsening according to the CHMP definition, were in CHEST-1 (riociguat) 3 (1.7%) and placebo 5 (5.7%) (p = 0.09).

2.5.2.2. Study 12934 (PATENT-1)

Methods

The methods in PATENT-1 were similar to those described in CHEST-1, but the study duration was 12 weeks (Figure E4).

Study Participants

To be eligible for inclusion, subjects had to have a diagnosis of symptomatic PAH (Group 1, Venice Clinical Classification of PH: idiopathic, familial, associated PAH due to connective tissue disease or congenital heart disease (i.e. atrial septal defect, ventricle septal defect, persistent ductus arteriosus), if patients underwent surgical correction more than 12 months before study inclusion, associated PAH due to portal hypertension with liver cirrhosis CHILD-Pugh class A (B and C excluded) and associated PAH due to anorexigen or amphetamine use); 6MWD test between 150 m and 450 m, a PVR >300 dyn·s·cm^{-5}, and a PAPmean >25 mmHg. Both treatment-naïve patients and patients on stable pre-treatment with an ERA or a prostacyclin analogue (inhaled or subcutaneous; oral administration permitted in Japan, as per amendment 7) could be included. These inclusion/exclusion criteria are generally acceptable.

Treatments

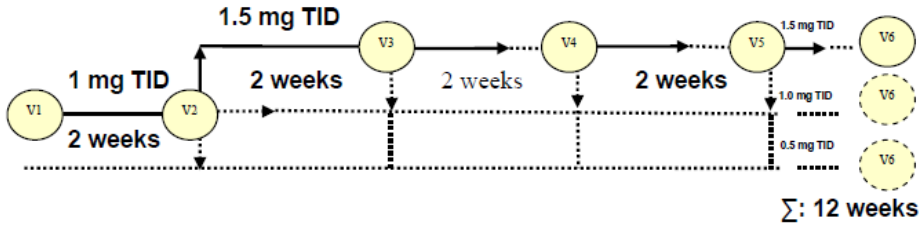
Subjects were randomised into one of the three study arms (4:2:1):

1. Placebo Arm (planned sample size: 132 subjects).

2. Riociguat Individual Dose Titration (IDT) Arm (same as CHEST-1): (planned sample size: 264 subjects)

3. Riociguat 1.5 mg Capped Titration Arm (figure E4): intended dose 1.5 mg based on a dose titration scheme with titration from 1.0 mg to 1.5 mg (planned sample size: 66 subjects). If during the titration phase the subject reached the 1.5 mg dose level, no further up-titration was possible. From that point in time on, the subject underwent a sham titration that only allowed dose maintenance or decrease (figure E4).

Figure E4: Titration scheme: Study 12934 (PATENT-1), riociguat 1.0-1.5 mg group



The utility of the addition of the arm with capped titration without formal statistical considerations is questioned as it does not allow any robust interpretation of the results of the different dose levels.

Outcomes/endpoints are the same as those measured in CHEST-1, but at 12 weeks. The definition used for TTCW in PATENT-1 generally follows that employed in CHEST-1, with the exclusion of rescue pulmonary endaterectomy (PEA) due to persistent worsening of PH, which is not relevant in PAH. In both studies transient deteriorations of clinical status requiring hospitalisation, treatable by, for example, short-term administration of i.v. diuretics, positive inotropic agents or non-invasive ventilation and allowing subject discharge within 48 hours, were not considered as "persistent" and not included as TTCW event. This definition is rather restrictive, and may not capture short-term PH related hospitalisations, which are also important events.

Objectives

To assess the efficacy and safety of oral riociguat in treatment-naïve subjects and subjects pre-treated with an endothelin receptor antagonist or a prostacyclin analogue with symptomatic PAH.

Outcomes/endpoints

The primary efficacy variable was the 6MWD.

Secondary efficacy variables were PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg CR 10 Scale or Modified Borg Dyspnoea Scale (subjects enrolled before amendment 4 only), EQ-5D questionnaire, and LPH questionnaire.

The main analysis of the secondary variables was performed in subjects valid for ITT. A per protocol analysis of these variables was performed as a supportive analysis.

Sample size

The primary efficacy outcome was defined as the change in 6MWD from baseline to week 12 (last observation until week 12).

Assuming an SD of 70 m, it was calculated that 375 subjects valid for ITT (250 in the riociguat 1.0-2.5 mg group, 125 in the placebo group, 4:2 randomization) 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%.

In addition, the exploratory riociguat 1.0-1.5 mg group would have a sample size of one half that of the placebo group, approximately 63 patients. Hence, the total number of subjects valid for ITT was to be 438. Allowing for an invalidity rate of 5%, a total of 462 randomized subjects were required.

Randomisation

Eligible subjects were randomly allocated to the riociguat 1.0-2.5 mg group (264 subjects planned), or the placebo group (132 subjects planned), or the riociguat 1.0-1.5 mg group (66 subjects planned) using an IVRS.

The randomization was done in a 4:2:1 ratio in accordance with a computer-generated random code.

Randomization took place at Visit 1 and was stratified according to previous PAH treatment (treatment-naïve subjects and subjects pre-treated with an endothelin receptor antagonist or a prostacyclin analogue).

Blinding (masking)

The blinding in PATENT-1 followed the same approach used in CHEST-1.

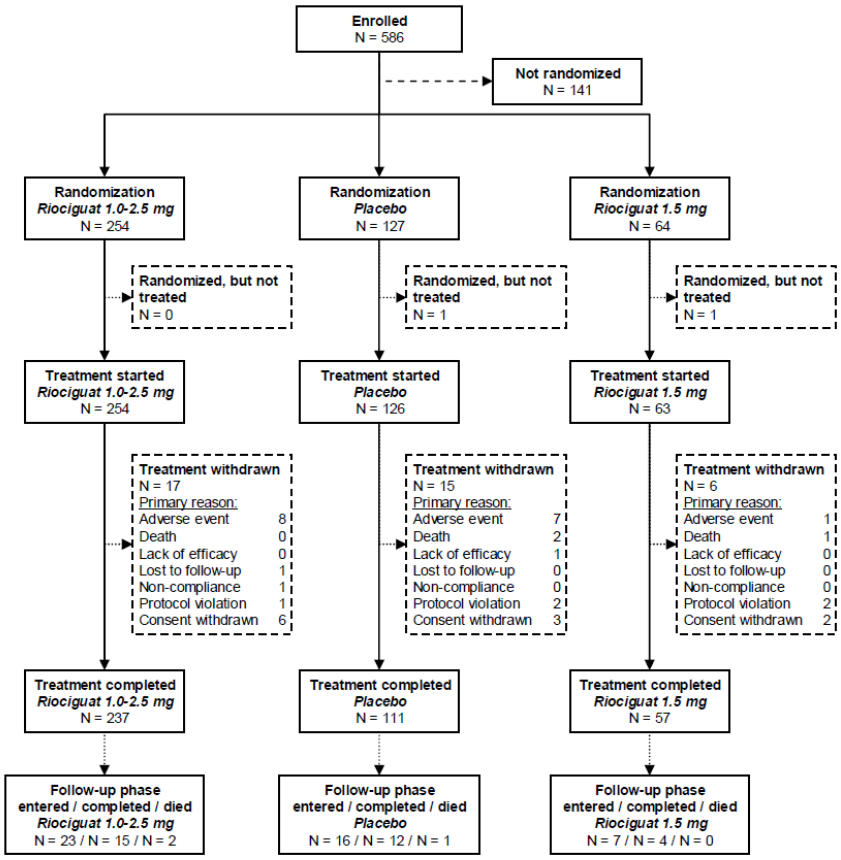
Statistical methods

The statistical methods of study 12934 (PATENT-1) were similar to the methods of study 11348 (see CHEST-1), and were considered acceptable by the CHMP.

Results

Participant flow

Figure E5: Participants flow in PATENT-1



Recruitment

The participant flow in the PATENT-1 is shown in Figure E5. In PATENT-1, 586 patients were enrolled in 124 study centres in 30 countries worldwide. Of these, 141 patients were not randomised. The most frequent primary reasons for non-randomisation were protocol violation and withdrawal by subject. Of the 586 subjects, 445 were randomised, of whom 443 received study medication (254 in the riociguat IDT group, 126 in the placebo group, 63 in the riociguat 1.0-1.5 mg group). Of the 445 randomised subjects, 405 (91.0%) completed the treatment phase. The remaining 40 randomised subjects prematurely discontinued study medication (38 subjects) or did not receive the study medication (2 subjects). Discontinuation rates were slightly higher in the placebo arm (12.6%) compared to riociguat IDT and riociguat 1.0-1.5 mg arms (6.7% and 10.9% respectively). There was a higher rate of AEs reported with the placebo group than the other two groups, which is surprising. Deaths were equally reported in the placebo and riociguat (1.6% each) while no deaths were reported in the riociguat IDT arm, which is reassuring.

Conduct of the study

Overall there were no major concerns regarding the conduct of the study but there is one issue to be discussed here. A number of 8 subjects which tested positive for riociguat at some time point in the PK analyses out of 126 assumed to receive placebo is rather high. Such a high number identified *post hoc* raises the question, whether there were relevant unidentified concerns related to GCP. The applicant provided data that showed that there was no regional preference for the mistakes. However, since there was no clue for an explanation, it is unclear, whether similar mistakesin patients on treatment occurred.

According to the applicant the studies were conducted in compliance with GCP. In addition, a summary of the results of GCP inspections conducted by the FDA at 5 sites is available, partially based on preliminary results. There were deviations from regulations but no significant or relevant deviations were identified. The applicant submitted further data regarding these inspections, and the data are reassuring regarding the conduct of the trials.

Baseline data

Characteristic	Riociguat 1.0–2.5 mg N=254 (100%)	Placebo N=126 (100%)	Riociguat 1.0–1.5 mg N=63 (100%)
Sex			
Male	51 (20.1%)	28 (22.2%)	14 (22.2%)
Female	203 (79.9%)	98 (77.8%)	49 (77.8%)
Race / Ethnicity			
White	161 (63.4%)	78 (61.9%)	33 (52.4%)
Black or African American	4 (1.6%)	1 (0.8%)	1 (1.6%)
Asian	79 (31.1%)	38 (30.2%)	22 (34.9%)
Multiple races	1 (0.4%)	1 (0.8%)	0 –
Hispanic or latino	9 (3.5%)	8 (6.3%)	7 (11.1%)
Age (years)			
N	254	126	63
Mean (SD)	51.1 (16.6)	50.7 (16.5)	48.8 (16.1)
Median (Min-Max)	52.5 (18-80)	51.0 (18-79)	49.0 (18-77)
Idiopathic PAH	149 (58.7%)	84 (66.7%)	39 (61.9%)
Familial PAH	7 (2.8%)	1 (0.8%)	1 (1.6%)
PAH due to connective tissue disease	71 (28.0%)	25 (19.8%)	15 (23.8%)
PAH due to congenital heart disease (operated)	15 (5.9%)	12 (9.5%)	8 (12.7%)
Portal PH	11 (4.3%)	2 (1.6%)	0 –
WHO functional class			
I	5 (2.0%)	4 (3.2%)	5 (7.9%)
II	108 (42.5%)	60 (47.6%)	19 (30.2%)
III	140 (55.1%)	58 (46.0%)	39 (61.9%)
IV	1 (0.4%)	3 (2.4%)	0 –
6MWD category			
<380 m	139 (54.7%)	53 (42.1%)	30 (47.6%)
≥380 m	115 (45.3%)	73 (57.9%)	33 (52.4%)
PVR (dyn*s*cm^{-5})			
N	232	107	58
Mean (SD)	791.0 (452.6)	834.1 (476.7)	847.8 (548.2)
Median (Min-Max)	685.2 (241.5-2613.3)	740.0 (286.1-2545.5)	729.7 (258.1-3617.4)

The main baseline characteristics of the recruited patients are depicted in Table E9. The demographics and baseline characteristics of the recruited patients generally reflect the known disease distribution, with middle-aged females, with idiopathic and APAH, of FC II/III predominating the picture. There is an equal distribution of treatment naïve patients and patients pre-treated with PAH medications, mainly ERAs; there is limited representation of patients on prostacyclins (5.6% to 7.9% per group). Most of the patients on the riociguat IDT arm (90%) were on 2-2.5 mg showing that these doses are well tolerated for at least 12 weeks.

Numbers analysed

The following table provides an overview of analysis set assignments.

Number of subjects in analysis sets.

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

Of the 586 subjects enrolled in the study, 445 were randomized and 443 received at least one dose of study medication.

In accordance with the definitions of analysis sets, all 443 treated subjects were valid for safety analysis and for ITT analysis. In this study, the safety analysis set and the ITT analysis set were identical in size. Two subjects were randomized but not treated.

A total of 64 treated subjects had a major protocol deviation and were not valid for per protocol analysis. Therefore the per protocol analysis set comprised 379 subjects.

Outcomes and estimation

Primary efficacy endpoint

In the primary efficacy analysis, treatment with riociguat IDT resulted in a significant improvement in 6MWD from baseline to week 12 as compared to placebo in the ITT analysis set. The estimated overall treatment effect from the ANCOVA was 35.78 m (95% CI: 20.06 m to 51.51 m). The per protocol analysis showed comparable results (estimate of 33.52, 95% CI: 18.99 m to 48.04 m). Further sensitivity analyses confirmed the results of the main analysis.

Results observed in patients administered riociguat in doses of 1-1.5 mg in the 'capped titration' arm show comparable results (change from baseline to last visit mean 31.1 m compared to 29.6 m for the riociguat IDT). Pre-trial it was anticipated that the riociguat capped titration (CT) group would confirm the rationale for the individual dose titration (IDT) regimen and that the riociguat IDT group would out-perform the riociguat CT group across all endpoints evaluated. However, this was not the case. Significant differences are already observed in riociguat CT versus placebo for 6MWD ($p<0.0001$), PVR ($p<0.0001$), NT proBNP ($p<0.0001$), but not observed for WHO functional class ($p=0.0674$), time to clinical worsening ($p=0.3939$) or Borg CR 10 ($p=0.1068$). The latter 2 endpoints are significantly better using the IDT regimen, implying that the full therapeutic effect is probably only achieved by that higher dose. The haemodynamic response is more obvious (PVR and CO) in the IDT regimen compared to the CT. The value of improvement of haemodynamic parameters *per se* on long term clinical outcomes is not established. However, a possible additive value of doses above 1.5 on these parameters cannot be excluded. In addition, efficacy in the different subgroups is more consistently observed with the IDT regime, specifically in patients with PAH associated with CTD, patients co-administered ERA and smokers probably benefit more from the IDT regimen. The fact that most subjects continued the dose they were titrated to, speaks to the safety and tolerability of the IDT regimen. As requested, efficacy data stratified to the main dose groups are also provided for CHEST 1 and PATENT 1. In

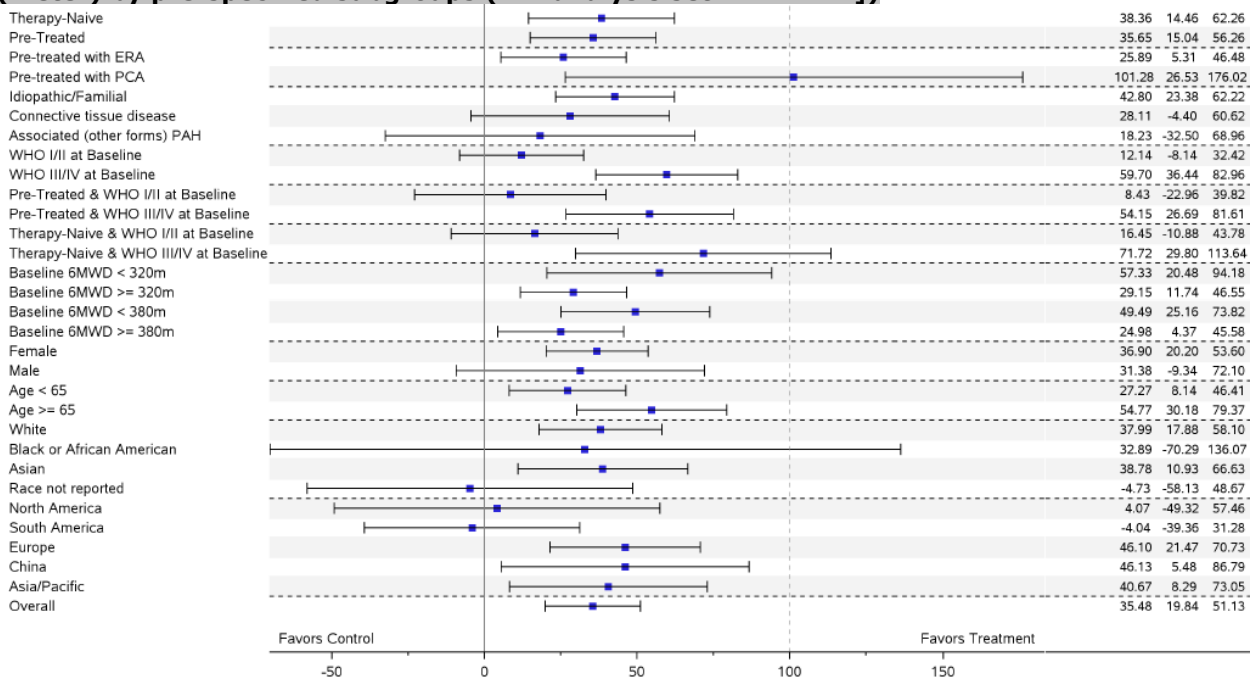
this analysis, no obvious dose response differences would be expected as the dose was not randomised but related to an efficacy parameter (blood pressure) and thus to individual PK properties. However, it is shown the 2.5 mg TID dose is accompanied by the most consistent response regarding the different endpoint measured.

Based on the above, it can be agreed that available data show robustly the efficacy of the proposed maximum dose of 2,5 mg t.i.d in most of the examined subgroups. However, it cannot be excluded that in some PAH patients a dose of 1,5 mg t.i.d appears quite adequate as well, with no justification for further dose escalation. This is mentioned in section 4.2 of the SmPC.

Subgroup analyses

Comparable improvements in 6MWT were observed in treatment naïve (38.36 m; 95% CI: 14.46-62.26) and combination therapy (35.65 m; 95% CI: 15.04-56.26) (Figure E6). This is a surprising observation, considering that the gain in 6MWT shown with combination therapies is usually quite limited compared to monotherapy. The result is driven by the small group of subjects who had prostanoids background therapy, while those on ERA background therapy responded more in line with published trials. The combination with prostacyclin appears to yield better results than when riociguat is combined with ERAs. It should be remembered that IV prostanoids were excluded in this trial and the Applicant did not specify how many used inhaled or subcutaneous prostanoids. Breakdown of the subgroup of patients co-administered prostanoids (n=31) shows that one third (n=10) was administered beraprost, which is only authorised in Japan. The remaining patients were administered iloprost or treprostinil. Regarding the results, it can be agreed with the applicant that generally comparable efficacy in this subgroup co-administered prostanoids was shown to that of the whole cohort. However, due to their limited representation (n= 21), their explicit mention in the indication is not supported. The results are mentioned in section 5.1 of the SmPC.

Figure E6: Mean treatment difference in change from baseline to last visit in 6MWD (meter) by pre-specified subgroups (ITT analysis set PATENT-1])



Efficacy in the subgroup of idiopathic PAH appears to be better than in the subgroups associated with connective tissue disease, or other forms. For the 6MWD the difference of means in favour of riociguat IDT was 42.8 m (95% CI: -23.4 to 62.2) for patients with idiopathic/familial PAH and 28.1 m (95% CI: -4.4 to 60.6) for patients with connective tissue disease associated PAH. Comparable results are however shown in the results of WHO FC. It can be agreed that experience with other PAH medications confirm these same findings, possibly related to the underlying co-morbidity in PAH associated with CTD. As discussed above, associated PAH is one of the groups that clearly benefit from IDT compared to the capped dosing regimen.

The presented analysis of patients of WHO FC II showed lower results for the 6MWT compared to patients with WHO FC III (least square difference in favour of riociguat IDT of 9.9 m (95% CI: -11.3 to 31.0) compared to 58.0 m (95% CI: -34.8 to 81.2). The applicant attributes this large variability to the difference in the placebo response; the placebo group in WHO FC II showed an improvement of 19.4 from baseline to last visit, the placebo group in WHO FC III shows deterioration by -27.2 m from baseline to last visit. However, the applicant maintains that as long as improvement from baseline to last visit in the riociguat groups is 29.4 m for patients of WHO FC II and 30.5 m for patients of WHO FC III, efficacy can be considered comparable in both subgroups. Please see discussion regarding WHO FC II in PAH below.

Limited treatment effect estimates were observed in the regions North America (4.1 m) and South America (-4.0 m). This was also recorded in the CTEPH study. Since this was a consistent finding in both studies, a chance finding appears unlikely. However, the Applicant has provided a thorough evaluation of factors potentially explaining the small/lack of effect of riociguat in North and South America. No single factor could be identified explaining this finding. It is, however, reassuring that efficacy has been demonstrated in the European population. Furthermore the applicant showed that there was no regional clustering of patients in the placebo groups with positive plasma levels of riociguat.

Secondary Efficacy Variables

The results of the secondary efficacy variables are shown in Table E10.

Table E10 Secondary efficacy variables: Summary of hierarchical testing - Study 12934 (PATENT-1), 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
6MWD (primary)	<0.0001	0.0001	**<0.0001**	Yes	Yes
PVR	<0.0001	0.0001	**<0.0001**	Yes	Yes
NT-proBNP	0.0157	0.0001	**<0.0001**	Yes	Yes
WHO functional class	–	–	**0.0033**	Yes	Yes
Time to clinical worsening	0.0285 [a]	–	**0.0046** [b]	Yes	Yes
Borg CR 10 scale [c]	–	–	**0.0022**	Yes	Yes
EQ-5D questionnaire	0.0197	0.0001	**0.0663**	No	No
LPH questionnaire	0.0009	0.0001	**0.0019**	Yes	No

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

Significant improvements in PVR were observed in the riociguat IDT arm compared to placebo. Improvements are also shown in relevant subgroups like treatment naïve/pre-treated patients, WHO II/WHO III and PAH due to different aetiologies, though with variable degrees. Other pulmonary and systemic haemodynamic parameters were also affected. The effects on systemic haemodynamics are more of a safety concern, although obviously they cannot be separated from the beneficial effects.

Significant improvements were also seen in NT-proBNP, WHO FC, time to clinical worsening and Borg CR 10 score. These results further support the primary efficacy endpoint.

Significant improvements in TTCW were mainly driven by lesser hospitalisations and starting of new PH medications (Table E11). Additional analyses of TTCW using the CHMP definition corroborate the results of the analyses of the definitions used in both CHEST-1 and PATENT-1. The pivotal studies used a broader definition including administration of a new PAH medication. The final differences between the analyses are small and only two patients are excluded when using the CHMP definition. The number of patients experiencing clinical worsening according to the CHMP definition, were in CHEST-1 (riociguat) 3 (1.7%) and placebo 5 (5.7%) (p = 0.09); in PATENT-1 (riociguat) 3 (1.2%), (riociguat capped dose) 2 (3.2%), (placebo) 7 (5.6%); p = 0.01 riociguat v placebo.

Table E11: Clinical worsening - Study 11348 (PATENT-1), ITT analysis set

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

Summary of main studies

Table E2 and Table E3 summarise the efficacy results from the main studies: study 11348 (**CHEST-1**) supporting the chronic thromboembolic pulmonary hypertension (CTEPH) indication and study 12934 (**PATENT-1**) supporting the pulmonary arterial hypertension PAH indication. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit/risk assessment (see later sections).

Table E2: Summary of Efficacy for Study 11348; CHEST-1

Title: A 16-week randomised placebo-controlled, double-blind multi-centre clinical trial investigating efficacy and safety of oral riociguat in subjects in patients with **CTEPH (CHEST-1).**				
Study identifier	11348			
Design	This was a multinational, multi-centre, double blind, parallel group study investigating efficacy and safety of oral riociguat in subjects in patients with **CTEPH.** After a pre-treatment phase of approximately 4 weeks, eligible subjects were randomised in a 2:1 ratio to receive riociguat TID as an individual dose titration (IDT, between 1.0 mg and 2.5 mg TID) or placebo TID in an 8-week titration phase. the dose of study medication was titrated from a starting dose of 1.0 mg TID by the investigators in steps of 0.5 mg every 2 weeks based on the subject's peripheral SBP to a maximum dose of 2.5 mg TID.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 weeks not applicable On-going	
Hypothesis	Superiority of riociguat over placebo			
Treatment groups	Riociguat		riociguat 1-2.5 mg t.i.d n= 173	
	Placebo		Placebo, n=88	
Endpoints and definitions	Primary endpoint	6MWD	Change from baseline in 6MWD after 16 weeks.	
	Secondary endpoint	Change from baseline in PVR, NT-proBNP, WHO functional class , TTCW, Borg CR 10 Scale or Modified Borg Dyspnoea Scale, EQ-5D questionnaire and in Living with Pulmonary		
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Full analysis set (all randomised patients), Intention to treat 16 weeks			
Descriptive statistics and estimate variability	Treatment group		Riociguat	Placebo
	Number of subjects		N = 173	N = 88
	6MWD (m) change from baseline to last visit SD		 38.9 79.3	 -5.5 84.3
	PVR [dyn s cm^{-5}] change from baseline to last visit SD		(n=151) –225.7 247.5	(n=82) 23.1 273.5
	NT-proBNP (pg/mL) change from baseline to last visit SD		(n=150) –290.7 1716.9	(n=73) 76.4 1446.6
Effect estimate per	Primary endpoint	6MWD	riociguat/placebo	

comparison		ANCOVA treatment difference	45.69 (24.74 to 66.63)
		P-value	<0.0001
	Secondary endpoint	PVR	−246.43 (−303.33 to −189.53) (p <0.0001)
		NT-proBNP	−443.99 (−842.95 to −45.03) (p= 0.0293)

Table E3: Summary of Efficacy for Study 12934 (PATENT-1)

Title: A 12-week a phase III, double-blind, randomised, multi-centre, multinational, placebo-controlled study of the efficacy and safety of oral riociguat in subjects with symptomatic PAH **(PATENT-1).**				
Study identifier	12934			
Design	This was a multinational, multi-centre, double blind, parallel group study investigating efficacy and safety of oral riociguat in patients with PAH, treatment naïve or on top of an ERA or prostanoids. Subjects were randomised into one of the three study arms (4:2:1) to receive riociguat TID as an individual dose titration (IDT, between 1.0 mg and 2.5 mg TID) or Riociguat 1.5 mg Capped Titration Arm or placebo TID.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks not applicable On-going	
Hypothesis	Superiority of riociguat over placebo			
Treatments groups	Riociguat		riociguat 1-2.5 mg tid n= 254 riociguat 1-1.5 mg tid n=63	
	Placebo		Placebo, n=126	
Endpoints and definitions	Primary endpoint	6MWD	Change from baseline in 6MWD after 12 weeks.	
	Secondary endpoint	Change from baseline in PVR, NT-proBNP, WHO functional class , TTCW, Borg CR 10 Scale or Modified Borg Dyspnoea Scale, EQ-5D questionnaire and in Living with Pulmonary		
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Full analysis set (all randomised patients), Intention to treat 12 weeks			
Descriptive statistics and estimate variability	Treatment group		Riociguat	Placebo
	Number of subjects		N = 218	N = 106
	6MWD (m) change from baseline to last visit SD		 29.6 65.8	 -5.6 85.5
	PVR [dyn s cm^{-5}] change from baseline to last visit SD		(n=232) −223.3 260.1	(n=107) -8.9 316.6
	NT-proBNP (pg/mL) change from baseline to last visit SD		(n=228) −197.9 1721.3	(n=106) 232.4 1011.1
	TTCW		N= 254 2.3%	N= 125 5.7%
Effect estimate per comparison	Primary endpoint	6MWD	riociguat/placebo	
		ANCOVA treatment difference	35.78 (20.06 - 51.51)	
		P-value	<0.0001	
	Secondary endpoint	PVR	-226 (-281 to -170) p <0.0001	
		NT-proBNP	-432 (-782 to -82) p <0.0001	
		WHO FC	20.9% riociguat 14.4% placebo p 0.0033	
		TTCW Borg CR 10 Scale	2.3% riociguat 5.7% placebo p 0.0046 -0.4 riociguat 0.1 placebo p 0.0022	

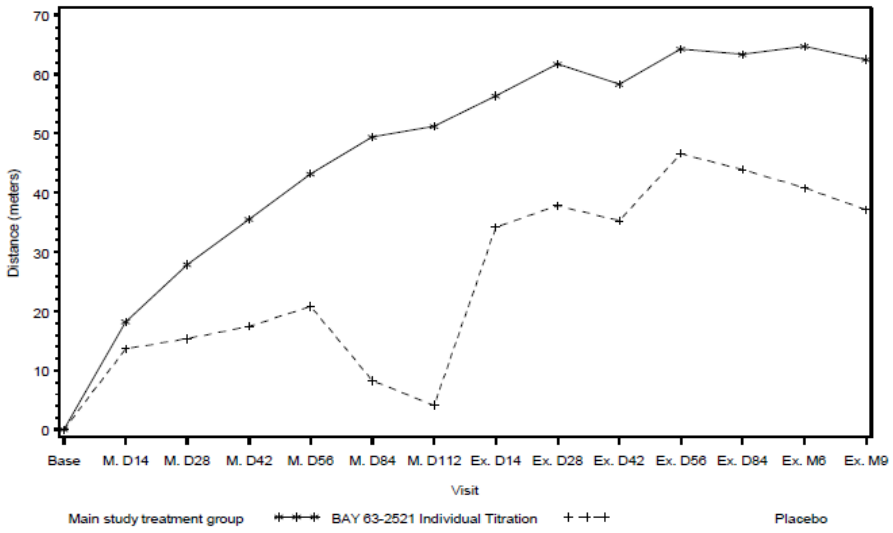
2.5.3. Supportive studies

Study 11349 (CHEST-2)

Study 11349 (CHEST-2) is an on-going Phase III, open-label, multi-centre, multinational, extension study of the long-term safety and efficacy of oral riociguat in subjects with CTEPH. At the end of study CHEST-1 subjects who had completed the double-blind part could be entered into study CHEST-2. The study includes an interim analysis which comprises 194 subjects (long-term safety analysis set): 129 subjects from the former riociguat IDT group and 65 from the former placebo group. Twelve patients had prematurely discontinued study medication at the time of the visit cut-off (03 May 2012) for the interim analysis. The most frequent primary reason was death (5/194 [2.6%]).

The mean change in 6MWD from baseline in study 11348 to week 12 of study 11349 (last observation by week 12; 28 weeks total in/on study for 11348 + 11349) was 63.3m in the former riociguat group and 35.3 m in the former placebo group. Mean change from baseline in study 11348 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 E7).

Figure E7: Mean change from baseline in 6 minute walking distance by visit (Long-term safety analysis set from study 11349 [CHEST-1])

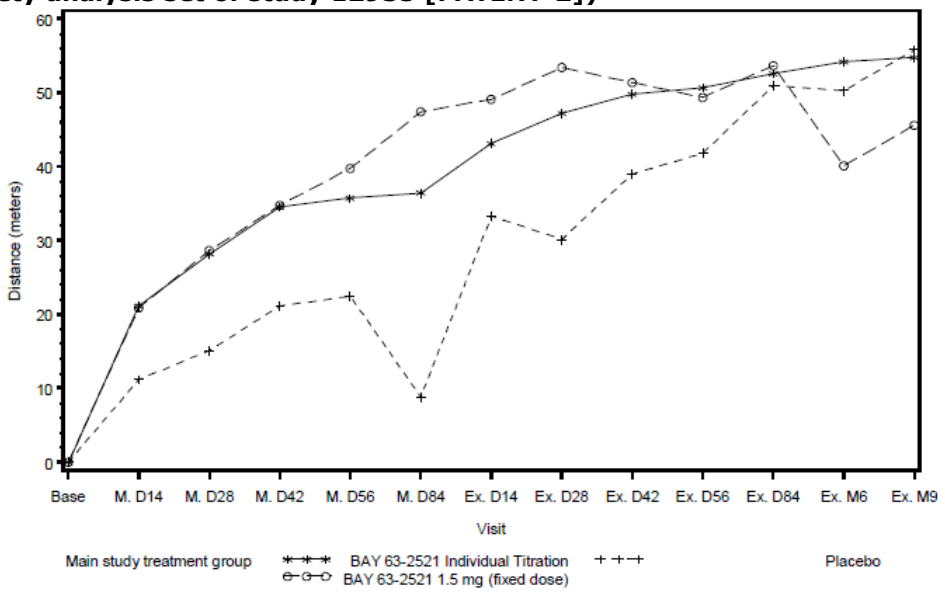


Study 12935 (PATENT-2)

Study 12935 (PATENT-2) is an on-going Phase III, open-label, multi-centre, extension study of the long-term safety and efficacy of oral riociguat in subjects with PAH. At the end PATENT-1, subjects who had completed the double-blind part could be entered into study PATENT-2. This interim analysis comprises 363 subjects (long-term safety analysis set): 215 subjects from the former riociguat IDT group, 52 subjects from the former riociguat capped titration group and 96 subjects from the former placebo group. Fifty-five patients had prematurely discontinued study medication at the time of the visit cut-off (16 April 2012) for the interim analysis, most of them either due to adverse event (55/363 [7.2%]) or due to death (14/363 [3.9%]).

The mean change in 6MWD from baseline in study 12934 to week 12 (last observation until week 12) in study 12935 (24 weeks on-study for 12934 + 12935) was 45.0 m in the former riociguat IDT group and 36.5 m in the former placebo group. Mean change from baseline in PATENT-1 for the total group (N=363) was 51.2 m at 6 months (n=289), 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 E8).

Figure E8: Mean change from baseline in 6 minute walking distance by visit (Long-term safety analysis set of study 12935 [PATENT-2])



2.5.4. Discussion on clinical efficacy

Dose response studies

The choice of the dose range of 1.0 mg to 2.5 mg t.i.d to be further investigated in phase II/III studies was based on the results shown in healthy subjects and the proof of concept study. Dose titration is necessary in order to improve tolerability (e.g. hypotension) and also takes into consideration the large inter-individual variability in PK. Dose selection is based on systemic blood pressure response. As pointed out in the SA procedure EMEA/H/SA/814/I/2006/III, this approach takes tolerability mainly into consideration but does not identify the least effective dose. A dose based on the response of the pulmonary haemodynamics or 6MWT would have been considered a more feasible approach to investigate the efficacy of riociguat. However, it is recognised that dosing based on systemic blood pressure response was employed in other PAH trials, and therefore the use of systolic blood pressure as a surrogate for the titration endpoint was accepted.

Patients with CTEPH

In CHEST-1, treatment with riociguat IDT for CTEPH resulted in a significant and clinically relevant improvement in 6MWD from baseline to week 16 (last observation until week 16) as compared to placebo in the ITT analysis set (45.69 m; 95% CI: 24.74 m to 66.63 m; p<0.0001). The robustness of the result is confirmed by the per protocol analysis which showed comparable results and sensitivity analyses. The placebo corrected increase of walking distance of 45.69 m is

in line with increases reported in early PAH studies. The results are also more convincing compared to those reported with bosentan using a comparable study design and resulting in a placebo corrected increase of walking distance of only 2.2 m (BENEFIT, Jais et al, JACC 2008; 52: 2127-34). A non-significant increase of +18 m was reported with sildenafil in yet another study (Suntharalingam et al., Chest 2008).

Benefits shown for the postoperative CTEPH (26.72 m; 95% CI: -9.68 - 63.13) appear to be of a lesser magnitude compared to the inoperable CTEPH (53.92 m; 95% CI: 28.53 - 79.31) in the 6 MWT, and also in the PVR. The Applicant explained that this smaller gain in 6MWD in patients with the postoperative CTEPH compared to inoperable CTEPH is still of clinical importance especially as other secondary efficacy parameters corroborate the benefit seen. There was no difference between postoperative and inoperable patients with respect to change in WHO FC. Albeit changes in NT-pro BNP were favourable, these are not an accepted surrogate for clinical benefit. The applicant has discussed baseline characteristics such as PVR and location of thrombi which could influence the results. Accordingly, it is agreed that confounding by indication may confuse the interpretation of the results, as (1) subjects that are selected for surgery are different from all (inoperable) CTEPH patients and (2) subjects that do not respond well to surgery are different from all surgically treated patients. Considering the overall positive result, the consistency in both subgroups, the expected higher variability of results in subgroups and the consistent results in secondary endpoints, it is agreed that patients with postoperative CTEPH should not be excluded from the overall indication in patients with CTEPH.

In a re-analysis of the data, the applicant presented the results of WHO FC II and III separately. As expected, patients with less severe disease have a smaller gain than patients with more advanced disease: with a least square difference in favour of riociguat of 25.4 m (95% CI: -9.9 to 60.6) for WHO FC II at baseline compared to 56.0 m (95% CI: -29.4 to 82.6) for patients with WHO FC III. This limited efficacy was not further supported by improvements in WHO status or improvement in clinical worsening events; although for PVR and NT pro-BNP the benefits were almost equal for WHO FC II and III.

The applicant attributes the differences at least in part, due to improvements in the WHO II placebo group. The placebo group improved in FC II (+19m) but worsened in FC III (16.9m), while the changes in the active groups were similar (+45.3m and +37.8m respectively). If non-specific effects of placebo are more relevant in WHO II, the treatment effect is actually lower. Similarly, in PATENT-1, efficacy in terms of 6MWT was limited in patients with WHO FC II. Please see the discussion on WHO FC II below.

Female CTEPH subjects showed a higher estimated treatment effect in analyses by gender compared to male subjects (54.21 m; 95% CI: 27.73 m to 80.70 m vs. 39.80 m; 95% CI: 8.60 m to 71.00 m). Summary statistics showed that male CTEPH subjects treated with placebo showed an increase in 6MWD although having relatively high baseline values. The treatment group by gender interaction test did not indicate that the observed difference in 6MWT between men and women is significant. Even in case where a true difference in the effect on the 6MWD was observed, such a difference was not reflected in relevant secondary endpoints as change in WHO class. Overall the data are consistent with a clinically relevant effect in male and female patients.

The reported results of the secondary endpoints further support the benefits shown in the 6MWT. Pulmonary haemodynamics are improved; specifically PVR shows a reduction of around 30%. This is line with results observed with bosentan (around -24%) (Jais et al., 2009) and sildenafil (around -27%) (Suntharalingam et al., 2008).

Patients with PAH

PATENT-1 investigated riociguat in the treatment of PAH. In this trial, the inclusion of both treatment naïve patients and patients on other PAH therapies was already a point of discussion in the scientific advice given to the Applicant in 2008. It was communicated to the Applicant that the inclusion of both these populations in one study is not encouraged as the benefit/risk assessment in each population could differ. As there is lack of authorised combination therapies, this would have been the preferred subgroup to be examined. Surprisingly, the estimate for the primary efficacy outcome in pre-treated and naïve patients was quite similar.

The study design follows that of pivotal studies that were the base of registration of the available medicinal products, e.g. bosentan, sildenafil and ambrisentan. This design was considered adequate at that time, but is becoming obsolete nowadays. Improvement of exercise capacity is still acceptable in the CHMP guideline (EMEA/CHMP/EWP/356954/2008) as an evidence of efficacy; however, this should be demonstrated in a comparative design and not placebo-controlled. For the treatment naïve patients, there are already around seven medicinal products; the investigation of a new medicinal product using the 6MWT with a placebo comparator raises ethical concerns. Besides withholding an effective therapy, it is observed that even when these placebo patients are switched to the active therapy in the long term extension studies, a lag in response is noticed compared to the patients randomised to the active arm from the beginning.

In the latest scientific advice requested by the company, following the publishing of the above guideline, it was clarified that the 6MWT was still a valid endpoint, however, investigations of clinical outcomes would be more relevant and TTCW should have been the preferred choice as primary or key secondary endpoint.

The estimated overall treatment effect from the ANCOVA was 35.78 m (95% CI: 20.06 m to 51.51 m). The per protocol analysis showed comparable results (estimate of 33.52, 95% CI: 18.99 m to 48.04 m). Further sensitivity analyses confirmed the results of the main analysis. This increase is also considered clinically relevant as it compares to results of pivotal studies of registered products for PAH.

In PATENT-1 the LS mean difference of the treatment effect for PVR was –225.72 $dyn \cdot s \cdot cm^{-5}$. The reduction in PVR was of the same magnitude as reported for sildenafil (SUPER: -122 to -261 in the active groups; tadalafil (PHIRST: -254 to -209), and bosentan (EARLY: -141). These results are comparable, taking into account the inherent difficulties of cross comparison between trials. Improvements are also shown in relevant subgroups like treatment naïve/pre-treated patients, WHO II/WHO III and PAH due to different aetiologies, though with variable degrees. Other pulmonary and systemic haemodynamic parameters were also affected.

The improvement in TTCW also reached statistical significance (riociguat: 3 events (1.2%), placebo 8 events 6.3%). This result was mainly driven by lesser hospitalisations and starting of new PH medications.

Significant improvements were also seen in NT-proBNP, WHO FC, and Borg CR 10 score. These results further support the primary efficacy endpoint.

WHO FC II (CTEPH and PAH).

In order to determine efficacy in this subgroup, the applicant was requested to further analyse the data regarding benefits in treatment naïve vs. patients on combination therapy (PATENT-1), and inoperable vs. post-operative CTEPH (CHEST-1). Long term data of these patients were also considered. Analysis did not reveal consistent results, with wide confidence intervals, which could be expected from the limited number of patients, the un-even distribution at baseline (which could be a chance finding) and the *post hoc* nature of the analysis. Also some subgroups showed unexplained placebo responses. However, clinical trial experience indicates that it is always difficult to show robust improvements in such patients as the margin in improvement is limited. Also, there was quite some improvement in the placebo group limiting the difference and there are wide confidence intervals in the results. In fact maintaining a patient to FC II is a goal of PAH therapy. It also does not appear plausible that riociguat would only work in the more ill patients and it can be assumed that at least in some less diseased patients a beneficial effect may occur. Considering that patients can shift between FC II and III, it does not appear practical to specifically exclude FC II patients from the indication; this would probably only lead to the off-label use of the drug in this subgroup. The proposed indication reflects the studied subgroups which were mainly FC II and III, rather than the efficacy shown in each subgroup (which is discrepant depending on the subgroup). There is a cross reference to section 5.1, where the results are described, allowing the prescriber to make an informed decision.

2.5.5. Conclusions on the clinical efficacy

Efficacy of riociguat in CTEPH and PAH is supported mainly by two pivotal studies in adult patients, and their long-term extensions. There are no data in children. The starting dose of 1 mg three times daily up to maximum total daily dose of 7.5 mg were seen to be well tolerated. However, in some PAH patients it cannot be excluded that lower doses (1.5 mg three times a day) would still be effective. This is mentioned in section 4.2 of the SmPC. Significant efficacy is observed in terms of improvement in exercise capacity; which although accepted in the relevant guideline is not the preferred endpoint due to lack of correlation with clinical outcomes. However, CHEST-1 is the only study to demonstrate a significant benefit for a pharmacological therapy for inoperable and persistent CTEPH after operation.

In PAH, PATENT-1 showed the efficacy of riociguat as monotherapy and in combination, mainly on top of ERAs. The results pertaining combination therapy are especially important.

In conclusion the CHMP agreed to grant an indication in both CTEPH and PAH populations.

2.6. Clinical safety

Main safety information for riociguat is based on the pivotal studies (CHEST-1 and PATENT-1; POOL-1 DB) and their on-going long term extensions (CHEST-2 and PATENT-2; POOL-1 LTE; cut-off date April/May 2012). In addition, pooled analysis of studies conducted in CTEPH and PAH was done and forms POOl-2. POOl-3 represents safety data from all completed phase II and

phase III clinical studies. In this report, focus is given on the analysis of POOL-1, in addition to results of each pivotal study. Reference is also made as appropriate to the other safety data.

2.6.1. Patient exposure

Safety data are presented per study and also as pooled data. Pooling of the main clinical studies CHEST-1 and PATENT-1 is supported due to the somewhat comparable patient populations. Controlled data are available for 490 patients administered riociguat compared to 214 patients administered placebo for at least 12 weeks (table S1). Although these numbers are limited, this safety database can be accepted in an orphan indication. Long term exposure (around one year) data available for 557 patients are considered adequate to assess long-term safety. These studies are on-going.

Table S1: Total number of subjects in the safety population: POOL- 1

Study	CHEST-1 and PATENT-1				CHEST-2 and PATENT-2	
Duration of treatment	Riociguat		Placebo			
N (= 100%)	490		214		557	
Duration of treatment (categ						
0–7 days	7	(1.4%)	5	(2.3%)	1	(0.2%)
8–21 days	8	(1.6%)	2	(0.9%)	2	(0.4%)
22–35 days	6	(1.2%)	3	(1.4%)	4	(0.7%)
36–49 days	6	(1.2%)	3	(1.4%)	1	(0.2%)
50–63 days	6	(1.2%)	5	(2.3%)	26	(4.7%)
64–91 days	286	(58.4%)	110	(51.4%)	52	(9.3%)
92–180 days	171	(34.9%)	86	(40.2%)	69	(12.4%)
181–270 days	0	–	0	–	65	(11.7%)
271–360 days	0	–	0	–	49	(8.8%)
361–450 days	0	–	0	–	48	(8.6%)
451–540 days	0	–	0	–	48	(8.6%)
541–630 days	0	–	0	–	55	(9.9%)
631–720 days	0	–	0	–	43	(7.7%)
721–810 days	0	–	0	–	40	(7.2%)
811–900 days	0	–	0	–	38	(6.8%)
901–990 days	0	–	0	–	13	(2.3%)
991–1080 days	0	–	0	–	3	(0.5%)
Duration of treatment (days)						
N with data	490		214		557	
Mean (SD)	90.7 (22.3)		91.4 (24.1)		422.8 (272.5)	
Median (Min–Max)	86.0 (1–130)		86.5 (1–126)		369.0 (1–1079)	

Patient exposure is further summarised in Table S2.

Table S2 Exposure of patients

	Patients enrolled	**Patients exposed** [a]	**Patients exposed** [a] **to the proposed dose range**		**Patients with long-term safety data**	
			At least 12 weeks	At least 16 weeks	**6 months** [b]	**12 months** [b]
Placebo-controlled studies [c] **in the applied indications**	1056	439 (100%)	371 (84.5%)	130 (29.6%)		

(11348, 12934, 15096)						
All placebo-controlled studies [d] (11348, 12934, 14308, 15096)	1420	634 (100%)	533 (84.1%)	222 (46.3%)		
Active-controlled	N/A					
Open studies (LTE)						
Pool 1 – submitted [e]		557 (100%)			443 (79.5%)	319 (57.3%)
Pool 1 - day 120 update [f]		633 (100%)			604 (95.4%)	515 (81.4%)
Pool 3 – submitted [e]		642 (100%)			505 (78.7%)	376 (58.6%)

2.6.2. Adverse events

The system organ class (SOC) disorders mostly seen and with a higher rate of reported adverse events in the riociguat treatment group were gastrointestinal disorders (53% riociguat vs. 35% placebo) and nervous disorders (46% vs. 33%). The most frequently reported adverse events with a higher rate in the riociguat treatment group were headache (27% vs. 17%) followed by dizziness (19% vs. 12%) and dyspepsia (18% vs. 8%) (see table S3). This profile is in line with the mechanism of action as a vasodilator.

Table S3: Summary of adverse events

Incidence of	Inoperable CTEPH Riociguat (N=121)	Inoperable CTEPH Placebo (N=68)	Postoperative CTEPH Riociguat (N=52)	Postoperative CTEPH Placebo (N=20)	Therapy naive Riociguat (N=328)	Therapy naive Placebo (N=154)	Combination ERA Riociguat (N=138)	Combination ERA Placebo (N=53)	Overall Pool Riociguat (N=490)	Overall Pool Placebo (N=214)
Any AE rel. death	0.8%	4.4%	1.9%	0%	1.2%	2.6%	0.7%	1.9%	1.0%	3.3%
Any TEAE	89.3%	89.7%	98.1%	75.0%	89.6%	85.7%	92.8%	86.8%	90.6%	86.0%
Any drug-rel. TEAE	57.9%	45.6%	63.5%	25.0%	59.5%	44.2%	70.3%	56.6%	62.0%	47.7%
Any TESAE	17.4%	16.2%	25.0%	15.0%	14.6%	14.3%	15.9%	22.6%	15.1%	17.3%
Any drug-rel. TESAE	2.5%	1.5%	5.8%	0%	2.7%	1.9%	4.3%	3.8%	3.3%	2.8%
Any AE resulting in disc. of study drug	3.3%	2.9%	1.9%	0%	3.0%	5.2%	2.2%	3.8%	2.9%	5.1%
Top 5 TEAEs (PTs) of the overall pool reported for riociguat treated subjects plus hypotension										
Headache	21.5%	11.8%	32.7%	20.0%	24.4%	11.7%	34.1%	34.0%	26.9%	17.3%
Dizziness	22.3%	11.8%	23.1%	15.0%	18.3%	11.7%	20.3%	15.1%	19.2%	12.1%
Dyspepsia	16.5%	8,8%	21.2%	5.0%	18.6%	7.8%	17.4%	7.5%	17.8%	7.9%
Oedema peripheral	14.0%	22.1%	19.2%	15.0%	16.2%	16.9%	21.0%	9.4%	17.3%	15.0%
Nausea	7.4%	8.8%	19.2%	5.0%	11.9%	8.4%	18.8%	15.1%	14.1%	10.7%
Hypotension	10.7%	4.4%	5.8%	0%	9.5%	1.9%	5.8%	5.7%	8.8%	2.8%

Table S4: Most frequent treatment-emergent adverse events and their assessment for drug-relationship (safety analysis set from controlled clinical studies in the claimed indication)

MedDRA Preferred term	TEAE All riociguat (double-blind studies) N = 490	TEAE assessed as drug-related All riociguat (double-blind studies) N = 490	TEAE All placebo (double-blind studies) N = 214	TEAE assessed as drug-related All placebo (double-blind studies) N = 214
Any adverse event	444 (90.6%)	304 (62.0%)	184 (86.0%)	102 (47.7%)
Headache	132 (26.9%)	93 (19.0%)	37 (17.3%)	26 (12.1%)
Dyspepsia	87 (17.8%)	70 (14.3%)	17 (7.9%)	15 (7.0%)
Dizziness	94 (19.2%)	63 (12.9%)	26 (12.1%)	26 (12.1%)
Nausea	69 (14.1%)	38 (7.8%)	23 (10.7%)	13 (6.1%)
Hypotension	43 (8.8%)	38 (7.8%)	6 (2.8%)	2 (0.9%)
Peripheral oedema	85 (17.3%)	20 (4.1%)	32 (15.0%)	12 (5.6%)
Vomiting	50 (10.2%)	20 (4.1%)	14 (6.5%)	4 (1.9%)
Diarrhoea	58 (11.8%)	19 (3.9%)	17 (7.9%)	11 (5.1%)
Palpitations	31 (6.3%)	19 (3.9%)	10 (4.7%)	5 (2.3%)
Gastrooesophageal reflux disease	25 (5.1%)	19 (3.9%)	4 (1.9%)	3 (1.4%)
Dyspnoea	28 (5.7%)	5 (1.0%)	26 (12.1%)	4 (1.9%)
Chest pain	29 (5.9%)	3 (0.6%)	15 (7.0%)	1 (0.5%)
Anemia	28 (5.7%)	3 (0.5%)	4 (1.9%)	1 (0.5%)
Nasopharyngitis	58 (11.8%)	0	22 (10.3%)	0

In general, the profile of drug-related AEs is similar to the profile of adverse events overall (table S4). The exceptions are the PTs dyspnoea, chest pain, anaemia and nasopharyngitis, which the investigators mostly assessed as not drug-related.

The incidence rate of AEs in the long-term extension studies was 91%. The most common AEs were nasopharyngitis (21%), dizziness (18%), peripheral oedema (17%), diarrhoea (13%), cough (13%), headache (13%), nausea (11%), and dyspepsia (10%).

The rate of riociguat nasopharyngitis reported with riociguat is comparable to those seen with ERA treatment. Nasal congestion is a typical event related to mode of action, and was identified as an ADR for riociguat. Nasopharyngitis per se is an infectious disease, and considered implausible to be caused by riociguat. Notably, nasopharyngitis was reported for over 10% of placebo subjects. The imbalance for nasopharyngitis reported as an adverse event for PATENT-1 and CHEST-1 might be caused by a certain degree of misreporting, e.g. if a patient had the feeling of a "stuffed nose" under verum caused by nasal congestion.

The rate of common adverse events per 100 person years during long-term treatment was lower than in the initial double-blind treatment phase; this probably indicates some adaptation to the haemodynamic changes induced by riociguat. However, the rate of pulmonary artery hypertension AEs increases during the long-term treatment phase from 2 events/100 person years in the riociguat treatment group during double-blind treatment (4 events/100 person years in the placebo group) to 7 events/100 person years. The incidence rate of adverse events reported as of severe intensity was higher during the long-term extension phase (22%) than reported in the riociguat treated subjects during the shorter double-blind treatment phase (11%).

2.6.3. Serious adverse events and deaths

2.6.3.1. SAEs

In POOL-1 DB, serious adverse events SAEs were reported for 15% of the riociguat groups and for 17% of placebo patients. The most common serious adverse events with an incidence rate ≥ 1% were syncope (1.4% [7/490] riociguat vs. 3.7% [8/214] placebo), right ventricular failure (2.2% [11/490] riociguat vs. 1.9% [4/214] placebo), and haemoptysis (1.0% [5/490] riociguat vs. 0% [0/214] placebo)(see table S5).

Table S5: Serious TEAEs: Most frequent MedDRA preferred terms – safety population of controlled Phase III studies

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	–

Specifically in CHEST-1, serious pulmonary hypertension and respiratory failure were more frequent in the riociguat-group than in placebo-group. Clarification of "deterioration of pulmonary

function" is based on an analysis of the occurrence of serious adverse events in the MedDRA SOC "Respiratory, thoracic and mediastinal disorders", for which 4 events were seen in the riociguat group compared to none in placebo. A detailed by-case evaluation revealed no identifiable reason for deterioration of respiratory function, apart from clinical worsening which is not uncommon in this patient population on the background of the disease and/or comorbidities. The serious TEAEs (PT) pulmonary hypertension were reported in 2 (1.2%) patients in riociguat versus 0 in placebo and serious respiratory failure events were reported in 2 (1.2%) patients in riociguat vs. 0 in placebo. A total of 4 patients experienced these SAEs, all in the riociguat arm. These events are generally expected in these patients, and the results of the TTCW analysis support that disease progression was not accelerated in the riociguat group.

Although the incidence of SAE appears comparable in both groups, there are a number of serious events that appear only in the riociguat treatment arm: haemoptysis (n=5) and acute renal failure (n=3) (see later). The rest of the reported serious events appear to be in line with the vasodilatation profile of riociguat.

The number of SAEs in the respective long-term extension studies was 36% and approximately two-fold higher than for any of the treatment groups during the shorter double-blind treatment phase. This is normalised if treatment duration is taken into consideration (event rate per 100 person years: 92 in all riociguat vs. 103 in placebo POOL-1 DB and 65 in riociguat POOL-1 LTE). The most common SAEs with an event rate of at least 2% from the long-term extension were syncope (5.4%), pulmonary arterial hypertension (4.5%), right ventricular failure (4.1%), pulmonary hypertension (2.9%), cardiac catheterisation (2.7%), and pneumonia (2.0%). The event rate per 100 person years increased for the PTs pulmonary arterial hypertension, right ventricular failure, pulmonary hypertension, and cardiac catheterisation.

2.6.3.2. Deaths

In POOL-1 DB, the incidence rate of death was numerically higher in the placebo group (3.3%; 7/214) compared to riociguat treated patients (1.0%; 5/490).

In CHEST-1, two deaths were reported in the riociguat group: one case was attributed to cardiac failure. The other case had an acute renal failure and deterioration of right heart failure complicated thereafter by a haemorrhage from the catheter site of the haemodialysis and consecutive anaemia. The subject died ten days after onset of renal failure. The investigator classified death as caused by renal impairment, bleeding and anaemia. In the placebo group three deaths were reported: cardiac arrest (n=2), and cardiopulmonary failure (n=1).

In PATENT-1, three deaths in the riociguat group were reported: one due to sepsis (riociguat IDT group), one due to right ventricular failure and pulmonary arterial hypertension (riociguat capped titration group) and one case due to haemoptysis. The subject had one event of haemoptysis already directly prior to enrolment in the study, another one two days after start of study medication with outcome resolved, was continued in the study and had a third event with fatal outcome 55 days after start of study medication. The investigator assigned death to haemoptysis. In the placebo group, the following causes were reported: pulmonary arterial hypertension (n=1), anxiety (n=1), and respiratory failure and circulatory collapse (n=1). (One patient on placebo died in PATENT-2).

During the long-term extension phase (mean treatment duration 14 months) 23/557 (4.1%) deaths were reported. The majority of deaths were sequelae of the underlying disease which include right ventricular failure (1), cardiac failure chronic (1), cardiac failure (1), pulmonary hypertension (5), pulmonary arterial hypertension (3), pneumonia (2), pulmonary haemorrhage (3), cardiac arrest (3), sudden cardiac death (1), cardiogenic shock (1) and shock (1) – note that more than one event could have a fatal outcome.

2.6.4. Adverse events of special interest

1. Hypotension

Hypertension was identified as an adverse event linked to the mode of action and was also used to guide the individual dose titration. Overall, treatment-emergent hypotension events (documented as AE or recorded SBP<90 mmHg) were reported in 23.3% of subjects in the pooled riociguat group and 12.1% in the pooled placebo group. Most of the treatment-emergent hypotension events were non-serious: hypotension (AE or SBP<90 mmHg) was reported as a serious TEAE in only two subjects (0.4%) in the riociguat group. Only one discontinuation due to hypotension as a TEAE was reported, also in the riociguat group. Comparing the rates recorded in the riociguat IDT with the capped titration (AR; table S4), an advantage in the incidence of hypotension is observed with the lower dose (3.2% capped dose vs. 9.8% with the IDT). This shows that even if patients can tolerate the higher doses by titration, they are still at risk of AEs related to hypotension during drug administration.

For age subgroups, the difference in incidence of hypotension (AE or SBP<90 mmHg) between the treatment groups was larger in the ≥75 years subgroup (29.5% for riociguat vs. 10.0% for placebo) than overall; in this subgroup hypotension was not reported as a serious TEAE, and no subjects discontinued study medication due to hypotension (AE or SBP<90 mmHg).

For renal function subgroups, the incidence of hypotension (AE or SBP<90 mmHg) in the pooled riociguat group was higher in subjects with moderate renal impairment (baseline eGFR (≥ 30 to <50 mL/min) than overall, and the difference in incidence between the treatment groups was larger in this subgroup (31.6% for riociguat vs. 8.3% for placebo) than overall. A smaller difference between treatment groups was observed in subjects with mild renal impairment (baseline eGFR (CGF) ≥50 to <80 mL/min): 23.3% for riociguat vs. 14.7% for placebo. These subgroups appear to be more vulnerable to the hypotensive effect of riociguat than other and such risk is highlighted in SmPC section 4.4. In addition, as the clinical studies excluded patients with SBP below 95 mm Hg and due to the risk of hypotension, this is currently a contraindication in the SmPC (this is also in line with the SmPC of sildenafil and tadalafil).

For subgroups on combination therapy, the difference in incidence of hypotension (AE or SBP<90 mmHg) between the treatment groups was smaller in the ERA pre-treated subgroup (21.7% for riociguat vs. 17.0% for placebo) than in the other subgroups for pre-treatment. The overall incidence of hypotension (AE or SBP<90 mmHg) in the pooled riociguat group was higher in subjects pre-treated with PCA (40.9%) than in subjects pre-treated with ERA (21.7%), but the total number of subjects in the pre-treated with PCA subgroup was small.

There could be some adaptation to the vasodilatory effects as shown by a lower incidence of AE in the longer term (15 events per 100 person years for placebo during double-blind treatment vs. 7 for all riociguat in LTE). For further discussion see the section "Discussion on clinical safety" of this report.

2. Syncope

Syncope can be a sign of the disease or related to the drug (e.g. through hypotension). Overall, syncope was reported in a slightly lower rate in the pooled riociguat group (n=16; 3.3%) compared to the pooled placebo group (4.7%). These events were assessed as serious in eight subjects (1.6%) in the pooled riociguat group and ten subjects (4.7%) in the pooled placebo group. Two subjects discontinued study medication because of syncope TEAEs (one with riociguat and one with placebo).

The overall rate of syncope declined in the pooled LTE studies (8.06 events per 100 person years in the LTE compared to 14.79 events per 100 person years for riociguat, 20.55 for placebo in the DB phase). Syncope events were assessed as serious in 31 subjects (5.6%). No subject discontinued study medication because of a syncope TEAE. The vast majority of subjects in both treatment groups had a single syncope event. Syncope events were not related to drug exposure or a change of riociguat dose during the titration phase, thus not directly connected to the intake of riociguat. Many of the syncope events occurred as exertional syncopes, which is typically observed in subjects with PH. There is no indication that syncope should be regarded as an adverse drug reaction related to administration of riociguat, as such syncope is not listed in section 4.8 of the SmPC.

3. Bleeding events

The overall incidence rate of bleeding events in all riociguat treated subjects 15.7% (77/490) was comparable to placebo subjects in POOL-1 14.5% (33/214). Most of the subjects in both groups had an outcome of recovered or resolved. However, SAEs (12/490 [2.4%] riociguat vs. none placebo), AE related deaths (2/490 [0.4%] riociguat vs. none placebo) and discontinuations due to AE (2/490 [0.4%] riociguat vs. none placebo) were reported for the riociguat group only. The two death cases comprise one subject with haemoptysis and one subject with catheter site haemorrhage. The investigators assessed both fatal events as not related to the study medication. The most frequent TE bleeding events in the pooled controlled studies were:

- Riociguat treatment group: epistaxis (2.9%), haemoptysis (2.0%), haematoma (1.2%), vaginal haemorrhage (0.8%), gingival bleeding (0.6%).
- Placebo treatment group: epistaxis (1.4%), haematoma (1.4%), conjunctival haemorrhage (0.9%), puncture site haemorrhage (0.9%), vessel puncture site haemorrhage (0.9%), menorrhagia (0.9%), and haemoptysis (0.9%).

Haemoptysis, reported with riociguat at a rate of 2.0% (10/490) vs. the placebo rate of 0.9% (2/214), was assessed as SAE in riociguat treated subjects only (5/490 [1.0%] riociguat vs. none placebo). One subject had a fatal outcome (see before), all other events had an outcome of recovered or resolved. During LTE additional 21/557 events were reported, 7 of them assessed as SAEs, 18 of them with an outcome of recovered or resolved and 3 not recovered or resolved.

In terms of the event rate per 100 person years haemoptysis decreased during the LTE phase (9 events per 100 person years in all riociguat vs. 6 in placebo and 5 for all riociguat during LTE). In POOL-3 haemoptysis was reported as AE in 13/754 (1.7%) riociguat vs. 2/289 (0.7%) placebo) and as SAEs in 5/754 (0.7%) riociguat vs. none placebo. No additional fatal outcome occurred in POOL-3; all other events had an outcome of recovered or resolved. During LTE additional 24/642 events were reported, 9 of them assessed as SAEs, 20 of them with an outcome of recovered or resolved and 4 not recovered or resolved. In terms of the event rate per 100 person years haemoptysis decreased during the LTE phase (8 events per 100 person years in all riociguat vs. 4 in placebo and 4 for all riociguat during LTE).

Pulmonary haemorrhages were reported with an incidence of 3/642 [0.5%] in POOL-1, all of them occurred during the long-term extended treatment; all of them had a fatal outcome. The data of POOL-3 did not contain additional events of pulmonary haemorrhage.

The Applicant informed the CHMP about this bleeding risk through a safety communication in November 2012. Investigators involved in the LTE studies were informed as well. These events are reported in both PAH and CTEPH.

For further discussion see the section "Discussion on clinical safety" of this report.

4. Anaemia

Anaemia was reported with a higher rate in the riociguat group (7.8% [38/490]) compared to placebo (1.9% [4/214]) (POOL-1 DB). This is reflected in the observed decrease of haemoglobin (approximately 0.5 mg/dL whereas the values in the placebo group remained stable) and of haematocrit (approximately 2% whereas the values in the placebo group remained stable). The decrease seen during the double-blind period tended to be lower during the LTE phase (23 events per 100 person years in all riociguat vs. 9 in placebo and 7 for all riociguat during LTE).

For further discussion see the section "Discussion on clinical safety" of this report.

5. GI disorders

GI disorders were reported in a higher frequency in the riociguat pool (255/490; 52%) compared to the placebo pool (72/214; 34%) in POOL-1 DB. AEs leading to discontinuation were reported in the riociguat group at 2/490 [0.4%] compared to 1/214 [0.5%] in placebo. The most frequent PTs with a higher rate in riociguat group compared to placebo were: dyspepsia (18% riociguat vs. 8% placebo), nausea (14% vs. 11%), diarrhoea (12% vs. 8%) and gastro-oesophageal reflux disease (5% vs. 2%). Serious cases of gastritis were only recorded in the riociguat group in POOL-1 DB.

Gastrointestinal disorders as SOC were observed both in riociguat and placebo groups. Serious adverse events of gastritis (4x) and bleedings (2x) as treatment-emergent SAEs were observed only in riociguat treated patients.

For further discussion see the section "Discussion on clinical safety" of this report.

6. Atrial fibrillation

Atrial Fibrillation was reported in a higher rate in the riociguat pooled arm [5/490 (1.0%) vs. none placebo in POOL-1 DB, and more so in POOL-3 (riociguat:13/754; 1.7% vs. none in placebo). AF was assessed as SAE in 4 out of the 13 events. In both long-term extension studies, CHEST-2 and PATENT-2, AF was observed at lower rate per 100 person years than during the double-blind phase (10/100 person years for all riociguat during double-blind treatment vs. 2/100 for all riociguat in LTE).

For further discussion see the section "Discussion on clinical safety" of this report.

7. Renal Impairment

There are conflicting data regarding the possible effects of riociguat on renal function. On one hand, analyses of respective laboratory parameters did not indicate a trend for renal function to worsen, but rather a small improvement compared to placebo was seen during the double-blind treatment phase (blood creatinine increased (8/754 [1.1%] for all riociguat and 11/289 [3.8%] for placebo), blood urea increased (3/754 [0.4%] for all riociguat and 7/289 [2.4%] for placebo), and creatinine renal clearance decreased (2/754 [0.3%] for all riociguat and 3/289 [1.0%] for placebo). On the other hand, there was an imbalance for AE relating to serious renal impairment: POOL-1 (3/490 [0.6%] all riociguat for each renal failure and renal failure acute; 2/490 [0.4%] all riociguat for renal failure chronic versus none in placebo subjects for any of these PTs. This imbalance was also apparent in POOL-3 (SAE of renal failure were observed in ten subjects (1.3%) in the riociguat group versus one subject (0.3%) in the placebo group).

For further discussion see the section "Discussion on clinical safety" of this report.

8. Bone disorders

In the repeat-dose toxicity studies, riociguat-related effects on the skeletal system consistent with stimulation of osteoblasts were restricted to juvenile and adolescent rats and mice (see "Non-clinical Toxicology" section of this report). The implications of the adverse effects on bone encountered in growing rats on paediatric patients in whom the epiphysis is not yet closed are not clear. Until more is known, the use of riociguat in children and in growing adolescents should be avoided (see sections 4.2, 4.4 and 5.3 of the SmPC).

According to the Applicant results of serum calcium, phosphate, and 1.25-dihydroxyvitamin D and the biomarkers type I collagen C-telopeptides (CTX) and osteopontin were evaluated in the study program and did not show a clinically meaningful change during treatment and no difference was observed between the riociguat and placebo groups. This view is not totally supported in view of the results of study 13790. In addition, the rate of bone fractures was overall low but was higher in the riociguat-group compared to the placebo-group. This risk is adequately addressed in the RMP as an important potential risk.

9. QT prolongation

No thorough QT study was performed. Pre-clinical data show possible QT prolongation in dogs, but this is considered a consequence of an inadequate correction rather than an intrinsic QT

prolonging effect of riociguat. Pooled analysis of PATENT-1 and CHEST-1 provides data on a sample which comprises 283 riociguat subjects and 100 placebo subjects. Mean changes from baseline do not indicate prolongation of QTcB (e.g. mean change from baseline to week 12/13 of 0 msec in the riociguat group compared to + 2 msec in the placebo group) (table S6) and QTcF (e.g. mean change from baseline to week 12/13 of +1 msec in the riociguat group compared to +1 msec in the placebo group).

Further supportive data regarding the QT assessment come from LEPHT Study (riociguat in patients with PH related to left hear failure). The database is limited (14 subjects of the 0.5 mg riociguat treatment group, 9 subjects of the 1.0 mg riociguat treatment group, 18 subjects of the 2.0 mg riociguat treatment group, and 22 subjects of the placebo group). The mean changes of the QT duration was clinically not different between the treatment groups (as indicated by the mean change from baseline to last visit of -16 msec in the riociguat 2.0 mg group compared to + 5 msec in the placebo group). Similar results were seen for QTcB.

In view of the available data QT prolongation is not considered an adverse drug reaction related to administration of riociguat, and as such is not listed in section 4.8 of the SmPC.

2.6.5. Laboratory findings

Haematology.

Imbalances in the mean changes from baseline to Week 12 were observed for:

- haemoglobin: riociguat group: –0.58 g/dL, placebo group: 0.13 g/dL

- haematocrit: riociguat group: –1.66%, placebo group: 0.45%

For the pooled non-controlled extension studies, changes in group values from baseline were again small for most of the haematology and coagulation parameters. For haemoglobin, mean change from baseline was –0.24 g/dL at Month 9 (n=254) and –0.28 g/dL at Month 21–23 (n=207). For haematocrit, mean change from baseline was –0.62% at Month 9 (n=253) and –0.78% at Month 21–23 (n=207). In the pooled controlled phase III studies, 80/443 subjects (18.1%) in the riociguat group, and 7/190 subjects (3.7%) in the placebo group reported haemoglobin abnormalities. In the pooled non-controlled extension studies, 141/504 subjects (28.0%) reported haemoglobin abnormalities (see above comments on anaemia).

Coagulation

In the pooled controlled phase III studies, imbalances in high laboratory abnormalities (a threefold increase compared to the upper limit of normal range18) were seen for:

- aPTT: riociguat group: 3/172 subjects (1.7%), placebo group: 6/71 subjects (8.5%)

- prothrombin INR: riociguat group: 18/185 subjects (9.7%), placebo group 5/64 subjects (7.8%)

Results are reassuring and do not raise concerns. However, for the pooled non-controlled extension studies, high laboratory abnormalities were reported for aPTT and prothrombin INR:

10/181 subjects (5.5%) reported a threefold increase for aPTT, and 28/200 subjects (14.0%) for prothrombin INR. At follow up, there was still an increase noticed in the terms "INR increased" and "aPTT prolonged" in the LTE compared to data with cut-off May 2013: 2.91 compared to 3.88; 1.91 compared to 2.79 per 100 person-years respectively. As anticoagulation is part of the routine management of PAH and CTEPH patients, the risk of bleeding is adequately reflected in the RMP as an important potential and also included as a warning in section 4.4 of the SmPC.

Vital signs.

Blood Pressure. In the pooled controlled phase III studies, the mean change in SBP at Week 12 was –6.83 mmHg (SD±12.85) in the riociguat group, and –1.80 mmHg (SD±13.14) in the placebo group. For the pooled non-controlled extension studies, the mean change was –4.39 mmHg at Month 9 (n=280), and –3.93 mmHg at Month 21-23 (n=221). The mean DBP change from baseline to Week 12 was –5.91 mmHg (SD±10.20) in the riociguat group, and -0.26 mmHg (SD±10.15) in the placebo group. In the pooled non-controlled extension studies, the mean DBP change from baseline to Month 9 (n=280) was –4.90 mmHg, and –5.24 mmHg at Month 21-23 (n=221) (see comments before in hypotension).

No relevant changes in **heart rate** or **body weight** were observed in the short controlled or longer term extension studies:

Heart rate. In the pooled controlled phase III studies, the mean change from baseline to Week 12 was 0.22 beats/min (SD±10.50) in the riociguat group, and 0.93 beats/min (SD±10.40) in the placebo group. In the pooled non-controlled extension studies, the mean change from baseline to Month 9 (n=280) was 1.33 beats/min, and 0.02 beats/min at Month 21-23 (n=220).

Body weight. The mean change from baseline to Week 12 was –0.30 kg (SD±2.84) in the riociguat group, and 0.26 kg (SD±2.26) in the placebo group. In the pooled non-controlled extension studies, the mean change from baseline to Month 9 (n=277) was –0.57 kg, and –0.55 kg at Month 21-23 (n=221).

ECG. See section QT prolongation, and atrial fibrillation before.

2.6.6. Safety in special populations

Renal impairment

Patients with mild or moderate renal impairment were adequately represented in the pivotal studies. More than 35% (189/490 [39%] for POOL-1 DB and 210/557 [38%] for POOL-1 (LTE) of riociguat treated subjects had mild renal impairment at baseline and approximately 20% (101/490 [21%] POOL-1 DB and 106/557 [19%] for POOL-1 LTE) of subjects had a moderate renal impairment. Event rates for TEAEs, TESAEs and most of the MedDRA PTs did not substantially increase with decreasing renal function in the riociguat treatment group when compared to placebo. Although the dose is individually titrated, there is still a higher incidence of hypotension reported in these patients (see before under hypotension). This is currently reflected as a warning in section 4.4 of the SmPC. Subjects with a creatinine clearance <30 mL/min at

baseline were excluded. Patients with severe renal impairment are generally more at risk for haemodynamic AEs and the use of riociguat should not be recommended in these patients.

Hepatic impairment

There is no clinical experience in the pivotal studies in patients with different degrees of hepatic impairment in general. In cirrhotic patients (non-smokers) with mild hepatic impairment (classified as Child Pugh A) riociguat mean AUC was increased by 35% compared to healthy controls which is within normal intra-individual variability, whereas riociguat mean AUC was increased by 51% compared to healthy controls in patients with moderate hepatic impairment (Child Pugh B). It is agreed with the Applicant that dose titration can be sufficient guidance for the balance of efficacy and safety in these patients.

There are no data in patients with severe hepatic impairment (classified as Child Pugh C), and considering available PK data in patients with moderate hepatic impairment, these patients are contraindicated. Likewise, use of riociguat in other patients with significant liver disease (e.g. cirrhosis, acute clinical or chronic active hepatitis, ALT > 3 x ULN, bilirubin > 2 x ULN) should not be recommended, due to lack of clinical experience.

Elderly

The frequency of SAEs, cardiac disorders (palpitation/tachycardia), vascular disorders (mostly hypotension), dizziness, peripheral edema and vomiting tended to increase with increasing age. Increased rate of hypotension did not lead to increased rate of syncope.

For further discussion see the section "Discussion on clinical safety" of this report.

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

Background PAH therapy

Hypotension among ERA-pre-treated patients occurred at a similar rate in the riociguat (5.8%) and placebo groups (5.7%), but among therapy-naive patients, hypotension was reported in the riociguat group only (9.7%).

The interaction with sildenafil was investigated in two studies. Both studies showed additive systemic hypotensive action. In study 15096, the combination resulted in a higher rate of discontinuation, more AEs related to hypotension and one case of death related to hypotension cannot be ruled out. The interaction is listed as a contraindication (see section 4.3 of the SmPC). The interaction with PDE5 inhibitors is discussed in the Pharmacodynamics section.

Peripheral oedema among both ERA-pre-treated and therapy-naive patients occurred more frequently in the riociguat (21% and 16.8% respectively) compared to the placebo group (9.4% and 12.1% respectively).

For further discussion see the section "Discussion on clinical safety" of this report.

2.6.8. Discontinuation due to adverse events

In the pooled controlled studies, TEAEs leading to discontinuations were reported less frequently in the riociguat group (n=14; 2.9%) than the placebo group (n=11; 5.1%). This is reassuring regarding the tolerability of riociguat. The most frequent TEAEs leading to discontinuations in the riociguat group across both studies were in the MedDRA primary system organ classes cardiac disorders (three subjects), gastrointestinal disorders (two subjects), general disorders and administration site conditions (two subjects) and nervous system disorders (two subjects). The most frequent TEAEs leading to discontinuations in the placebo group across both studies were in the primary system organ classes cardiac disorders (two subjects) and respiratory, thoracic and mediastinal disorders (5 subjects).

In the pooled LTE studies, TEAEs leading to discontinuations were reported in 31 subjects (5.6%). The most frequent TEAEs leading to discontinuations by preferred term were: pulmonary hypertension (1.0%) in CHEST-2 and pulmonary arterial hypertension (1.1%) and pulmonary hypertension (0.8%) in PATENT-2. These reasons for discontinuation probably signify disease progression.

2.6.9. Discussion on clinical safety

Riociguat belongs to a new pharmacological class, soluble guanylate cyclase stimulators; so there is no previous safety experience. Safety data is presented per study and also as pooled data. Pooling of the main clinical studies CHEST-1 and PATENT-1 is supported due to the somewhat comparable patient populations. Controlled data is available for 490 patients administered riociguat compared to 214 patients administered placebo for at least 12 weeks. Though limited numbers, it can be accepted in an orphan indication. Long term exposure (around one year) available for 557 patients; this exposure is considered adequate to reveal possible long term safety.

The reported adverse event profile in the placebo-controlled trials is in line with the mechanism of action as a vasodilator; the most common drug related AE are headache, dyspepsia, dizziness and nausea and hypotension. Results are comparable to those reported with PDE5 inhibitors. The rate of reported AE declines in the long term extensions, which probably indicates some adaptation to the haemodynamic changes induced by riociguat. The increased incidence of AE related to PAH in the long-term extension studies may be related to disease progress.

Although the incidence of serious adverse events (SAEs) appears comparable in both groups, there are a number of serious events that appear only in the riociguat treatment arm: haemoptysis (n=5) and acute renal failure (n=3). The rest of the reported serious events appear to be in line with the vasodilatory profile of riociguat. The overall higher rate of serious events in the long term extension studies is normalised once it is corrected to the duration. This could also signify deterioration in the disease process rather than reflecting the AE profile of riociguat.

In the controlled studies, the rate of death was higher in the placebo group (3.3%) compared to the riociguat groups (1%). In the long-term extension studies, the rate of death was 4.1%, which is comparable to that reported in controlled studies with other PAH agents. The causes of death in both the placebo and riociguat were generally in line with would be expected in this population, e.g. cardiac failure, PAH. However, the deaths due to haemoptysis, pulmonary

haemorrhages and acute renal impairment deserve accurate follow-up and are adequately reflected in the RMP.

Hypertension was identified as an adverse event linked to the mode of action and was also used to guide the individual dose titration. For renal function subgroups, the incidence of hypotension (AE or SBP<90 mmHg) in the pooled riociguat group was higher in subjects with moderate renal impairment (baseline eGFR (≥ 30 to <50 mL/min) than overall, and the difference in incidence between the treatment groups was larger in this subgroup. A smaller difference between treatment groups was observed in subjects with mild renal impairment. These subgroups appear to be more vulnerable to the hypotensive effect of riociguat than other and such risk is highlighted in SmPC section 4.4. In addition, as the clinical studies excluded patients with SBP below 95 mm Hg and due to the risk of hypotension, this is currently a contraindication in the SmPC. This is also in line with the SmPC of sildenafil and tadalafil.

Some other reported AEs are of concern considering the reported imbalance with the placebo group, e.g. haemoptysis, pulmonary haemorrhages and renal impairment. Apart from the pathology of the pulmonary vessels, the co- administration of anticoagulants or PAH medications can also increase this bleeding risk. It can be agreed that a direct PK/PD interaction is not the main mechanism: there is no evidence for an influence of riociguat on platelet function in humans (aspirin interaction study 14204), nor evidence for an interaction with warfarin (warfarin interaction study 11918). One hypothesis proposed by the Applicant is that this might be related to riociguat's strong vasodilatory effect on bronchial arteries, influencing vasocontractility in case of severe lung bleeding, which the CHMP considered plausible.

During the procedure the Applicant provided additional discussion on this subject. Treatment-emergent respiratory tract bleeding events (haemoptysis and pulmonary haemorrhage) occurred in a total of 12 subjects in the riociguat treatment arms in PATENT-1 and CHEST-1 (10/490 [2.0%]) vs. 2/214 [0.9%] from the placebo groups. In the LTE studies PATENT-2 and CHEST-2 the frequency was 33/633 [5.2%]. Serious events were recorded in 5 subjects during PATENT-1 and CHEST-1 (all in the riociguat treatment groups) and 14 subjects during the LTE phase. In total, there were 4 fatal outcomes recorded with riociguat (one in the DB phase, and 3 in LTE). The rate of respiratory tract bleeding events per 100 person years did not increase during long-term treatment (9 events per 100 person years in CHEST-1/PATENT-1 and 5 events per 100 person years in LTE.

The causality of these respiratory bleedings is difficult to assess. Respiratory bleedings, although rare, are a known complication of the underlying disease of PH. In accordance with clinical guidelines a high percentage of patients were anti-coagulated (more than 90% of the patients in the CHEST-1 trial, and more than 50% of the patients in the PATENT-1 trial). In addition, some of the patients in PATENT-1 were on prostacyclins, where haemoptysis is reported as a very common AEs (Ventavis (iloprost) SmPC). CTEPH patients seem even more susceptible than the general PAH population, explained in part by higher use of anti-coagulants, and also by the pathology of the lesions.

The applicant investigated several risk factors that could have contributed to this higher risk of respiratory bleeding reported with riociguat. These included demographic, medical history, baseline and disease characteristics and co-medications; none appeared to be of consistent risk. For example, in the DB studies and the LTE 10/12 and 28/33 respiratory tract bleeding events

occurred in subjects without a history of respiratory bleeding. However all the cases reported in patients with serious events had a previous history of respiratory bleeding. A tendency was observed for respiratory tract bleeding events to occur rather in younger patients, particularly in patients with higher PAP_{mean} and PVR. However, the data did not indicate that PAP_{mean} and PVR could be used to predict the individual risk. In addition, there was a tendency for higher rates occurring in Asian patients. A link to respiratory tract infections cannot be ruled out; concomitant respiratory tract infections were recorded in 5/10 subjects in the riociguat group vs. 0/2 subjects in the placebo group. Co-administration of prostacyclins may be another associated risk factor, but no temporal association between administration of clopidogrel, ERAs and vasodilators was seen. 16% of subjects who had received any antithrombotic agent had a haemorrhagic event in both treatment groups (riociguat and placebo) in CHEST-1 and PATENT-1. The administration of VKAs or the quality of the INR did not result in an increased rate of any bleeding event in riociguat treated subjects: 18% of subjects who had received VKAs had a haemorrhagic event in both treatment groups (riociguat and placebo) in the DB studies.

The Applicant acknowledges that the risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious haemoptysis including those managed by bronchial arterial embolisation. The SmPC states that riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolization. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit-risk of treatment continuation.

Ultimately, this increased risk of (potentially fatal) respiratory tract bleeding must be weighed against the benefits of increased exercise tolerance as shown in the trials. Serious haemoptysis/pulmonary haemorrhage is adequately listed as important identified risks in the RMP and the risk is adequately reflected in section 4.4 of the SmPC.

Anaemia was reported with a higher rate in the riociguat group compared to placebo. These increased rates of anaemia and the associated laboratory changes were not accompanied by differences between the treatment groups in therapy directed to counteract anaemia or in obvious differences of bleeding events as an explanation of the observation. Anaemia, probably dilutional, is also reported with bosentan and sildenafil.

The applicant further discussed the improvement of the pulmonary hypertension with consequent erythropoietin decrease and neocytolysis as a possible explanation for the occurrence of anemia in the clinical studies; however, the observed reticulocytosis in these studies does not fit into this scheme. On the other hand the reticulocytosis is consistent with the conclusion that bone-marrow toxicity is not the cause of the anemia. Also the submitted data analysis does not point at bone-marrow toxicity. It is realized that anemia was a common (>5%) baseline medical history finding in the study population (CHEST and PATENT) with 11.5% in the riociguat group vs. 7.5% in the placebo group. It could be shown that Hb decrease occurred in patients with high baseline hemoglobin (14-16g/dl) and not in patients with low baseline values (< 12g/dl). In addition, no correlation between anemia and bleeding events could be established. The Applicant´s opinion is endorsed that haemodilution caused by an increase in intravascular volume due to vasodilating effect of riociguat is likely the cause of the observed anemia. The submitted data does not indicate that the anemia represents a clinically relevant risk for the

outcome of the patients treated chronically with riociguat. Anaemia is listed as a common treatment emergent adverse event in section 4.8 of the SmPC.

GI disorders were reported in a higher frequency in the riociguat pool compared to the placebo pool in POOL-1 DB. GI related AEs are also reported in preclinical studies. Smooth muscle relaxation in an otherwise unaffected GI tract explains rather the typical adverse events such as reflux disease, diarrhea or vomiting, which especially in combination with gastritis/enteritis could lead to GI bleedings. Serious adverse events of gastritis and bleeding were low in number; however, for the future use of riociguat in the daily practice, this issue is clinically important as many patients with PH receive concomitant anticoagulation. These adverse events are reflected in section 4.8 of the SmPC.

Atrial Fibrillation was reported in a higher rate in the riociguat pooled arm vs. none placebo in POOL-1 DB, and more so in POOL-3. In a further analysis of atrial fibrillation or atrial flutter (AF/AFL) in the main and LTE studies the rate of AF/AFL reported as TEAEs was slightly higher in the riociguat group (1.2%) compared to the placebo group (0.5%); whereas the reported SAE were comparable (0.4% and 0.5% respectively). The applicant explained that in 2 of 6 reported TEAE with riociguat the arrhythmia was recorded before the administration of riociguat. This balances the incidence between the 2 treatment arms. In addition, 3 of these 6 patients had a medical history of arrhythmia. In the LTE, the incidence of AF/AFL reported as TEAEs was 2.5%, with 2.3% reported as serious. The incidence of treatment-emergent atrial fibrillation or atrial flutter events was 2.8 per 100 patient-years. It can be agreed that the reported incidence rate in the riociguat-treated group is consistent with published data in patients with PH, (e.g. 5.6% in a cohort of 231 patients, Tongers et al., Am Heart J 2007;153:127-32). Atrial fibrillation is therefore not regarded as an adverse drug reaction related to administration of riociguat, and as such is not listed in section 4.8 of the SmPC. Treatment of patients with pre-existing atrial fibrillation is however considered as an important potential risk which is captured in the RMP.

There are conflicting data regarding the possible effects of riociguat on renal function. On one hand, analyses of respective laboratory parameters did not indicate a trend for renal function to worsen, but rather a small improvement compared to placebo was seen during the double-blind treatment phase. On the other hand, there was an imbalance for AE relating to serious renal impairment. The Applicant attributes this to the associated co-morbidities at the time of the event explaining the events rather than a drug-effect. One out of these subjects with a fatal outcome had received dialysis, whereas most other subjects had an outcome of recovered/resolved.

In an additional case-by-case analysis, the Applicant could not identify a specific signal for a potential negative impact of riociguat on renal function after analysis of all AEs and laboratory parameters. Creatinine, creatinine clearance and urea are rather stable over the course of 3 to 4 months of treatment in riociguat and placebo-treated patients, and even show a trend to a slight improvement of renal function in the riociguat group when compared with placebo.

Overall, in patients in the CHEST and PATENT studies, events of renal impairment were very often associated with inter-current medical conditions. In all cases, contributing factors were present without uncovering a particular risk pattern.

The Applicant’s conclusion, pointing out that other factors contribute to the cases of renal insufficiency that were seen, was agreed by the CHMP. However, the numerical imbalance

between the active and the placebo groups shows that 'riociguat use' may well be one of the factors contributing to renal failure. The mechanism for this may be hypotension in some or all cases; however this hypotension may have other contributing factors. Patients with renal disease are especially prone to haemodynamic instability. There is currently a warning regarding the associated hypotension in patients with renal impairment in section 4.4 of the SmPC. In addition, renal failure is adequately address in the RMP and captured as an important potential risk.

In the repeat-dose toxicity studies, riociguat-related effects on the skeletal system consistent with stimulation of osteoblasts were restricted to juvenile and adolescent rats and mice (see "Non-clinical Toxicology" section of this report). The implications of the adverse effects on bone encountered in growing rats on paediatric patients in whom the epiphysis is not yet closed are not clear. Until more is known, the use of riociguat in children and in growing adolescents should be avoided (see sections 4.2, 4.4 and 5.3 of the SmPC).

The data from the clinical programme is not fully conclusive with regards to bone disorders. Therefore, in light of the additional non-clinical data the risk is included in the RMP as an important potential risk.

No thorough QT study was performed. Pre-clinical data show possible QT prolongation in dogs, but this is considered a consequence of an inadequate correction rather than an intrinsic QT prolonging effect of riociguat. QT prolongation is not considered an adverse drug reaction related to administration of riociguat, and as such is not listed in section 4.8 of the SmPC.

Patients with mild or moderate renal impairment were adequately represented in the pivotal studies. Although the dose is individually titrated, there is still a higher incidence of hypotension reported in these patients. This is currently reflected as a warning in section 4.4 of the SmPC. Subjects with a creatinine clearance <30 mL/min at baseline were excluded. Patients with severe renal impairment are generally more at risk for haemodynamic AEs, and the use of riociguat should not be recommended in these patients (see section 4.4 of the SmPC).

There is no clinical experience in the pivotal studies in patients with different degrees of hepatic impairment in general. It is agreed with the Applicant that dose titration can be sufficient guidance for the balance of efficacy and safety in patients with mild hepatic impairment.

There are no data in patients with severe hepatic impairment (classified as Child Pugh C), and considering available PK data in patients with moderate hepatic impairment, these patients are contraindicated. Likewise, use of riociguat in other patients with significant liver disease (e.g. cirrhosis, acute clinical or chronic active hepatitis, ALT > 3 x ULN, bilirubin > 2 x ULN) should not be recommended, due to lack of clinical experience.

The frequency of SAEs, cardiac disorders (palpitation/tachycardia), vascular disorders (mostly hypotension), dizziness, peripheral edema and vomiting tended to increase with increasing age. Increased rate of hypotension did not lead to increased rate of syncope. The applicant has included in section 4.2 of the SmPC information regarding the use of riociguat in elderly population, stating that "In elderly patients (65 years or older) there is a higher risk of hypotension and therefore particular care should be exercised during individual dose titration (sees section 5.2)". In the section 5.2 of the SmPC it is stated that the AUC values are ca. 40% higher in elderly patients due to reduced clearance. This information is considered adequate by the CHMP.

The reported higher rates of some AEs like headache and nausea in patients co-administered riociguat on top of ERA is expected. Hypotension among ERA-pre-treated patients occurred at a similar rate in the riociguat and placebo groups, but among therapy-naive patients, hypotension was reported in the riociguat group only. According to the applicant, this can be explained by a potential selection bias: ERA-pre-treated patients had tolerated their vasodilator pre-treatment for at least 90 days, whereas therapy-naive patients experienced the vasodilator effect for the first time. The CHMP considered this explanation plausible.

The interaction with sildenafil was investigated in two studies. Both studies showed additive systemic hypotensive action. In study 15096, the combination resulted in a higher rate of discontinuation, more AEs related to hypotension and one case of death related to hypotension cannot be ruled out. The interaction is listed as a contraindication (see section 4.3 of the SmPC). The interaction with PDE5 inhibitors is discussed in the Pharmacodynamics section.

Peripheral oedema among both ERA-pre-treated and therapy-naive patients occurred more frequently in the riociguat compared to the placebo group. This finding was explained by the applicant as an additive vasodilatory effect of the combination of 2 compounds with vasodilatory effects, ERAs and riociguat. The CHMP considered this explanation acceptable. Peripheral oedema is included as an ADR in section 4.8 of the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

Riociguat belongs to a new pharmacological class, soluble guanylate cyclase stimulators; so there is no previous safety experience, but it can be predicted from other vasodilatation which increase cGMP. The safety database is limited, but this can be expected in an orphan indication. Relevant long term data are available which is reassuring. Generally, the AE associated with riociguat use reflect its mechanism of action as a vasodilator, e.g. headaches, hypotension, GI AEs. However, some reported AEs are of concern considering the reported imbalance with the placebo group, e.g. haemoptysis, pulmonary haemorrhages and renal impairment. Implemented SmPC and RMP changes are considered adequate to reflect and manage these risks.

Periodic Safety Update Reports (PSURs) should be submitted in line with the standard PSUR cycle (i.e. six-monthly, yearly and thereafter three-yearly). The international birth date (IBD) will be used as basis for calculating the Data Lock Point.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.2, the PRAC considers by consensus that the risk management system for Riociguat (Adempas) in the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) is acceptable. The following points should be taken into account in the next update:

- The applicant is requested to submit the adapted riociguat-specific questionnaire, which will be added to the standard pregnancy monitoring forms, for review.

- The applicant has agreed to undertake a feasibility evaluation to examine if, and how far it may be possible to distinguish different clinical classes of pulmonary hypertension, using additional medical and procedural information recorded in the statutory health insurance data. The applicant is requested to submit the results of this feasibility study upon completion.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP to which the PRAC agreed:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Hypotension • Including hypotension due to drug interactions with: o organic nitrates o phosphodiesterase-5 inhibitors o strong multi-pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp)/ breast cancer resistance protein (BCRP) inhibitors o strong CYP1A1 inhibitors and strong P-gp/BCRP inhibitors Upper gastrointestinal motility disorders Worsening of pulmonary venous occlusive disease Serious haemoptysis/pulmonary haemorrhage

Summary of safety concerns	
Important potential risks	Bleeding Embryo–foetal toxicity Medication error Renal failure Off-label use in patients aged < 18 years Treatment of patients with pre-existing atrial fibrillation Bone changes and fractures Concomitant smoking (induction of CYP1A1)
Missing information	Patients with systolic blood pressure < 95 mmHg at baseline Patients with severe hepatic impairment (Child–Pugh C) Patients with creatinine clearance < 30 mL/min or on dialysis Pregnancy and lactation Patients aged < 18 years Patients with chronic thromboembolic pulmonary hypertension (CTEPH) or pulmonary arterial hypertension (PAH) in World Health Organisation (WHO) functional class IV Long-term safety in clinical practice Patients with uncontrolled hypertension

Pharmacovigilance plans

Table 2.2: Ongoing and planned studies in the PhV development plan

Study/activity type, title and category (1–3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
EXPosur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension (EXPERT) (riociguat exposure registry, 3)	The main goal of this global registry is to monitor the safety of riociguat in real life clinical use	**Important identified risks:** Hypotension • Including hypotension due to drug interactions with: o organic nitrates o phosphodiesterase-5 inhibitors o strong multi-pathway CYP and P-gp/BCRP inhibitors o strong CYP1A1 inhibitors and strong P-gp/BCRP inhibitors	Planned	Available data will be presented in PSUR/ PBRER Final report estimated beginning 2019

Study/activity type, title and category (1–3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
		Serious haemoptysis/ pulmonary haemorrhage **<u>Important potential risks:</u>** Bleeding Embryo–fetal toxicity Renal failure Off-label use in patients aged < 18 years Treatment of patients with pre-existing atrial fibrillation Bone changes and fractures Concomitant smoking (induction of CYP1A1) **<u>Missing information:</u>** Patients with systolic blood pressure < 95 mmHg at baseline Patients with severe hepatic impairment (Child–Pugh C) Patients with creatinine clearance < 30 mL/min or on dialysis Pregnancy and lactation Patients aged < 18 years Patients with CTEPH or PAH in WHO functional class IV Long-term safety in clinical practice Patients with uncontrolled hypertension		
In vitro studies to determine the substrate characteristics of riociguat and metabolite M-1 towards human transporters (3)	To further define drug drug interaction potential of riociguat and M-1	N/A	Ongoing /initiated	Estimated December 2014
In vitro studies to determine the M-1 potential to inhibit renal efflux transporters MATE1 and MATE2K (3)	To further define drug drug interaction potential of riociguat and M-1	Unknown potential for drug drug interactions	Ongoing	Estimated May 2014

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: hypotension	Proposed text in SmPC **Dose titration scheme described in section 4.2:** *Dose titration* The recommended starting dose is 1 mg three times daily for 2 weeks. Tablets should be taken three times daily approximately 6 to 8 hours apart. Dose should be increased by 0.5 mg three times daily every two weeks to a maximum of 2.5 mg three times daily, if systolic blood pressure is ≥ 95 mmHg and the patient has no signs or symptoms of hypotension. In some pulmonary arterial hypertension (PAH) patients, an adequate response on the 6MWD may be reached at a dose of 1.5 mg three times a day. If systolic blood pressure falls below 95 mmHg, the dose should be maintained provided the patient does not show any signs or symptoms of hypotension. If at any time during the up-titration phase systolic blood pressure decreases below 95 mmHg and the patient shows signs or symptoms of hypotension the dose should be decreased by 0.5 mg three times daily. *Maintenance dose* The established individual dose should be maintained unless signs and symptoms of hypotension occur. The maximum total daily dose is 7.5 mg, i.e. 2.5mg three times daily. If a dose is missed, treatment should be continued with the next dose as planned. If not tolerated, dose reduction should be considered at any time. *Treatment discontinuation* In case treatment has to be interrupted for 3 days or	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	more, restart treatment at 1 mg three times daily for 2 weeks, and continue treatment with the dose titration regimen as described above. Special populations *Elderly population* In elderly patients (65 years or older) there is a higher risk of hypotension and therefore particular care should be exercised during individual dose titration. *Renal impairment* Patients with moderate renal impairment (creatinine clearance <50–30 mL/min) showed a higher exposure to this medicine. There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration. **Posology described in section 4.2:** Tablets can generally be taken with or without food. For patients prone to hypotension, as a precautionary measure, switches between fed and fasted Adempas intake are not recommended because of increased peak plasma levels of riociguat in the fasting compared to the fed state. **Contraindications in section 4.3:** Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form. Co-administration with PDE-5 inhibitors (such as sildenafil, tadalafil, vardenafil). Patients with systolic blood pressure < 95 mmHg at treatment initiation. **Warnings in section 4.4:** Riociguat has vasodilatory properties which may result in lowering of blood pressure. Before prescribing riociguat, physicians should carefully consider whether patients with certain underlying conditions, could be adversely affected by vasodilatory effects (e.g. patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction). Riociguat must not be used in patients with a systolic blood pressure below 95 mmHg. Patients older than 65	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	years are at increased risk of hypotension. Therefore, caution should be exercised when administering riociguat in these patients. Renal impairment Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis, therefore riociguat is not recommended in these patients. Patients with mild and moderate renal impairment were included in the pivotal studies. There is increased riociguat exposure in these patients. There is a higher risk of hypotension in these patients; particular care should be exercised during individual dose titration. Concomitant use with other medicinal products The concomitant use of riociguat with strong multi-pathway CYP and P-gp/BCRP inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or human immunodeficiency virus (HIV) protease inhibitors (e.g. ritonavir) is not recommended, due to the pronounced increase in riociguat exposure. The concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-gp/BCRP inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure. These medicinal products should be used with caution. Blood pressure should be monitored and dose reduction of riociguat be considered. **Listed in section 4.8 (undesirable effects)** Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	
Important identified risk: upper gastrointestinal motility disorders	Proposed text in SmPC **Listed in section 4.8 (undesirable effects)** Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	None proposed
Important identified risk: worsening of pulmonary venous	Proposed text in SmPC **Warning in section 4.4:**	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
occlusive disease	Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with PVOD. Therefore, administration of riociguat to such patients is not recommended. Should signs of pulmonary oedema occur, the possibility of associated PVOD should be considered and treatment with riociguat should be discontinued. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	
Important identified risk: serious haemoptysis/ pulmonary haemorrhage	Proposed text in SmPC **Warning in section 4.4:** In pulmonary hypertension patients there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. A careful monitoring of patients taking anticoagulants according to common medical practice is recommended. The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious haemoptysis including those managed by bronchial arterial embolisation. Riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolisation. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit–risk of treatment continuation with each individual patient. Serious bleeding occurred in 2.4% (12/490) of patients taking Adempas compared to 0/214 of placebo patients. Serious haemoptysis occurred in 1% (5/490) patients taking Adempas compared to 0/214 patients taking placebo, including one event with fatal outcome. Serious haemorrhagic events also included 2 patients with vaginal haemorrhage, 2 with catheter site haemorrhage, and 1 each with subdural haematoma, haematemesis, and intra-abdominal haemorrhage. **Listed in section 4.8 (undesirable effects)** Prescription only medicine	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	
Important potential risk: bleeding	Proposed text in SmPC **Warning in section 4.4:** In pulmonary hypertension patients there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. A careful monitoring of patients taking anticoagulants according to common medical practice is recommended. The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious haemoptysis including those managed by bronchial arterial embolisation. Riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolisation. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit–risk of treatment continuation with each individual patient. Serious bleeding occurred in 2.4% (12/490) of patients taking Adempas compared to 0/214 of placebo patients. Serious haemoptysis occurred in 1% (5/490) patients taking Adempas compared to 0/214 patients taking placebo, including one event with fatal outcome. Serious haemorrhagic events also included 2 patients with vaginal haemorrhage, 2 with catheter site haemorrhage, and 1 each with subdural haematoma, haematemesis, and intra-abdominal haemorrhage. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	None proposed
Important potential risk: embryo–fetal toxicity	Proposed text in SmPC **Contraindication in section 4.3:** Pregnancy. **Addressed in section 4.6:** <u>Pregnancy</u> There are no data from the use of riociguat in pregnant women. Studies in animals have shown reproductive	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	toxicity and placental transfer. Therefore, Adempas is contraindicated during pregnancy. Monthly pregnancy tests are recommended. <u>Women of childbearing potential</u> Women of childbearing potential must use effective contraception during treatment with Adempas. <u>Breast-feeding</u> No data on the use of riociguat in breast-feeding women are available. Data from animals indicate that riociguat is secreted into milk. Due to the potential for serious adverse reactions in nursing infants Adempas should not be used during breast-feeding. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Adempas. **Described in section 5.3:** Moderate passage across the placental barrier was observed. Developmental toxicity studies in rats and rabbits have shown reproductive toxicity of riociguat. In rats, an increased rate of cardiac malformation was observed as well as a reduced gestation rate due to early resorption at maternal systemic exposure of about 7-fold of human exposure (2.5 mg three times daily). In rabbits, starting at systemic exposure of about 3-fold of human exposure (2.5 mg three times daily) abortion and fetal toxicity were seen. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	
Important potential risk: medication error	Proposed text in SmPC N/A Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH Each dose strength is available as a single tablet to be taken three times daily; dose titration will therefore involve a change in the tablet strength rather than a change in the number of tablets to be taken by the patient. To distinguish between different dose strengths, colour-coding will be applied to the primary packaging and outer packaging. The tablets will have a specific, distinctive colour scheme and will also be marked with the dose	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	strength.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risk: renal failure	Proposed text in SmPC **Addressed in section 4.2:** Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis. Therefore use of Adempas is not recommended in these patients. Patients with moderate renal impairment (creatinine clearance <50–30 mL/min) showed a higher exposure to this medicine. There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration. **Warning in section 4.4:** Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis, therefore riociguat is not recommended in these patients. Patients with mild and moderate renal impairment were included in the pivotal studies. There is increased riociguat exposure in these patients. There is a higher risk of hypotension in these patients, particular care should be exercised during individual dose titration. **Described in section 5.2:** Overall, mean dose- and weight-normalised exposure values for riociguat were higher in subjects with renal impairment compared to subjects with normal renal function. Corresponding values for the main metabolite were higher in subjects with renal impairment compared to healthy subjects. In non-smoking individuals with mild (creatinine clearance 80–50 mL/min), moderate (creatinine clearance <50–30 mL/min) or severe (creatinine clearance < 30 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 53%, 139% or 54%, respectively. Data in patients with creatinine clearance < 30 mL/min are limited and there are no data for patients on dialysis. Due to the high plasma protein binding riociguat is not expected to be dialysable. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	None proposed
Important potential risk: off-label use in	Proposed text in SmPC **Warning in section 4.4:**	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
patients aged < 18 years	The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone. Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided. **Described in section 5.2:** No studies have been conducted to investigate the pharmacokinetics of riociguat in paediatric patients. **Described in section 5.3:** In growing juvenile and adolescent rats, effects on bone formation were seen. In juvenile rats, the changes consisted of thickening of trabecular bone and of hyperostosis and remodeling of metaphyseal and diaphyseal bone, whereas in adolescent rats an overall increase of bone mass was observed. No such effects were observed in adult rats. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	
Important potential risk: treatment of patients with pre-existing atrial fibrillation	Proposed text in SmPC N/A Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	None proposed
Important potential risk: bone changes and fractures	Proposed text in SmPC N/A Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risk: concomitant smoking (induction of CYP1A1)	Proposed text in SmPC **Addressed in section 4.2:** *Smokers* Current smokers should be advised to stop smoking due to a risk of a lower response. Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. A dose increase to the maximum daily dose of 2.5 mg three times daily may be required in patients who are smoking or start smoking during treatment. A dose decrease may be required in patients who stop smoking. **Warning in section 4.4:** Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. Dose adjustment may be necessary in patients who start or stop smoking during treatment with riociguat. **Described in section 4.5:** *Smoking* In cigarette smokers riociguat exposure is reduced by 50–60%. Therefore, patients are advised to stop smoking. **Described in section 5.2:** CYP1A1 catalyses the formation of riociguat's main metabolite in liver and lungs and is known to be inducible by polycyclic aromatic hydrocarbons, which, for example, are present in cigarette smoke. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	None proposed
Missing information: patients with systolic blood pressure < 95 mmHg at baseline	Proposed text in SmPC **Contraindication in section 4.3:** Patients with systolic blood pressure < 95 mmHg at treatment initiation. **Warning in section 4.4:** Riociguat must not be used in patients with a systolic	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	blood pressure below 95 mmHg. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	
Missing information: patients with severe hepatic impairment (Child–Pugh C)	Proposed text in SmPC **Contraindication in section 4.3:** Severe hepatic impairment (Child–Pugh C). **Addressed in section 4.2:** Patients with severe hepatic impairment (Child–Pugh C) have not been studied and therefore use of riociguat is contraindicated in these patients. Patients with moderate hepatic impairment (Child–Pugh B) showed a higher exposure to Adempas. Particular care should be exercised during individual dose titration. **Warning in section 4.4:** There is no experience in patients with severe hepatic impairment (Child–Pugh C); riociguat is contraindicated in these patients. Pharmacokinetic data show that higher riociguat exposure was observed in patients with moderate hepatic impairment (Child–Pugh B). Particular care should be exercised during individual dose titration. There is no clinical experience with riociguat in patients with elevated liver aminotransferases (> 3 x upper limit of normal [ULN]) or with elevated direct bilirubin > 2 x ULN) prior to initiation of treatment; riociguat is not recommended in these patients. **Described in section 5.2:** In cirrhotic patients (non-smokers) with mild hepatic impairment (classified as Child–Pugh A), riociguat mean AUC was increased by 35% compared to healthy controls, which is within normal intra-individual variability. In cirrhotic patients (non-smokers) with moderate hepatic impairment (classified as Child–Pugh B), riociguat mean AUC was increased by 51% compared to healthy controls. There are no data in patients with severe hepatic impairment (classified as Child–Pugh C). Patients with ALT > 3 x ULN and bilirubin > 2 x ULN	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	were not studied. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information: patients with creatinine clearance < 30 mL/min or on dialysis	Proposed text in SmPC **Addressed in section 4.2:** Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis. Therefore use of Adempas is not recommended in these patients. Patients with moderate renal impairment (creatinine clearance <50–30 mL/min) showed a higher exposure to this medicine. There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration. **Warning in section 4.4:** Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis, therefore riociguat is not recommended in these patients'. Patients with mild and moderate renal impairment were included in the pivotal studies. There is increased riociguat exposure in these patients. There is a higher risk of hypotension in these patients; particular care should be exercised during individual dose titration. **Described in section 5.2:** Overall, mean dose- and weight-normalised exposure values for riociguat were higher in subjects with renal impairment compared to subjects with normal renal function. Corresponding values for the main metabolite were higher in subjects with renal impairment compared to healthy subjects. In non-smoking individuals with mild (creatinine clearance 80–50 mL/min), moderate (creatinine clearance <50–30 mL/min) or severe (creatinine clearance < 30 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 53%, 139% or 54%, respectively. Data in patients with creatinine clearance < 30 mL/min are limited and there are no data for patients on dialysis. Due to the high plasma protein binding riociguat is not expected to be dialysable. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	None proposed
Missing information:	Proposed text in SmPC **Contraindication in section 4.3:**	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
pregnancy and lactation	Pregnancy. **Addressed in section 4.6:** <u>Pregnancy</u> There are no data from the use of riociguat in pregnant women. Studies in animals have shown reproductive toxicity and placental transfer.Therefore, Adempas is contraindicated during pregnancy. Monthly pregnancy tests are recommended. <u>Women of childbearing potential</u> Women of childbearing potential must use effective contraception during treatment with Adempas. <u>Breast-feeding</u> No data on the use of riociguat in breast-feeding women are available. Data from animals indicate that riociguat is secreted into milk. Due to the potential for serious adverse reactions in nursing infants Adempas should not be used during breast-feeding. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Adempas. **Described in section 5.3:** Moderate passage across the placental barrier was observed. Developmental toxicity studies in rats and rabbits have shown reproductive toxicity of riociguat. In rats, an increased rate of cardiac malformation was observed as well as a reduced gestation rate due to early resorption at maternal systemic exposure of about 7-fold of human exposure (2.5 mg three times daily). In rabbits, starting at systemic exposure of about 3-fold of human exposure (2.5 mg three times daily) abortion and fetal toxicity were seen. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information: patients aged < 18 years	Proposed text in SmPC **Warning in section 4.4:** The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone. Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided. **Described in section 5.2:** No studies have been conducted to investigate the pharmacokinetics of riociguat in paediatric patients. **Described in section 5.3:** In growing juvenile and adolescent rats, effects on bone formation were seen. In juvenile rats, the changes consisted of thickening of trabecular bone and of hyperostosis and remodeling of metaphyseal and diaphyseal bone, whereas in adolescent rats an overall increase of bone mass was observed. No such effects were observed in adult rats. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	None proposed
Missing information: patients with CTEPH or PAH in WHO functional class IV	Proposed text in SmPC **Indication in section 4.1:** <u>Chronic thromboembolic pulmonary hypertension (CTEPH)</u> Adempas is indicated for the treatment of adult patients with WHO Functional Class II – III with • inoperable CTEPH, • persistent or recurrent CTEPH after surgical treatment to improve exercise capacity <u>Pulmonary arterial hypertension (PAH)</u> Adempas, as monotherapy or in combination with	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity. Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease. Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	
Missing information: long-term safety in clinical practice	Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	None proposed
Missing information: patients with uncontrolled hypertension	Proposed text in SmPC N/A Prescription only medicine Treatment initiated and monitored by a physician experienced in the treatment of PAH or CTEPH	None proposed

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

The CHMP endorsed this advice with changes. These changes concerned a request for the following *in vitro* studies be included in the RMP (category 3 studies):

- The applicant agrees to test if synthesis of 3H-labeled compound is feasible. When 3H labelled compound is available the applicant will determine the substrate characteristics of M-1 for OAT1 and OAT3 at the lowest feasible concentration. For riociguat, the applicant will determine the substrate characteristics towards OAT1 and OAT3 at the lowest feasible concentration using 3H-labelled compound, under the prerequisite that the synthesis of 3H-labeled compound is successful. In addition, the applicant agrees to determine the substrate characteristics towards OCT1, OCT3 (riociguat and M-1) and OCT2 (M-1) at the lowest feasible concentrations. Based on current results, lowest achievable test concentrations are in the range of 150 nM, but lower concentrations might be feasible when 3H labeled compound is available. The reports, which are expected to be available by end of 2014, are awaited.
- The concentrations used to test the inhibitory potential of M-1 covered the clinically relevant plasma concentration range. No inhibition of the OAT1, OAT3, OATP1B1 and OATP1B3 transporters at these clinically relevant concentrations by M-1 was observed.

The inhibitory potential of riociguat and M-1 towards BSEP was evaluated in human sandwich-cultured hepatocytes with taurocholic acid (TCA) as probe substrate and potential effects of riociguat and M-1 on the BSEP-mediated efflux of TCA were determined. Riociguat is not an inhibitor of BSEP at clinically relevant concentrations (IC50 >20 µM and 50 × Cmax,unbound = 50 × 0.05 × 0.5 µM = 1.25 µM). M-1 is also not an inhibitor of BSEP at clinically relevant concentration (IC50 >10 µM and Cmax,unbound = 50 × 0.04 ×0.3 µM = 0.6 µM). In conclusion, at clinical relevant concentrations of riociguat and M-1 no significant inhibition of BSEP is expected.

The applicant agrees to provide a study to determine the inhibitory potential of M 1 towards MATE1 and MATE2 in overexpressing cells. The report will be available in May 2014. If these studies indicate that riociguat and M-1 are inhibitors of one of these transporters, the Applicant is requested to change the SmPC accordingly.

The CHMP justified these changes as follows:

According to the EMA Drug-Drug-Interaction guideline the provision of these studies is imperative. The study outcome directly relates to predicting DDI in clinical practice, and even though the outcome of the studies will not lead to changes in the benefit/risk they are relevant for warnings in the SmPC. As such they should form part of the RMP as category 3 studies. The studies will be classified as post-authorisation RMP measures.

In addition to the above, the CHMP also considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

- The applicant is requested to submit the adapted riociguat-specific questionnaire, which will be added to the standard pregnancy monitoring forms, for review.

- The applicant has agreed to undertake a feasibility evaluation to examine if, and how far it may be possible to distinguish different clinical classes of pulmonary hypertension, using additional medical and procedural information recorded in the statutory health insurance data. The applicant is requested to submit the results of this feasibility study upon completion.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Both pivotal studies investigated the same primary endpoint of change from baseline in the 6-minute walk distance (6MWD); at 16 weeks in CHEST-1 (CTEPH indication) and at 12 weeks in PATENT-1 (PAH indication).

CTEPH

Results: In CHEST-1, riociguat resulted in a significant improvement in 6MWD from baseline to week 16 as compared to placebo in the ITT analysis set (45.69 m; 95% CI: 24.74 m to 66.63 m; p<0.0001). The results were confirmed by multiple sensitivity analyses.

Subgroups: In CHEST-1, benefits shown for postoperative CTEPH (26.72 m; 95% CI: -9.68 to 63.13) were less compared to the inoperable CTEPH (53.92 m; 95% CI: 28.53 to 79.31). For the other investigated subgroups (WHO FC, age, sex, region) the response was generally consistent, though results were not always statistically significant.

Secondary endpoints: The same secondary endpoints were investigated in both studies, for which a hierarchical testing procedure was defined. In CHEST-1, significant improvement in riociguat individual dose titration (IDT) treatment group was shown for pulmonary vascular resistance (PVR) (LS mean difference –246.43 dyn·s· cm^{-5}), NT-proBNP (-444 pg/ml) and WHO FC (32.9% riociguat IDT vs. 14.9% placebo subjects with improvement of at least one FC). The hierarchical test procedure stopped with time to clinical worsening (TTCW) due to lack of significance (p>0.05).

Long-term non-controlled data: Interim data from the on-going non-controlled long-term extension study CHEST-2 was submitted (cut-off April/May 2012).

The mean change in 6MWD from baseline in study CHEST-1 to week 12 of study CHEST-2 (last observation by week 12, with a 28-week total in study for CHEST 1 and 2) was 63.3 m in the former riociguat group and 35.3 m in the former placebo group. The mean change from baseline in CHEST-1 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).

In patients continuing treatment in CHEST-2 efficacy in terms of 6MWD is maintained in later interim analyses (up to 30 months).

PAH

Results: In PATENT-1 riociguat resulted in a significant improvement in 6MWD from baseline to week 12 as compared to placebo in the ITT analysis set (35.78 m; 95% CI: 20.06 m to 51.51 m; p<0.0001). The results were confirmed by multiple sensitivity analyses.

Subgroups: In PATENT-1, comparable improvements in 6MWT were observed in treatment naïve patients (38.36 m; 95% CI: 14.46 to 62.26) and patients receiving combination therapy (35.65 m; 95% CI: 15.04 to 56.26).

Secondary endpoints: In PATENT-1, significant improvement for the riociguat IDT treatment group was shown for PVR (LS mean difference - 226 dyn·s·cm^{-5}), NT-proBNP (- 432 pg/mL), WHO FC (20.9% riociguat IDT vs. 14.4% placebo subjects with improvement of at least one FC), time to clinical worsening (1% riociguat and 6% placebo) and Borg CR 10 score (-0.4 for riociguat IDT vs. +0.1 for placebo). The significant improvements in TTCW were mainly driven by events of hospitalisations and starting of new PH medications. The original results using a broad definition for TTCW were confirmed by an analysis using the CHMP definition of TTCW.

Long-term non-controlled data: Interim data from the on-going non-controlled long-term extension study PATENT-2 were submitted (cut-off Mar 2013).

In the PAH studies, the mean change in 6MWD from baseline in PATENT-1 to week 12 (last observation until week 12) in PATENT-2 (24 weeks on-study for PATENT-1 &2) was 45.0 m in the former riociguat IDT group and 36.5 m in the former placebo group. Mean change from baseline in PATENT-1 for the total group (N=363) was 51.2 m at 6 months (n=289), 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).

In patients continuing treatment in PATENT-2, efficacy in terms of 6MWD is maintained in later interim analyses (up to 30 months).

Uncertainty in the knowledge about the beneficial effects.

Primary Endpoint: The choice of the 6MWD as the primary endpoint is in line with the relevant CHMP guideline. However, the same guideline underscores the importance of investigating more clinically relevant endpoints like TTCW as a primary endpoint. If the 6MWT is investigated, an actively-controlled study design should have been used, also in line with the relevant guideline.

Subgroups: In CTEPH, the clinical relevance of the effect in the 6-MWD is less clear in WHO II as compared to WHO III patients. The borderline improvement by 25 m is not supported by results on quality of life, WHO status or clinical worsening events.

In PATENT-1, patients with a better WHO FC (II) benefit much less [9.9 m (95% CI: -11.3 to 31.0)] than patients with worse WHO FC (III) (58.0 m (95% CI: -34.8 to 81.2).

Secondary Endpoints: Only results of TTCW in PATENT-1 were significant. Although it is acknowledged that these are different disease populations, results were expected to be comparable. In addition, the results would have been expected to be positive in the longer study, i.e., CHEST-1 of 16 weeks, rather than the 12-weeks PATENT-1 study. This discrepancy casts some doubts on the robustness of the results.

Posology: In both studies, a slow titration procedure over 8 weeks was employed to ensure a better tolerability and was justified by the PK/PD relationship. This is supported. However, the approach may impose practical disadvantages due to the extra clinic visits it may imply.

In the pivotal studies, most of the patients could be up-titrated to 2.5 mg tid, which is reassuring with regards to tolerability. However, in the exploratory arm in PATENT-1, where patients (n=63) were administered a capped titration (CT) (1 to 1.5 mg), efficacy results appear comparable to the riociguat arm titrated to 2.5 mg (mean change from baseline= 31.1±79.3 m vs. 29.6±65.8 m respectively). Significant differences are already observed in riociguat CT versus placebo for 6MWD ($p<0.0001$), PVR ($p<0.0001$), NT proBNP ($p<0.0001$), but not observed for WHO functional class ($p=0.0674$), time to clinical worsening ($p=0.3939$) or Borg CR 10 ($p=0.1068$). The latter 2 endpoints are significantly better using the IDT regimen, implying that the full therapeutic effect is probably only achieved by that higher dose. Efficacy in the different subgroups is more consistently observed with the IDT regime, specifically, patients with PAH associated with CTD, patients co-administered ERA and smokers probably benefit more from the IDT regimen. Nevertheless, the need to uptitrate all patients to the maximum dose is questioned.

Risks

Unfavourable effects

Riociguat belongs to a new therapeutic group, sGC stimulators. As such its safety profile is limited to data from the current application, but generally this can be predicted to be in line with other agents which increase cGMP. However, the interaction with other therapies used in PAH, and the disease characteristics may add complexity to the safety profile.

Although quite usual in orphan products, the extent of the safety database is limited and only the common adverse events (AEs) are well characterised.

Bleeding events: The incidence rate of all bleeding events was comparable in the treatment groups, e.g. 15.7% (77/490) in all riociguat treated subjects vs. 14.5% (33/214) in placebo subjects in POOL-1. Most of the subjects in both groups had an outcome of recovered or resolved. However, there is a slight imbalance in the more serious events which were reported in the riociguat group only: SAEs (12/490 [2.4%] riociguat vs. none placebo, including two cases of GI bleeding), AE related deaths (2/490 [0.4%] riociguat vs. none placebo) and discontinuations due to AE (2/490 [0.4%] riociguat vs. none placebo). The two death cases comprise one subject with haemoptysis and one subject with catheter site haemorrhage. The investigators assessed both fatal events as not related to the study medication.

The risk of bleedings is aggravated by the concomitant use of anticoagulants, which is the standard of care in CTEPH and recommended in PAH.

Haemoptysis was reported with a higher incidence with riociguat (10/490 [2.0%]) vs. the placebo rate (2/214 [0.9%]), and was assessed as a SAE in riociguat treated subjects only (5/490 [1.0%] vs. none placebo). One subject had a fatal outcome.

During long term extension (LTE) phase an additional 21/557 events were reported, 7 of them assessed as SAEs, 18 of them with an outcome of recovered or resolved and 3 not recovered or resolved. However, the rate of haemoptysis decreased during the LTE phase (9 events per 100 person years in all riociguat vs. 6 in placebo and 5 for all riociguat during LTE).

In POOL-3 (phase II and phase III studies), haemoptysis was also reported at a higher rate in the riociguat (13/754; 1.7%) vs. (2/289; 0.7%) placebo and as SAEs (riociguat: 5/754; 0.7%) vs. none in placebo. No additional fatal outcome occurred in POOL-3. During LTE phase an additional 24/642 events were reported, 9 of them assessed as SAEs, 20 of them with an outcome of recovered or resolved and 4 not recovered or resolved. This rate is less than the placebo controlled period (8 events per 100 person years in all riociguat vs. 4 in placebo and 4 for all riociguat during LTE).

Pulmonary haemorrhages were reported with an incidence of 3/642 [0.5%] in the long-term extension studies; all of them had a fatal outcome. No other events were reported in other studies.

Further analysis of the reported cases did not reveal any specific risk factors that could have contributed to the causality (see below).

Renal impairment: There was an imbalance for the preferred terns (PTs) renal failure, renal failure acute and chronic as well as renal impairment, which was small in POOL-1 (3/490 [0.6%]

all riociguat for each renal failure and renal failure acute; 2/490 [0.4%] all riociguat for renal failure chronic and none in placebo subjects for any of these PTs; no AE renal impairment in all riociguat vs.1/214 [0.5%] placebo). This difference was also present in POOL-3: (5/754 [0.7%] all riociguat for each renal failure acute, renal failure chronic, and renal impairment plus 6/574 [0.8%] for renal failure vs. none of each for placebo. A case-by-case analysis showed that renal impairment in these patients occurred in complex situations with many contributing factors, but riociguat use was associated with more of these situations than placebo, possibly through hypotension.

Bone: Preclinical data show a variable effect depending on the species and the age of the animal tested. For example, chronic administration of riociguat in adolescent rats, growth plate alterations, epiphyseal cartilage thickening and increases in bone mass of the primary and secondary spongiosa were observed. However, these findings have not been further explored in other species. Until further data are available, the use in children and growing adolescents should be avoided.

According to the Applicant results of serum calcium, phosphate, and 1.25-dihydroxyvitamin D and the biomarkers type I collagen C-telopeptides (CTX) and osteopontin were evaluated in the study program and did not show a clinically meaningful change during treatment and no difference was observed between the riociguat and placebo groups. However, data from the PD study 13790 do not exclude an effect of riociguat on bone metabolism. Long-term data are also missing currently.

Anaemia was reported with a higher rate in the all riociguat group (7.8% [38/490]) compared to placebo (1.9% [4/214]) which is reflected in the observed decrease of haemoglobin (approximately 0.5 mg/dL) and of haematocrit (approximately 2%) during double blind treatment in the all riociguat group compared to a stable placebo values. This decrease tended to normalise during the LTE phase (23 events per 100 person years in all riociguat vs. 9 in placebo and 7 for all riociguat during LTE). Haemodilution may explain this finding, at least partially.

Atrial fibrillation: In the controlled studies, there was an imbalance for AF, (5/490 [1.0%] all riociguat vs. none placebo). This was also observed in POOL-3 resulting in a total of 13/754 (1.7%) events of atrial fibrillation vs. none reported from placebo subjects respectively. An analysis of atrial fibrillation or atrial flutter (AF/AFL) in the main and LTE studies showed that the rate of AF/AFL reported as TEAEs was slightly higher in the riociguat group (1.2%) compared to the placebo group (0.5%); whereas the reported SAE were comparable (0.4% and 0.5% respectively). The applicant explains that in 2 of 6 reported TEAE with riociguat the arrhythmia was recorded before the administration of riociguat. This balances the incidence between the 2 treatment arms. In addition, 3 of these 6 patients had a medical history of arrhythmia. In the LTE phase, the incidence of AF/AFL reported as TEAEs was 2.5%, with 2.3% reported as serious. The incidence of treatment-emergent atrial fibrillation or atrial flutter events was 2.8 per 100 patient-years, in line with registry data for PAH.

Benefit-risk balance

Importance of favourable and unfavourable effects

CTEPH: CHEST-1 is the first randomised controlled study to show significant results in terms of improvement in exercise capacity and pulmonary haemodynamics in adult patients with CTEPH.

Previous studies with bosentan or sildenafil failed to show significant results. Benefits in terms of the 6MWT are clinically relevant compared to results observed in PAH studies. Secondary endpoints further support efficacy demonstrated by significant improvements in pulmonary haemodynamics, NT-proBNP and WHO FC. However, improvement in time to clinical worsening was not shown, as would have been expected with the short study duration.

PAH: The study design of PATENT-1 follows that used in most of the previous PAH drug applications. However, several recent metanalyses illustrate the limitations of investigating the 6MWT. It was communicated to the Applicant during the scientific advice given in 2009 that clinical outcome/endpoints were preferred to the 6MWT. The advice given was that if the 6MWT was chosen as the primary outcome, it should rather be studied in a comparative setting with one of the established therapies and not in placebo-controlled design, as also indicated in the CHMP guideline. This would have clarified the position of riociguat in the treatment armamentarium, at least when given as monotherapy. Using historical comparisons, the improvement in exercise capacity observed in treatment-naïve subjects is of the same magnitude as that observed in monotherapy clinical studies with registered PAH specific drugs (SUPER [sildenafil] 45 m to 50 m; BREATHE-1 [bosentan] 44m; ARIES-1 and ARIES-2 [ambrisentan] 31m to 59m; SERAPHIN [macitentan 6MWD after 6 months]: 17m to 22m). Such data regarding efficacy are reassuring.

For the combination therapies in PAH patients, there are very limited controlled data, although different combinations are described by the European Society of Cardiology (ESC) guideline and are practiced clinically. As such, the presented data for combination therapy appears additive and reassuring. In PATENT-1, there is adequate representation of patients administered riociguat on top of ERAs and relevant efficacy has been shown. There was limited representation of patients administered prostanoids (n=31), and of whom one third were on an un-authorised prostanoid (beraprost). The relevance of the results are accordingly doubtful.

In both CTEPH and PAH, there is limited benefit demonstrated for patients in WHO FC II in terms of improvement of exercise capacity. In order to address this issue, the applicant was requested to further analyse the data regarding benefits in treatment naïve vs. patients on combination therapy (PATENT-1), and inoperable vs. post-operative CTEPH (CHEST-1). Also long term data of these patients were considered. Analysis did not reveal consistent results, with wide confidence intervals, which could be expected from the limited number of patients, the uneven distribution at baseline (which could be a chance finding) and the *post hoc* nature of the analysis. Also some subgroups showed unexplained placebo responses.

Safety data are based on the pivotal controlled studies as well as their long-term extensions, providing a mean exposure for around 550 patients for a year. Though limited, it can be acceptable for an orphan indication. The common AEs are mainly related to the mechanism of action of vasodilatation and reflected as neurological and gastrointestinal AEs. Most of these AEs are observed with a lower frequency in the long-term extensions, which is reassuring.

Haemoptysis and acute renal failure were SAEs only reported in the riociguat group, which is of concern, especially for haemoptysis. The Applicant informed the CHMP about the possible higher incidence of haemoptysis and pulmonary haemorrhage through a safety communication in November 2012. Further analysis of the reported cases of haemoptysis did not reveal any specific risk factors that could have contributed to the causality. However, all the cases reported

in patients with serious events had a previous history of respiratory bleeding. A tendency was observed for respiratory tract bleeding events to occur more often in younger patients, particularly in patients with higher PAPmean and PVR. However, the data did not indicate that PAPmean and PVR could be used to predict the individual risk. In addition, there was a tendency for higher rates occurring in Asian patients. A link to respiratory tract infections cannot be ruled out. The co-administration of vitamin K antagonists or the quality of the INR did not result in an increased rate of any bleeding event in riociguat treated subjects: 18% of subjects who had received VKAs had a haemorrhagic event in both treatment groups (riociguat and placebo) in the double blind studies.

In general, these SAEs did not cause an unfavourable outcome in time to clinical worsening.

The observed anaemia in association with riociguat use is also noted with endothelin receptor antagonists. The mechanism of this adverse event can be attributed to vasodilatation.

Benefit-risk balance

For both the CTEPH indication and the PAH indication, the overall benefit/risk is considered to be positive.

Discussion on the benefit-risk balance

In this application, riociguat administered in a dose range of 1-2.5 mg t.i.d., is shown to have beneficial effects in two different forms of pulmonary hypertension: CTEPH and PAH. The dose is up-titrated every 2 weeks during 8 weeks guided by systemic blood responses. Though the titration scheme was complicated it was successfully applied in the phase II and phase III clinical studies ensuring that patients reached their optimal and well-tolerated, individualized dose of riociguat. It was also is sufficiently justified by inter-individual differences in PK/PD and susceptibility. Importantly, dose titration process did not lead to a delay in attaining efficacy (usually shown by week 4 in both studies). To avoid medication errors, due to the five available strengths, adequate preventive measures will be in place as soon as riociguat is commercially available. This was considered adequate by the CHMP.

Based on the favourable data with the capped dose regimen of 1.5 mg tid in PAH, it cannot be excluded that this dose could be adequate for some patients; with no need for further up-titration to the maximum dose of 2.5 mg tid. This is clarified in the SmPC.

Benefits are investigated in short-term studies, and shown in terms of improvement of exercise capacity; improvement in clinical outcomes was investigated as a secondary endpoint, and results were positive in only one study (PATIENT-1 in PAH). However, the duration of the studies was too short to be conclusive. Efficacy is limited in patients with WHO FC II (both in PAH and CTEPH). However, clinical trial experience indicates that it is always difficult to show robust improvements in such patients as the margin in improvement is limited. There was also a substantial improvement in the placebo group limiting the difference, with wide confidence intervals in the results. In fact maintaining a patient to FC II is a goal of PAH therapy. It also does not appear plausible that riociguat would only work in only the more severely diseased patients and it can be assumed that at least in some patients a beneficial effect may occur. Considering that patients can shift between FC II and III, it does not appear practical to specifically exclude FC II patients from the indication; this would probably only lead to the off-label use of the drug in this subgroup. Therefore, as reflected in the indication, riociguat is

indicated in patients with both FC II and III (both in PAH and CTEPH) with a cross reference to section 5.1, where the results are separately described for each functional class. This allows the prescriber to make an informed decision.

These benefits are coupled to unfavourable effects related to the ensuing vasodilatation, in the form of headache, dizziness and hypotension or reflected on the gastrointestinal tract. There is an observed risk of haemoptysis and pulmonary haemorrhages, for which the underlying mechanism or possible riociguat causality is not yet clear. Haemoptysis is a rare complication of PAH, more seen in congenital forms than idiopathic PAH. In CTEPH, haemoptysis occurs more often and may be recurrent, as a result of dilated and hypertrophied bronchial collateral circulation. Survival rates of 60%, 43% and 36% at 1, 3 and 12 months respectively were documented in registries following an episode of haemoptysis. It can be agreed with the Applicant that a direct PK/PD interaction is not the main mechanism: there is no evidence for an influence of riociguat on platelet function in humans (aspirin interaction study 14204), nor evidence for an interaction with warfarin (warfarin interaction study 11918). A case-by-case analysis did not identify risk factors except for previous respiratory tract bleeding event. One hypothesis proposed by the Applicant is that this might be related to riociguat's strong vasodilatory effect on bronchial arteries, influencing vasocontractility in case of severe lung bleeding, which is plausible. This hampers implementation of further risk minimisation measures. The SmPC includes data regarding the risk of other types of serious bleeding.

As can be expected the safety experience with riociguat is quite limited, especially when compared with both PDE5 inhibitors and ERAs, whose safety profile is well established. Still the analysis of time to clinical worsening suggests that these disadvantages have only limited consequences, and the safety data from the long-term extension phases are reassuring.

CTEPH is an orphan disease; the treatment is mainly surgical by pulmonary endarterectomy. However, some patients are considered inoperable, or have recurrent pulmonary hypertension post-operative. Considering the similarities between CTEPH and PAH, medicinal products authorised for PAH are often administered and even have a class IIb-C recommendation, as no randomised clinical trial (RCT) has shown a significant benefit. In one RCT (BENEFIT) bosentan was shown to have significant effects on pulmonary haemodynamics, but not on 6MWT. In another study, sildenafil resulted in a non-significant increase in 6MWT. As such, CHEST-1 is the only study to show both statistically and clinically relevant improvements in 6MWT, pulmonary haemodynamics, pro-PNB, and FC WHO.

For the PAH indication, the application addresses two sub-indications: monotherapy and combined therapy. Efficacy in both sub-populations appears comparable. For monotherapy, although direct comparative data are lacking, the benefits in terms of improvement in exercise capacity appear to be in line to those already observed for the authorised ERAs and PDE5 inhibitors. Riociguat's mechanism of action is comparable to that of PDE5 inhibitors, e.g. sildenafil and tadalafil in the sense that both compounds increase cGMP. The difference is that riociguat does not require NO for activity, but it is not clear if this is an advantage clinically. It would have been very informative to have a head-to-head comparison with one of the PDE5 inhibitors to help assess the whole B/R profile of riociguat and identify its place in the treatment of PAH in clinical practice.

Regarding combination therapy, direct comparative data with other combinations are also lacking. Although different combinations are described by the ESC guideline and practiced clinically, these combinations may be complicated and one specific reference therapy is difficult to identify. As such, the current positive clinical results in PATENT-1 addressing the combination of riociguat with ERAs in comparison with placebo with ERAs are considered reassuring and sufficient to include in the indication.

Taking into account the above considerations the CHMP concluded that based on the current level of data the benefit/risk balance of riociguat is positive in the proposed indications.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Adempas is not similar to Volibris, Revatio, Ventavis and Opsumit within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Adempas in the treatment of adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment, and adult patients with pulmonary arterial hypertension (PAH) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that riociguat is qualified as a new active substance.