EU RISK MANAGEMENT PLAN (RMP)

ADEMPAS®

BAY 63-2521
(Riociguat)

No. 9.3

Date of Report:
04 MAR 2025

[redacted]

EU Risk Management Plan for Adempas (Riociguat)

RMP version to be assessed as part of this application:

- RMP Version number: 9.3
- Data lock point for this RMP: 19 SEP 2024
- Date of final sign off: 04 MAR 2025

Rationale for submitting an updated RMP:

The EU RMP version 9.2 is updated due to the following procedures:

Procedure No. EMEA/H/C/002437/X/0041, Responses to CHMP D150 LoQ

Summary of significant changes in this RMP:

Minor update of:

- Part I alignment with proposed SmPC
- Part VI alignment with proposed SmPC

Other RMP versions under evaluation: Not applicable/None

Details of the currently approved RMP:

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List of Abbreviations

%	Percent
<	Less Than
>	Greater Than
≥	Greater Than or Equal To
6MWD	Six Minute Walking Distance
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under the concentration time Curve
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
bmp	Beats Per Minute
BMPR2	Bone Morphogenetic Protein Type II Receptor
BPA	Balloon Pulmonary Angioplasty
BRCP	Breast Cancer Resistance Protein
BSEP	Bile Salt Export Pump
cGMP	Cyclic Guanosine Monophosphate
CHD	Congenital Heart Disease
CHEST	Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial
cm	Centimetre
C_{max}	Maximum Concentration
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CTD	Connective Tissue Disease

CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CYP	Cytochrome P450
DVT	Deep Vein Thrombosis
EMA	European Medicines Agency
EMEA	Europe, Middle East and Africa
EOS	End of Study
EPAR	European Public Assessment Report
ERA	Endothelin Receptor Antagonist
EU	European Union
EXPERT	Exposure Registry Riociguat in Patients with Pulmonary Hypertension
F	Female
FC	Functional Class
FPAH	Familial Pulmonary Arterial Hypertension
FPFV	First Patient First Visit
FSFV	First Subject First Visit
g	Gram
GVP	Good Pharmacovigilance Practices
hERG	Human Ether-A-Go-Go-Related Gene
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
IAS	Integrated Analysis of Safety
IC_{50}	Half Maximal Inhibitory Concentration
IIP	Idiopathic Interstitial Pneumonia
ILD	Interstitial Lung Disease

INN	International Non-proprietary Name
Kg	Kilogram
L	Litre
LEPHT	Left Ventricular Systolic Dysfunction Associated with Pulmonary Hypertension Riociguat Trial
LMP	Last Menstrual Period
LPLV	Last Patient Last Visit
LTE	Long-Term Extension
LVD	Left Ventricular Disease
M	Male
M-1	Main Metabolite
MATE1	Multidrug and Toxin Extrusion Protein 1
MATE2K	Multidrug and Toxin Extrusion Protein 2K
MedDRA	Medical Dictionary for Regulatory Activities
Mfr	Manufacturer
mg	Milligram
min	Minute
mL	Millilitre
mmHg	Millimetre of Mercury
MRHD	Maximum Recommended Human Dose
MRP2	Multidrug Resistance Protein 2
MSSO	Maintenance and Support Services Organization
N/A	Not Applicable
NO	Nitric Oxide
NT-proBNP	N-terminal-pro hormone B-type Natriuretic Peptide

OAT1	Organic Anion Transporter 1
OAT3	Organic Anion Transporter 3
OATP1B1	Organic Anion Transporting Polypeptide 1B1
OATP1B3	Organic Anion Transporting Polypeptide 1B3
OCT1	Organic Cation Transporter 1
OCT2	Organic Cation Transporter 2
OCT3	Organic Cation Transporter 3
PaCO2	Partial Pressure of Carbon Dioxide
PAH	Pulmonary Arterial Hypertension
PaO2	Partial Pressure of Oxygen
PASS	Post-Authorisation Safety Study
PATENT	Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial
PBRER	Periodic Benefit-Risk Evaluation Report
PCA	Prostacyclin Analogue
PD	Pharmacodynamic(s)
PE	Pulmonary Embolism
PEA	Pulmonary Endarterectomy
P-gp	P-Glycoprotein
PH	Pulmonary Hypertension
PH-IIP	Pulmonary Hypertension Idiopathic Interstitial Pneumonias
PhV	Pharmacovigilance
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic(S)
PoPH	Porto-pulmonary Hypertension

PSUR	Periodic Safety Update Report
PVOD	Pulmonary Venous Occlusive Disease
PVR	Pulmonary Vascular Resistance
REVEAL	Registry To Evaluate Early And Long-Term Pulmonary Arterial Hypertension Disease Management
RHC	Right Heart Catheterization
RMP	Risk Management Plan
SaO2	Oxygen Saturation
SBP	Systolic Blood Pressure
sGC	Soluble Guanylate Cyclase
sGMP	Soluble Granule Membrane Protein
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
SN	Study Number
SmPC	Summary of Product Characteristics
TEAEs	Treatment-Emergent Adverse Events
TESAEs	Treatment-Emergent Serious Adverse Events
TID	*Ter In Die* (Three Times A Day)
UK	United Kingdom
ULN	Upper Limit of Normal
US(A)	United States (of America)
WHO	World Health Organization

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Part I: Product(s) Overview

PART I: Product(s) overview

Table Part I-1: Product overview

Active substance(s) (INN or common name):	Riociguat
Pharmaco-therapeutic group (ATC Code):	Anti-hypertensives for pulmonary arterial hypertension (C02KX05)
Name of Marketing Authorisation Holder or Applicant:	Bayer AG
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	Adempas
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Adempas comprises film-coated tablets and granules for oral suspension containing the active substance riociguat, for oral use. Chemical name: Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo [3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate Summary of mode of action Pulmonary hypertension is associated with endothelial dysfunction, impaired synthesis of NO and insufficient stimulation of the NO-sGC-cGMP pathway. Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). When NO binds to sGC, the enzyme catalyses synthesis of the signalling molecule cyclic guanosine monophosphate (cGMP). Intracellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Riociguat has a dual mode of action. It sensitises sGC to endogenous NO by stabilising the NO–sGC binding. Riociguat also directly stimulates sGC independently of NO. Riociguat restores the NO–sGC–cGMP pathway and leads to increased generation of cGMP. Important information about its composition Excipients are as follows: Tablets: cellulose microcrystalline, crospovidone, hypromellose, magnesium stearate, lactose monohydrate and sodium lauryl sulphate. In

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Table Part I-1: Product overview

	addition, the film coat contains the following: hydroxypropylcellulose, hypromellose, propylene glycol and colouring. Granules for oral suspension: citric acid, anhydrous, strawberry flavour (consist of maltodextrin (maize), propylene glycol E1520, triethyl citrate E1505, flavoring substances and flavoring preparations), hypromellose 5 cP, mannitol, microcrystalline cellulose and carmellose sodium (syn.: Microcrystalline cellulose and carboxymethylcellulose sodium), sodium benzoate, sucralose and xanthan gum.
Hyperlink to the Product Information	Proposed updated Product Information as available in Module 1.3.1
Indication(s) in the EEA	*Chronic thromboembolic pulmonary hypertension (CTEPH)* 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. *Pulmonary arterial hypertension (PAH)* *Adults* Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with PAH with WHO Functional Class (FC) II to III to improve exercise capacity. *Paediatric PAH* Adempas is indicated for the treatment of PAH in paediatric patients aged 6 to less than 18 years with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists. .
Dosage in the EEA	*Tablets:* *Starting Dose:* The recommended starting dose is 1 mg 3 times daily for 2 weeks. Tablets should be taken 3 times daily approximately 6 to 8 hours apart Adult patients Dose should be increased in 2-week intervals by

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Table Part I-1: Product overview

	0.5 mg 3 times daily to a maximum of 2.5 mg 3 times daily, if systolic blood pressure is ≥95 mmHg and the patient has no signs or symptoms of hypotension. In some PAH patients, an adequate response on the 6-minute walk distance (6MWD) may be reached at a dose of 1.5 mg 3 times a day (see section 5.1). 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 current dose should be decreased by 0.5 mg 3 times daily. *Paediatric PAH patients aged 6 to < 18 years with body weight ≥ 50 kg* Adempas is available for paediatric use as a tablet for those with body weight ≥ 50 kg. Titration of riociguat dose is to be performed based on the patient's systolic blood pressure and general tolerability at the discretion of the treating physician/healthcare provider. If the patient has no signs or symptoms of hypotension and systolic blood pressure is ≥ 90 mmHg for the 6 to < 12 year age group or ≥ 95 mmHg for the 12 to < 18 year age group, the dose should be increased in 2-week intervals by 0.5 mg 3 times daily to a maximum daily dose of 3 times 2.5 mg. If systolic blood pressure falls below these specified levels the dosage should be maintained as long as 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 the specified levels, and the patient shows signs or symptoms of hypotension the current dose should be decreased by 0.5 mg 3 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., 2.5 mg 3 times daily) for adults and paediatric patients with body weight of at least 50 kg. 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.

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Table Part I-1: Product overview

	Granules *Paediatric PAH patients weighing less than 50 kg* Adempas is available as granules for oral suspension to treat paediatric PAH patients at least 6 years of age and weighing less than 50 kg – see Summary of Product Characteristics for Adempas granules for oral suspension for further direction. Patients may switch between tablets and oral suspension during therapy due to body weight changes. .
Pharmaceutical form(s) and strengths	
	0.5 mg film-coated tablets 1.0 mg film-coated tablets 1.5 mg film-coated tablets 2.0 mg film coated tablets 2.5 mg film coated tablets 0.15 mg/ml granules for oral suspension
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: Safety specification

PART II: Module SI: Epidemiology of the indication(s) and target population(s)

SI.1 Indications: Chronic Thromboembolic Pulmonary Hypertension (CTEPH); World Health Organization (WHO) Group 4 (1)

Epidemiology of the Disease

Incidence and prevalence

Annual incidence of CTEPH in adults:

- 0.9/1,000,000 in Spain (2)
- 0.16/100 person-years after pulmonary embolism (PE) in the Netherlands (3) (estimates of cumulative incidence after PE: 0.5–2% (4), 3.8% (5), and 6.5% (6)).

Prevalence of CTEPH:

- 3.2/1,000,000 adults in Spain (2)
- 63–1,007/1,000,000 individuals in the United States of America (USA) (claims database study) (7).

Demographics of the target population

Age at diagnosis of CTEPH:

- median: 63 years (international registry) (8)
- mean: 51.2–60.5 years in Japan (range of means in 4 study subgroups) (9).

Percentage of women in CTEPH populations:

- 50% (international registry) (8)
- 60% in Spain (2)
- 70–72% in the Netherlands and Germany (inoperable CTEPH) (10, 11)
- 69% in Japan (9).

In a registry of patients with CTEPH in Europe and Canada, 95.9% were white (8).

Risk factors for the disease

Risk factors for CTEPH include the following: previous PE and deep vein thrombosis (DVT), previous splenectomy, ventriculoatrial shunt, myeloproliferative disorders, and chronic inflammatory diseases (4, 12).

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Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Main treatment options

Patients with CTEPH usually receive an anticoagulant drug to reduce the risk of recurrent PE (13). However, other than Adempas and treprostinil, no drugs have yet been approved for the treatment of CTEPH itself in the EU. The 'gold standard' treatment for 'operable' patients are pulmonary endarterectomy (PEA), a highly specialised surgical procedure that can be curative. However, not all patients can be treated with PEA. Co-morbidities such as renal or hepatic dysfunction increase the risk associated with PEA, and patients with a substantial degree of microvascular disease (distal CTEPH) are less likely to have a successful surgical outcome than patients with proximal CTEPH (13). There is currently considerable off-label use of other pulmonary arterial hypertension (PAH)-approved therapies in patients with CTEPH (14). Emerging therapy balloon pulmonary angioplasty (BPA) is included in the current European Respiratory Society/European Society of Cardiology guidelines and is recommended in patients who are technically inoperable or have residual PH after PEA and distal obstructions amenable to BPA (class I, level b). BPA may also be considered for technically operable patients with a high proportion of distal disease and an unfavourable risk-benefit ratio for PEA (class IIb, level c). (16).

The treatment consists of a standard balloon angioplasty technique which aims to re-open occluded vessels by inserting and inflating a balloon catheter. The treatment is split across 3-5 sessions, and during each session a single area is targeted to minimize risk (15).Mortality and morbidity (natural history)

CTEPH is characterised clinically by progressive dyspnoea and development of right heart failure and, ultimately, death. The clinical course of CTEPH reflects the progressive increase in pulmonary vascular resistance (PVR), which is markedly elevated in this patient population. CTEPH continues to be an under-recognised and under-diagnosed disease, and most patients with CTEPH present late in the course of the disease because patients may remain asymptomatic for many years. The signs and symptoms of CTEPH are similar to those of other forms of pulmonary hypertension and depend on the severity of disease at presentation. Exertional dyspnoea and/or an unexplained decline in functional status are the most frequent presenting complaints. With the development of a significant degree of right ventricular dysfunction, symptoms such as exertional pre-syncope and physical signs including peripheral oedema, jugular venous distention, and hepatomegaly may become evident. If unrecognised or untreated, progressive right ventricular dysfunction with the ultimate development of right heart failure is the expected outcome (17).

Mortality associated with PEA varies depending on the experience of the surgical centre, the accessibility of the vascular obstructions and the PVR (13). Table Part II SI-1 summarises recent data.

Table Part II SI-1: Recent PEA mortality data

Country [reference]	Patients with CTEPH, n	Pre- or post-operative mortality
Europe and Canada (18)	679 (386 operated)	4.7%
USA (19)	500 operated	4.4%

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Table Part II SI-1: Recent PEA mortality data

Country [reference]	Patients with CTEPH, n	Pre- or post-operative mortality
China (20)	504 (360 operated)	4.4% (surgical treatment) 3.5% (non-surgical)[a]
Japan (9)	72 (40 operated)	7.7% (proximal CTEPH) 21.4% (distal CTEPH)

CTEPH = Chronic thromboembolic pulmonary hypertension, PEA = Pulmonary endarterectomy, USA = United States of America
[a] In-hospital mortality.

Longer-term survival rates in CTEPH are shown in Table Part II SI-2.

Table Part II SI-2: CTEPH long-term survival rates

Country [reference]	Survival					
After PEA:	**1 year**	**3 years**	**5 years**	**6 years**	**10 years**	**15 years**
International (18)	93%					
UK (21, 22)		76–83%				
UK (23)			90%			
Italy (24)			84%			
Japan (9)				79%[a] 92%[b]		
China (20)					72%[a] 95%[b]	30%[a] 91%[b]
Non-surgical patients:						
The Netherlands (10)	93%	78%	68%			
Japan (9)				77.6%[a]		
China (20)					70%[a] 81%[b]	33%[a] 56%[b]

CTEPH = Chronic thromboembolic pulmonary hypertension, PEA = Pulmonary endarterectomy, UK = United Kingdom
[a] Distal CTEPH.
[b] Proximal CTEPH

Concomitant Medication(s) in the Target Population

In Switzerland, 79%–98% of patients with CTEPH were receiving oral anticoagulant therapy (25). A study in the USA found that 98%–99% of patients undergoing PEA were receiving anticoagulation, 47%–59% were taking diuretics, 7%–22% were taking spironolactone, and 6-14% were treated with digoxin (14).

Important Co-morbidities Found in the Target Population

Co-morbidities in patients with CTEPH were identified from an international registry (8); co-morbidities with a prevalence >10% in the registry are described in the sections below. Smoking and renal impairment are also discussed.

Previous PE

Previous PE was confirmed for 74.8% of patients with CTEPH in Europe and Canada (77.5% and 70.0% of operable and inoperable patients, respectively) (8).

Among patients in Europe and Canada who underwent surgical treatment for CTEPH and had a history of confirmed PE, 3.9% died in hospital and 6.2% died by 1 year (18).

Previous DVT

Prevalence of previous DVT in patients with CTEPH:

- 56.1% in an international registry (60.4% and 49.0% of operable and inoperable patients, respectively) (8)
- 69% in Europe (history of venous thromboembolism) (26)
- 49.5% in Japan (27).

No study was identified that reported the mortality associated with DVT in patients with CTEPH.

Thrombophilic disorder

No epidemiological study was found that reported the incidence of thrombophilic disorder in patients with CTEPH.

Prevalence of thrombophilic disorder in patients with CTEPH:

- 31.9% in an international registry (37.1% and 23.5% of operable and inoperable patients, respectively) (8).

In patients with a thrombophilic disorder and CTEPH undergoing PEA, in-hospital mortality was 5.0% and mortality at 1 year was 9.2% (18).

Previous major surgery

Prevalence of previous major surgery in patients with CTEPH:

- 21.7% in an international registry (18.8% and 26.7% of operable and inoperable patients, respectively) (8)
- 3.8% in Japan (recent major operation) (28).

No study was identified that reported the mortality associated with previous major surgery in patients with CTEPH.

Varicose veins

No epidemiological study was found that reported the incidence of varicose veins in patients with CTEPH.

Prevalence of varicose veins in patients with CTEPH:

- 20.8% in an international registry (20.4% and 21.1% in operable and inoperable patients, respectively) (8).

No study was identified that reported the mortality associated with varicose veins in patients with CTEPH.

Obesity

No epidemiological study was found that reported the incidence of obesity (body mass index [BMI] ≥30 kg/m^2) in patients with CTEPH.

Prevalence of obesity in patients with CTEPH:

- 17.6% in an international registry (16.7% and 19.0% in operable and inoperable patients, respectively) (8).

No study was identified that reported the mortality associated with obesity in patients with CTEPH.

Chronic venous insufficiency

No epidemiological study was found that reported the incidence of chronic venous insufficiency in patients with CTEPH.

Prevalence of chronic venous insufficiency in patients with CTEPH:

- 15.5% in an international registry (16.0% and 14.6% in operable and inoperable patients, respectively) (8).

No study was identified that reported the mortality associated with chronic venous insufficiency in patients with CTEPH.

History of cancer

No epidemiological study was found that reported the incidence of cancer in patients with CTEPH.

Prevalence of history of cancer in patients with CTEPH:

- 12.7% in an international registry (10.1% and 16.6% of operable and inoperable patients, respectively) (8)
- 12.2% in Europe (compared with 4.3% of patients with non-thromboembolic pulmonary hypertension) (26)
- 7.5% had active cancer in Japan (28).

No study was identified that reported the mortality associated with cancer in patients with CTEPH.

Coronary disease and/or myocardial infarction

No epidemiological study was found that reported the incidence of coronary disease and/or myocardial infarction in patients with CTEPH.

Prevalence of coronary disease and/or myocardial infarction in patients with CTEPH:

- 11.8% in an international registry (11.0% of operable patients and 13.4% of inoperable patients) (8).

In patients with CTEPH and coronary heart disease or myocardial infarction, in-hospital mortality was 10.0% and 1-year mortality was 15.0% (18). Patients without these co-morbidities had a significantly lower risk of mortality (in-hospital mortality, 2.1%; 1-year mortality, 5.1%).

Smoking

No epidemiological study was found that reported the incidence of smoking in patients with CTEPH.

The prevalence of tobacco use in patients with CTEPH was 45% and overall tobacco smoke exposure (active or second-hand) was reported to be 75% (Swiss study) (29).

No study was identified that reported the mortality associated with smoking in patients with CTEPH.

Renal impairment

Renal insufficiency was reported as a post-operative complication in 20.4% of patients with CTEPH undergoing PEA (Czech study) (30).

Approximately one-third of patients with CTEPH undergoing PEA had renal insufficiency at baseline (Czech study) (30).

In a study of patients undergoing PEA in the United Kingdom (UK), the mean pre-operative glomerular filtration rate was 75.7 L/min in those who survived at least 3 months after surgery, and 65.7 L/min in those who did not survive. However, this difference was not statistically significant (31).

SI.2 Indication: PAH; WHO Group 1 (1)

Epidemiology of the Disease

Incidence and prevalence

Annual incidence of PAH

In adults:

- 2.3/1,000,000 in the USA (32)
- 2.4–3.7/1,000,000 in Europe (2, 33).

In children:

- 0.5-2.2/1,000,000 (34-36).

Prevalence of PAH:

- 12.4/1,000,000 adults in the USA (32) (or 109–451/1,000,000 in a claims database study (7))
- 15–16/1,000,000 adults in France and Spain (2, 33)
- 26–52/1,000,000 in the UK (Scotland) (37)
- 2-16/1,000,000 in children (34-36).

Demographics of the target population

Mean age of patients with PAH:

- 71 years in Europe (median; idiopathic, heritable, or drug-associated PAH) (38)
- 54 years in the UK (21)
- 47–48 years in the USA (32)
- 45 years in Spain (2)
- 36 years in China (idiopathic or heritable PAH) (39).

Percentage of women in PAH populations:

- 78% in the USA (32)
- 71% in Spain (2)
- 71% in China (39)
- 65%–70% in the UK and France (21, 33)
- 60% in Europe (idiopathic, heritable or drug-associated PAH) (38).

Ethnicity among patients with PAH in the USA:

- 72.8% white
- 12.2% black
- 8.9% Hispanic
- 3.3% Asian/Pacific Islanders (32).

In a registry in China, the majority of patients with PAH (67/72) were Han Chinese (39).

Risk factors for the disease

Risk factors for PAH include the following: connective tissue disease (CTD), human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease (CHD), schistosomiasis, chronic haemolytic anaemia, and exposure to specific drugs/toxins (e.g., aminorex, fenfluramine, dexfenfluramine, toxic rapeseed oil, and benfluorex, likely also amphetamines, L-tryptophan, and methamphetamines). Mutations in the bone morphogenetic protein receptor 2 gene are a major genetic predisposing factor (4, 12).

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Main treatment options

The following classes of vasodilators – each with a different risk-benefit profile – are currently used to treat PAH: new class of therapy – soluble guanylyl cyclase stimulators – Adempas; phosphodiesterase 5 inhibitors (sildenafil and tadalafil); endothelin receptor antagonists (bosentan and ambrisentan); and prostacyclins/prostacyclin analogues (epoprostenol, treprostinil, iloprost, and beraprost). Despite treatment, most patients with PAH experience progression of their disease.

Mortality and morbidity (natural history)

PAH is a rare, chronic, progressive, and uniformly fatal disease that affects adults and children, and for which there is no cure. Despite advances in diagnosis and an increased awareness of the disease, incidence and prevalence data are based on regional registries and indicate that the disease is still under-diagnosed due to diagnosis in late stages (33, 40-42).

Recent studies in the USA have reported median survival times for patients with PAH of 3.6-4.5 years (42, 43), and one group estimated median survival to be approximately 9 years based on extrapolated data (44). Data from the US-based Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) were used to formulate a prognostic equation that enabled stratification of patients into 5 risk groups, from 'low' (>95% survival at 1 year) to 'very high' (<70% survival at 1 year) (45). In a meta-analysis of PAH clinical trials (average study duration, 14.3 weeks), mortality was 3.8% in the placebo groups and 1.5% in the active treatment groups (46). A summary of survival rates in epidemiological studies is given in Table Part II SI-3.

Table Part II SI-3: Summary of survival rates in epidemiological studies

Country [reference]	Patients with PAH, n	Survival			
		1 year	2 years	3 years	5 years
Europe (38)	587	92%	83%	74%	–
Spain (2)	1,028[a]	87%	–	75%	65%
UK (21)	598	88%	–	68%	–
France (47)	121 (incident cohort)	88%	65%	51%	–
USA (44)	2,635	85%	–	68%	57%
China (39)	72 (idiopathic and familial)	68.0%	56.9%	38.9%	20.8%

CTEPH = Chronic thromboembolic pulmonary hypertension, PAH = Pulmonary arterial hypertension, UK = United Kingdom, USA = United States of America
[a] 866 patients with PAH and 162 patients with CTEPH; no difference in mortality between the 2 groups.

Concomitant Medication(s) in the Target Population

Anticoagulation is recommended for all patients with idiopathic PAH (12), and background therapy may also include diuretics, oxygen, and digoxin (4). In a US-based PAH registry, the proportions of patients receiving various concomitant medications were as follows: diuretics, 69%; warfarin, 53%; oxygen, 40%; digoxin, 26%; synthetic thyroid replacement, 21%; calcium channel blockers, 26%; selective serotonin re-uptake inhibitors, 19%; other

antidepressants, 8%; aspirin, 16%; other anti-inflammatory drugs, 5%; statins, 16%; beta-blockers, 12%; psychotropic drugs, 10%; corticosteroids, 12%; angiotensin converting enzyme inhibitors, 11%; and clopidogrel, 2% (48). The reported prevalence of oral anticoagulant use in patients with PAH outside the USA was 59% in Europe (38), 50% in China (39) and 59%–84% in Switzerland (25).

Important Co-morbidities Found in the Target Population

Co-morbidities in patients with PAH were identified from a recent large registry study in the USA (REVEAL) (48); all PAH co-morbidities with a prevalence >10% in REVEAL are described in the sections below. In addition, subtypes of associated PAH (WHO Group 1.4 (49): PAH associated with CTD, HIV infection, portal hypertension, CHD, schistosomiasis, and chronic haemolytic anaemia) are included in this section, and smoking and renal impairment are also discussed.

CTD

Incidence of PAH associated with CTD:

- 1.55/1,000,000 in the UK in 2005 (50)
- 18% of incident PAH cases during 1 year in France (33)
- 40% of incident PAH cases during 2 years in the USA (42).

Prevalence of CTD in patients with PAH:

- 31% in the UK (21)
- 29% in the USA (48)
- 20% in Europe (38)
- 18% in Spain (2)
- 15.3% in France (33).

Survival rates in patients with PAH and CTD or systemic sclerosis (a major subtype of CTD) are shown in Table Part II SI-4.

Table Part II SI-4: Survival rates in patients with PAH and CTD or systemic sclerosis

Country [reference]	PAH associated with:	Survival (%)		
		1 year	2 years	3 years
UK (21, 50)	Systemic sclerosis	78%	58%	47–52%
USA (51)	CTD	78%	–	–

CTD = Connective tissue disease, PAH = Pulmonary arterial hypertension, UK = United Kingdom, USA = United States of America

HIV infection

Incidence of PAH associated with HIV infection:

- 10% of incident PAH cases during 1 year in France (33)

- 1% of incident PAH cases during 2 years in the USA (42).

Prevalence of HIV in patients with PAH:

- 6.2%–6.6% in France, Spain, and Switzerland (2, 33, 41)
- 2.4% in Europe (38)
- 1.6%–2.2% in the USA (32, 52)
- 0.5% in the UK (21).

Survival rates in patients with HIV-associated PAH:

- at 1 year: 93.3%
- at 3 years: 75.1%
- at 5 years: 63.8%
- at 7 years: 63.8% (USA) (44).

Portal hypertension

PAH associated with portal vein hypertension is also referred to as portopulmonary hypertension (PoPH).

Incidence of PoPH:

- 14.9% of incident PAH cases during 1 year in France (33)
- 9% of incident PAH cases during 2 years in the USA (42).

Prevalence of PoPH in patients with PAH:

- 10.4% in France (33)
- 5.6%–7% in the USA (42, 48)
- 4.0% in the UK (21)
- 3.9% in Europe (38).

Survival rates in patients with PoPH:

- at 1 year: 74.9%
- at 3 years: 51.6%
- at 5 years: 39.4%
- at 7 years: 29.3% (USA) (44).

PoPH was independently associated with increased mortality at 1 year (hazard ratio:3.6; 95% CI: 2.4–5.4) (45), and patients with PoPH had reduced survival at 2 years compared with patients with idiopathic or familial PAH (67% *vs.* 85%, respectively, p<0.001) (53).

CHD

Incidence of PAH associated with CHD:

- 0.3/1,000,000 in France (37)
- 2.2/1,000,000 in Scotland (37)
- 4% of incident PAH cases during 1 year in France (33)
- 13% of incident PAH cases during 2 years in the USA (42).

Prevalence of CHD in patients with PAH:

- 33.1% in the UK (21)
- 19.3% in Spain (2)
- 11.3% in France (33)
- 10%–11% in the USA (42, 48)
- 7.4% in Europe (38).

Survival rates in patients with PAH associated with CHD:

- at 1 year: 88.3% (USA) (44)
- at 3 years: 81.4%–85% (USA and UK) (21, 44)
- at 5 years: 74.4% (USA) (44)
- at 7 years: 67.3% (USA); the survival rate at 7 years was higher than that for any other subcategory of PAH (44).

Schistosomiasis

Schistosomiasis was not present in >10% of the REVEAL population (48), but it is listed in the WHO pulmonary hypertension classification as a specific subcategory of PAH (WHO Group 1.4.5) (1).

Incidence of PAH associated with schistosomiasis:

- no data found.

Prevalence of schistosomiasis in patients with PAH:

- 28% in Brazil (54).

Survival rates in patients with PAH associated with schistosomiasis:

- at 3 years: 85.9% in Brazil (similar to idiopathic PAH [82%]) (55).

Chronic haemolytic anaemia

Chronic haemolytic anaemia was not present in >10% of the REVEAL population (48), but it is listed in the WHO pulmonary hypertension classification as a specific subcategory of PAH (WHO Group 1.4.6) (1).

Incidence of PAH associated with chronic haemolytic anaemia:

- no data found.

Prevalence of chronic haemolytic anaemia in patients with PAH:

- 1.7% in the UK (21)
- 0.3% in Europe (38)
- 0.3% (sickle cell disease) and 0.2% (haemoglobinopathy) in the USA (45).

Survival in patients with PAH associated with sickle cell disease:

- 25.6 months (median) from time of cardiac catheterisation (56)
- 49 months (mean) from diagnosis of PAH (57).

Hypertension

No epidemiological study was found that reported the incidence of hypertension in patients with PAH. The prevalence of hypertension (and/or reported use of beta-blockers as a concomitant medication) in adults with PAH was 40.2% in the USA (48). No study was identified that reported mortality associated with hypertension in patients with PAH.

Obesity

No epidemiological study was found that reported the incidence of obesity (BMI≥30 kg/m^2) in patients with PAH.

Prevalence of obesity in adults with PAH:

- 33.3% in the USA (48)
- 14.8% in France (32).

No study was identified that reported the mortality associated with obesity in patients with PAH.

Clinical depression

PAH is a debilitating and ultimately fatal disease and may therefore have a detrimental effect on mental health. No epidemiological study was found that reported the incidence of clinical depression in patients with PAH, but prevalence data are available.

In the USA, 25.2% of patients with PAH reported the co-morbidity of clinical depression and/or reported the use of selective serotonin reuptake inhibitors (48). In another study, 35% of patients with pulmonary hypertension (78% of whom had PAH) had mental disorders (58). The most common mental disorders were major depressive disorder (15.9%) and panic disorder (10.4%).

No study was identified that reported the mortality associated with clinical depression in patients with PAH.

Diabetes

No epidemiological study was found that reported the incidence of diabetes in patients with PAH.

Prevalence of diabetes in patients with PAH:

- 1.4% (type 1) and 10.6% (type 2) in a US-based registry (48).

No study was identified that reported the mortality associated with diabetes in patients with PAH.

Hypothyroidism, obstructive airway disease, and sleep apnoea

Pulmonary hypertension associated with hypothyroidism, obstructive airway disease, or sleep apnoea is categorised as a separate entity from PAH (and CTEPH) in the WHO pulmonary hypertension classification (1). Nevertheless, hypothyroidism, obstructive airway disease, and sleep apnoea were recorded as co-morbidities in >10% of patients diagnosed with PAH in the US-based REVEAL registry:

- 21.6% had hypothyroidism
- 21.9% had obstructive airway disease
- 21.0% had sleep apnoea (48).

Smoking

No epidemiological study was found that reported the incidence of smoking in patients with PAH.

The prevalence of tobacco use was significantly higher in patients with PAH (61%) than in the general population (49%) (Swiss study) (29). Overall tobacco smoke exposure (active or second-hand) was also significantly higher in patients with PAH than in the general population (82% *vs.* 59%, respectively).

No study was identified that reported the mortality associated with smoking in patients with PAH.

Renal impairment

No epidemiological study was found that reported the incidence of renal impairment in patients with PAH.

Prevalence of renal impairment in patients with PAH:

- 4.5% (renal insufficiency) or 12% (chronic kidney disease) in the USA (48, 59)
- creatinine clearance (German study) (60):
    - ≥90 mL/min: 35%
    - 60–89 mL/min: 48%
    - 30–59 mL/min: 14%

- <30 mL/min: 3%.

Incidence of acute kidney injury in patients with PAH hospitalised for acute right heart failure:

- 32% of patients, 23% of hospitalisations (61).

Mortality among patients with PAH over a median follow-up of 3.5 years was:

- 44% in patients with serum creatinine <1 mg/dL
- 61% in patients with serum creatinine 1.0–1.4 mg/dL
- 84% in patients with serum creatinine >1.4 mg/dL (59).

PART II: Module SII: Non-Clinical Part of the Safety Specification

Key Safety Findings

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
General systemic toxicity	
• After single oral as well as intravenous administration, riociguat revealed only unspecific signs of toxicity. Clinical signs as well as mortality at high dose levels were most likely related to the exaggerated haemodynamic effects of riociguat. • After single and repeated dosing, there was no major difference in the qualitative or quantitative toxicological response in male and female rodents. • The toxicological profile after repeated administration was characterised by effects secondary to the intracellular cGMP increase. In all species tested, as a consequence of this pharmacological mode of action, effects secondary to an exaggerated smooth muscle cell relaxation in the cardiovascular system (e.g., blood pressure decrease, reflex tachycardia) and gastrointestinal system (vomitus, diarrhoea, intestinal dilation, tympany) were observed.	Single- and repeated-dose toxicity studies in mice, rats, and dogs did not reveal any off-target adverse effects that are considered of relevance to humans. Consistent with the proposed pharmacological mode of action, haemodynamic effects were observed in all species tested. In addition, due to the relaxation of smooth muscle cells, motility disorders of the upper and lower gastrointestinal tract were observed. Haemodynamic effects and gastrointestinal findings were also observed in patients.
Nephrotoxicity	
• In repeated-dose systemic toxicity studies in mice, rats, and dogs, including carcinogenicity studies in rats and mice, no riociguat-induced nephrotoxicity was seen. Considering systemic riociguat unbound exposure ($AUC_{unbound}$) in rats after chronic, 6-month administration, safety margins of 11-fold were established. • In repeated-dose toxicity studies in rats with the riociguat metabolite M-1 (BAY 60-4552), morphological changes in the kidneys at high dose levels (≥30 mg/kg) were seen. Safety margins of 13-fold in terms of $AUC_{unbound}$ when compared with human M-1 exposure at the MRHD of riociguat were established.	In the light of the extensive non-clinical data set, from the toxicological point of view, considering the established 2-digit safety margins after chronic dosing of M-1 in rats and the clean safety profile of riociguat in mice, rats, and dogs after chronic or even life-long exposure, the M-1-related renal findings in rats do not pose a clinically relevant risk to humans.

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Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Hepatotoxicity	
• In repeated-dose toxicity studies no signal for hepatotoxicity was detected.	Preclinical testing revealed no evidence for a human risk.
Bone metabolism	
• In non-clinical safety studies using juvenile and adolescent rodents, supra-therapeutic exposure of riociguat induced effects on bone morphology consisting mainly of growth-plate thickening (rats and mice) and cortical remodelling (rats). Considering the known effect of cGMP on proliferation, differentiation, and function of cartilage and bone cells, either regulated by the NO-sGC-cGMP or the C-type natriuretic peptide–particulate guanylate cyclase–cGMP signalling pathway, the thickening of growth plates and hyperostotic cortical remodelling are considered to be secondary to the pharmacological mechanism of riociguat and do not represent unexpected adverse effects of riociguat. • Chronic administration of riociguat in adult rats did not result in morphological changes of the skeletal system or in bone mineral density. • In dogs, no riociguat-related morphological bone changes were observed. • Overall, the findings rather represent an overall increase in bone mass and the morphology of the findings is not consistent with changes seen in osteoporosis models or osteochondrosis dissecans.	Preclinical data indicate that these changes occur only under conditions of rapid bone turnover as they are found only under fast-growing conditions in juvenile and adolescent rodents. Thus, for the adult, full-grown patient population, the bone changes are seen as not relevant. Furthermore, it is important to note that the findings do not indicate a loss of bone mass as in osteoporotic patients. Based on preclinical data, the NO–sGC–cGMP pathway had been considered as a potential target for the treatment of osteoporosis. However, clinical data did not show a meaningful benefit in clinical trials. This further supports the assessment that this pathway is not clinically relevant for full-grown patients with low bone turnover. In order to further support this assessment, a mechanistic study was performed in healthy male volunteers (study 13790; report no. PH-36405) applying a study design that was shown to be sufficiently sensitive to demonstrate early and minor effects on bone metabolism in humans. The minor effects observed on bone formation and resorption markers, as well as on calcium homeostasis, were clearly attributed to the haemodynamic effects of riociguat on kidney and liver perfusion resulting in increased clearances of the respective biomarkers, and do not indicate a risk for riociguat-related adverse effects on bone. This assessment is further supported by the phase 3 data which were consistent with the expected rate of bone fracture in the studied population. Overall, it can be concluded that neither the non-clinical finding nor the effects seen in the mechanistic study in healthy male volunteers are considered of relevance for adult patients with pulmonary hypertension. With respect to the paediatric population, it has to be kept in mind that effects in rapidly growing juvenile and adolescent rats were only observed at

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Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
	supratherapeutic exposures. In addition, effects were shown to be reversible after cessation of treatment in adolescent rats and there is indication of full normalization after end of rapid bone growth despite continuous treatment. Moreover, although the mechanism *per se* is relevant across species, it is of note that growth rates are different between species, and the very rapid bone growth in rats cannot be directly transferred to children due to species specific differences in skeletal development and bone turnover. Even during growth spurts in human childhood, bone growth and bone turnover is slower in children than in rats that multiply their body weight and bone length during the duration of the repeat dose toxicity studies. In line with this, in the PATENT-CHILD study (15681) no abnormal effects on bone growth or morphology were observed. The LTE phase of this study is still ongoing.
Reproductive and developmental toxicity	
• Riociguat had no impact on fertility and early embryonic development. In a fertility study in rats, decreased testes weights occurred at systemic exposure of about 7-fold of human exposure, whereas no effects on male and female fertility were seen. • Moderate passage across the placental barrier was observed. • Maternal tolerability and embryo-foetal as well as pre- and early post-natal development were mainly influenced by the haemodynamic properties of riociguat. In rats at a systemic exposure of about 8-fold the human exposure in terms of $AUC_{unbound}$ at the MRHD, an increase in cardiac malformations was seen. These cardiac malformations are regarded as secondary to the haemodynamic effects of riociguat and its anti-proliferative effects on undifferentiated mesenchymal cells during cardiac development. The findings are not considered to indicate an off-target intrinsic toxic effect of riociguat on the developing heart.	In order to assure safety for patients and foetuses, riociguat is contraindicated during pregnancy. Women of childbearing potential must use effective contraception during treatment with riociguat.
Genotoxicity	
• Riociguat was negative in an extended	Preclinical tests found no evidence for a genotoxic

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Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
battery of *in vitro* and *in vivo* genotoxicity tests.	risk to patients.
Carcinogenicity	
• In the carcinogenicity study in mice, riociguat showed an increase in pre-neoplastic as well as neoplastic lesions of the large intestine. These effects are seen as secondary to smooth muscle cell relaxation in the gastrointestinal tract followed by chronic motility reduction, intestinal dysbiosis, chronic inflammation, mucosal degeneration, regeneration and regenerative hyperplasia, and neoplasms. This sequence of events is a typical reaction of mice to a stimulus such as chronic intestinal inflammation or degeneration (62-67). • In rats and dogs, despite the presence of similar chronic motility disorders, no sequelae indicating inflammation, degeneration, or regeneration were observed. • In rats, no treatment-related increase in overall tumour rate or rate of any specific tumour type was observed.	Based on the totality of preclinical safety data in mice, rats, and dogs, and in line with published literature, the secondary changes in mice following mode of action-related intestinal motility disorders are seen as a mouse-specific phenomenon. Thus, from the preclinical point of view, the increase of large-intestinal tumours in mice is regarded to be of no relevance for humans. In conclusion, there is no carcinogenic risk for riociguat in humans.
General pharmacology	
• *In vitro*, riociguat showed a weak concentration-dependent inhibition of platelet aggregation induced by collagen (IC_{50}: 59 µM), adenosine diphosphate (IC_{50}: 41 µM) and thrombin receptor activator peptide 6 (IC_{50}: 34 µM) at concentrations of about 1,000-fold of human $C_{max, unbound}$. • *In vivo* interaction studies in rats showed an additive prolongation of the tail transection bleeding time after coadministration with acetylsalicylic acid. • Coadministration with iloprost, rivaroxaban, and clopidogrel did not reveal a prolongation of bleeding time. • In mice, at toxicologically relevant doses, a slight, less than 2-fold increase in tail transection bleeding time was seen. The mechanism remains open.	*In vitro* effects on inhibition of platelet aggregation at high riociguat concentrations were shown not to be relevant for humans at therapeutically relevant concentrations (study 14204; report no. PH-36360). Overall, preclinical data do not indicate an increased bleeding risk.

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Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Safety pharmacology	
Cardiovascular	
• In dogs, based on the pharmacological mode of action of riociguat, a decrease of peripheral vascular resistance resulting in blood pressure decrease and reflex tachycardia was seen. • *In vitro* (hERG) and *in vivo* testing (conscious dog) did not reveal a proarrhythmic risk to humans.	Riociguat did not show a proarrhythmic risk and did not indicate a cardiotoxic potential.
Nervous system	
• Riociguat did not show any effects in the CNS.	Riociguat showed no risk for CNS effects.
Supplementary organ systems	
• Due to its smooth muscle-relaxing effects, riociguat dose-dependently inhibited intestinal barium sulphate transport in rats.	Effects on gastrointestinal motility were also seen in patients.
Mechanisms for drug interactions	
• See general pharmacology and bleeding time. • Transporter Characteristics: In *in vitro* studies to evaluate the drug-drug interaction potential towards transporters for riociguat as victim, several drugs were capable of potently inhibiting P-gp- or BCRP-mediated transport of riociguat.	Strong P-gp and BCRP inhibitors might lead to increased plasma concentrations of riociguat.
Riociguat and its main metabolite (M-1) do not inhibit P-gp, BCRP, MRP2, BSEP, MATE1, and MATE2K at relevant therapeutic concentrations. In addition, riociguat and M-1 do not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and OCT3.	The risk of clinically relevant drug-drug interactions due to inhibition of the transport proteins investigated by riociguat and its main metabolite (M-1) is regarded as very low.
Other toxicity-related information or data	
• Juvenile animal testing revealed no new findings or target organs of toxicity when compared with studies in adult rats.	The safety and efficacy of Adempas in children and adolescents below 18 years of age with chronic thromboembolic pulmonary hypertension and in children with pulmonary arterial hypertension below 6 years have not been established. Riociguat use should be avoided in these populations, and is addressed in section 4.2

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Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
	(special populations) of the SmPC.

AUC = Area under the concentration-time curve, BCRP = Breast cancer resistance protein, BSEP = Bile salt export pump, cGMP = Cyclic guanosine monophosphate, C_{max} = Maximum concentration, CNS = Central nervous system, hERG = Human ether-a-go-go-related gene, IC_{50} = Half maximal inhibitory concentration, MATE1 = Multidrug and toxin extrusion protein 1, MATE2K = Multidrug and toxin extrusion protein 2K, MRHD = Maximum recommended human dose, MRP2 = Multidrug resistance protein 2, NO = Nitric oxide, OAT1 = Organic anion transporter 1, OAT3 = Organic anion transporter 3, OATP1B1 = Organic anion transporting polypeptide 1B1, OATP1B3 = Organic anion transporting polypeptide 1B3, OCT1 = Organic cation transporter 1, OCT2 = Organic cation transporter 2, OCT3 = Organic cation transporter 3, PAH = Pulmonary arterial hypertension, P-gp = P-glycoprotein, sGC = Soluble guanylate cyclase, SmPC = Summary of Product Characteristics

PART II: Module SIII: Clinical Trial Exposure

For the integrated safety analysis described in the Summary of Clinical Safety (Module 2.7.4), three study pools were defined. These are based on all Bayer sponsored phase 2 to 3 studies, which were finalized until 19 JUN 2012, with riociguat tablets in pulmonary hypertension (PH) patients. Studies of all indications (i.e., pulmonary arterial hypertension [PAH], or chronic thromboembolic pulmonary hypertension [CTEPH], PH due to interstitial lung disease, PH due to left ventricular dysfunction, PH related to chronic obstructive pulmonary disease) were included in pool 3. The first pool was a pure subset of the second pool which was a pure subset of the third pool (Integrated analysis of safety [IAS] PH-37089):

- Pool 1 – all phase 3 studies, placebo-controlled studies in pulmonary PAH or CTEPH
- Pool 2 – all studies in PAH or CTEPH with multiple doses
- Pool 3 – all riociguat studies.

The safety analysis focused on the pivotal studies in Pool 1 and all riociguat studies in Pool 3.

Table Part II SIII-1 lists all relevant studies that were included in the IAS and shows to which of the 3 study pools they belong

Table Part II SIII-1: List of studies for integrated analysis of safety (cut-off 09 SEP 2012)

Study		Indication	Study phase	Number of subjects analysed	Analysis population		
					Phase 3 placebo-controlled studies in PAH or CTEPH	Multi-dose studies in PAH or CTEPH	Riociguat studies
11348	(CHEST-1)	CTEPH	3	261	X	X	X
11349	(CHEST-2)	CTEPH	3	194	X[a]	X	X
12166		PAH, CTEPH	2	75		X	X
12915		PH-COPD	2a	23			X[b]
12916		PH-ILD	2a	21			X
12934	(PATENT-1)	PAH	3	443	X	X	X
12935	(PATENT-2)	PAH	3	363	X[a]	X	X
14308	(LEPHT)	PH-LVD	2	201			X
14549	(HEARTWORK)	PH-LVD	2a	1			X[b]

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Table Part II SIII-1: List of studies for integrated analysis of safety (cut-off 09 SEP 2012)

Study	Indication	Study phase	Number of subjects analysed	Analysis population		
				Phase 3 placebo-controlled studies in PAH or CTEPH	Multi-dose studies in PAH or CTEPH	Riociguat studies
15096 (PATENT-plus)	PAH	2b	18		X	X

COPD = Chronic obstructive pulmonary disease, CTEPH = Chronic thromboembolic pulmonary hypertension, ILD = Interstitial lung disease, LVD = Left ventricular disease, PAH = Pulmonary arterial hypertension, PH = Pulmonary hypertension.
[a] Extension study following on from a placebo-controlled study, but not placebo-controlled itself.
[b] Single-dose study.

Table Part II SIII-2: Duration of exposure (Pool 3, by indication)

Duration of exposure (at least)[a]	Persons	Person-years
CTEPH		
1 day	280	392.9
1 month	275	392.8
3 months	252	388.5
6 months	198	368.7
12 months	137	325.0
18 months	104	285.0
24 months	78	240.6
36 months	32	128.5
48 months	17	71.9
Total person time		**392.9**
PAH		
1 day	464	616.1
1 month	445	615.4
3 months	390	603.8
6 months	332	579.9
12 months	250	515.2
18 months	184	430.2
24 months	109	295.0
36 months	22	87.3
48 months	14	59.2

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Table Part II SIII-2: Duration of exposure (Pool 3, by indication)

Duration of exposure (at least)[a]	Persons	Person-years
Total person time		**616.1**
PH-LVD		
1 day	133	36.2
1 month	117	35.6
3 months	109	34.4
Total person time		**36.2**
PH-ILD		
1 day	21	4.3
1 month	18	4.2
3 months	6	1.5
Total person time		**4.3**
PH-COPD		
1 day	23	0.2
Total person time		**0.2**

COPD = Chronic obstructive pulmonary disease, CTEPH = Chronic thromboembolic pulmonary hypertension, IAS = Integrated analysis of safety, ILD = Interstitial lung disease, LVD = Left ventricular disease, PAH = Pulmonary arterial hypertension, PH = Pulmonary hypertension, RMP = Risk Management Plan.
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.1/6, 7, 8, 9 and 10]
[a] Duration for ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.

Table Part II SIII-3: Duration of exposure (Pool 1 pivotal trials)

Duration of exposure (at least)	Persons	Person-years
Total exposed population in randomised, blinded trials (PATENT-1 and CHEST-1)		
1 dose	490	123.5
2 weeks	478	123.3
4 weeks	474	123.1
6 weeks	466	122.3
8 weeks	461	121.7
12 weeks	419	112.4
Total person time		**123.5**
Total exposed population in PATENT-1, CHEST-1, and uncontrolled LTEs (PATENT-2 and CHEST-2)		
Duration of exposure (at least)[a]	**Persons**	**Person-years**
1 dose	651	777.6

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Table Part II SIII-3: Duration of exposure (Pool 1 pivotal trials)

Duration of exposure (at least)	Persons	Person-years
2 weeks	638	777.4
4 weeks	633	777.1
6 weeks	625	776.4
8 weeks	617	775.3
12 weeks	599	771.6
24 weeks	503	742.3
36 weeks	429	703.3
48 weeks	353	644.3
60 weeks	304	594.9
72 weeks	260	539.6
84 weeks	215	472.4
96 weeks	165	385.1
108 weeks	112	279.8
120 weeks	70	186.2
132 weeks	41	114.1
144 weeks	14	41.0
Total person time		**777.6**

IAS = Integrated analysis of safety, LTE = Long-term extension, RMP = Risk Management Plan
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.1/11 and 12]
[a] Duration for ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.

Table Part II SIII-4: Duration of exposure (totals in Pool 3 – all riociguat studies)

Duration of exposure (at least)[a]	Persons	Person-years
Total exposed population in all randomised blinded clinical trials (PATENT-1, CHEST-1, PATENT PLUS, and LEPHT)		
1 day	634	162.4
1 month	600	161.2
3 months	295	91.6
Total person time		**162.4**

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Table Part II SIII-4: Duration of exposure (totals in Pool 3 – all riociguat studies)

Duration of exposure (at least)[a]	Persons	Person-years
Total exposed population in all clinical trials in Pool 3		
Duration of exposure (at least)[a]	**Persons**	**Person-years**
1 day	921	1,049.6
1 month	855	1,048.1
3 months	757	1,028.3
6 months	530	947.8
12 months	387	839.4
18 months	288	714.5
24 months	185	531.4
36 months	54	215.8
48 months	31	131.1
Total person time		**1,049.6**

IAS = Integrated analysis of safety, RMP = Risk Management Plan.
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.1/1 and 2]
[a] Duration for ongoing subjects is calculated by using the study-specific cut-off date as day of last treatment.

Table Part II SIII-5: By dose (by indication – Pool 3)

Dose of exposure[a]	Persons	Person-years
CTEPH		
0.5 mg TID	7	0.8
1.0 mg TID	278	21.1
1.2 mg TID[b]	2	0.1
1.5 mg TID	271	41.6
2.0 mg TID	253	33.5
2.5 mg TID	242	276.2
3.0 mg TID	1	0.1
7.5 mg TID	1	0.0
Total		**373.4**
PAH		
0.5 mg TID	20	7.1
1.0 mg TID	464	31.1
1.2 mg TID[b]	1	0.0
1.3 mg TID[b]	2	0.1

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Table Part II SIII-5: By dose (by indication – Pool 3)

Dose of exposure[a]	Persons	Person-years
1.5 mg TID	435	46.1
1.8 mg TID[b]	1	0.0
2.0 mg TID	411	71.0
2.5 mg TID	386	447.6
3.0 mg TID	1	0.0
7.5 mg TID	1	0.0
Total		**603.0**
PH-LVD		
0.5 mg TID	132	15.8
1.0 mg once per day	1	0.0
1.0 mg TID	80	11.3
2.0 mg TID	43	8.9
Total		**36.0**
PH-ILD		
0.5 mg TID	1	0.0
1.0 mg TID	21	1.0
1.5 mg TID	19	1.0
2.0 mg TID	17	0.8
2.5 mg TID	13	1.6
Total		**4.4**
PH-COPD		
1.0 mg once per day	10	0.1
2.5 mg once per day	13	0.1
Total		**0.2**

COPD = Chronic obstructive pulmonary disease, CTEPH = Chronic thromboembolic pulmonary hypertension, ILD = Interstitial lung disease, IAS = Integrated analysis of safety, LVD = Left ventricular disease, mg = Milligram, PAH = Pulmonary arterial hypertension, PH = Pulmonary hypertension, RMP = Risk Management Plan, TID = *Ter in die* (three times a day).
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.2/6, 7, 8, 9 and 10]
[a] Due to titration scheme and dose modifications during studies, subjects may be counted on several dose levels.
[b] For a few subjects of study 12166, total daily doses were documented that were outside the regular dose levels. Dividing them by 3 resulted in differing single doses.

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Table Part II SIII-6: By dose (Pool 1 pivotal trials)

Total exposed population in randomised, blinded trials (PATENT-1 and CHEST-1)		
Dose of exposure[a]	**Persons**	**Person-years**
0.5 mg TID	12	1.2
1.0 mg TID	490	23.2
1.5 mg TID	459	30.5
2.0 mg TID	377	20.9
2.5 mg TID	323	46.6
Total		**122.4**
Total exposed population in PATENT-1, CHEST-1, and uncontrolled LTEs (PATENT-2 and CHEST-2)		
Dose of exposure[a]	**Persons**	**Person-years**
0.5 mg TID	21	7.3
1.0 mg TID	651	42.6
1.5 mg TID	622	61.2
2.0 mg TID	590	80.0
2.5 mg TID	556	581.0
Total		**772.1**

IAS = Integrated analysis of safety, LTE = Long-term extension, mg = Milligram, RMP = Risk Management Plan, TID = *Ter in die* (three times a day).
[Source: IAS additional analyses for the RMP, PH-37087, Table 2.2/11 and 12]
[a] Due to titration scheme and dose modifications during studies, subjects may be counted on several dose levels.

Table Part II SIII-7: By dose (totals in Pool 3 – all riociguat studies)

Total exposed population in all randomised blinded clinical trials (PATENT-1, CHEST-1, PATENT PLUS and LEPHT)		
Dose of exposure[a]	**Persons**	**Person-years**
0.5 mg TID	144	17.0
1.0 mg TID	582	35.0
1.5 mg TID	471	31.1
2.0 mg TID	431	30.5
2.5 mg TID	331	47.5
Total		**161.1**
Total exposed population in all clinical trials in Pool 3		
Dose of exposure[a]	**Persons**	**Person-years**
0.5 mg TID	160	23.7
1.0 mg once	11	0.1
1.0 mg TID	843	64.4

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Table Part II SIII-7: By dose (totals in Pool 3 – all riociguat studies)

1.2 mg TID[b]	3	0.1
1.3 mg TID[b]	2	0.1
1.5 mg TID	725	88.6
1.8 mg TID[b]	1	0.0
2.0 mg TID	724	114.1
2.5 mg once per day	13	0.1
2.5 mg TID	641	725.4
3.0 mg TID	2	0.1
7.5 mg TID	2	0.1
Total		**1,016.8**

IAS = Integrated analysis of safety, mg = Milligram, RMP = Risk Management Plan, TID = *Ter in die* (three times a day).
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.2/1 and 2]
[a] Due to titration scheme and dose modifications during studies, subjects may be counted on several dose levels.
[b] For a few subjects of study 12166, total daily doses were documented that were outside the regular dose levels. Dividing them by 3 resulted in differing single doses.

Table Part II SIII-8: By age group and gender (by indication – Pool 3)

CTEPH				
Age group	**Persons**		**Person-years**	
	M	**F**	**M**	**F**
<65 years	65	98	104.4	143.0
≥65–<75 years	29	59	34.8	81.8
≥75 years	12	17	18.3	10.5
Total	**106**	**174**	**157.5**	**235.3**
PAH				
Age group	**Persons**		**Person-years**	
	M	**F**	**M**	**F**
<65 years	64	278	83.5	396.9
≥65–<75 years	27	71	25.1	91.2
≥75 years	10	14	9.5	9.8
Total	**101**	**363**	**118.2**	**497.9**

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Table Part II SIII-8: By age group and gender (by indication – Pool 3)

PH-LVD				
Age group	**Persons**		**Person-years**	
	M	**F**	**M**	**F**
<65 years	74	19	20.5	5.3
≥65–<75 years	32	6	8.0	1.8
≥75 years	6	2	1.8	0.6
Total	**112**	**21**	**30.2**	**6.0**
PH-ILD				
Age group	**Persons**		**Person-years**	
	M	**F**	**M**	**F**
<65 years	6	6	1.0	1.5
≥65–<75 years	4	1	1.0	0.0
≥75 years	3	1	0.6	0.2
Total	**13**	**8**	**2.6**	**1.7**
PH-COPD				
Age group	**Persons**		**Person-years**	
	M	**F**	**M**	**F**
<65 years	2	5	0.0	0.0
≥65–<75 years	7	5	0.1	0.0
≥75 years	3	1	0.0	0.0
Total	**12**	**11**	**0.1**	**0.1**

< = Less than, ≥ = Greater than or equal to, COPD = Chronic obstructive pulmonary disease, CTEPH = Chronic thromboembolic pulmonary hypertension, F = Female, IAS = Integrated analysis of safety, ILD = Interstitial lung disease, LVD = Left ventricular disease, M = Male, PAH = Pulmonary arterial hypertension, PH = Pulmonary hypertension, RMP = Risk Management Plan.
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.3/6, 7, 8, 9 and 10]

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Table Part II SIII-9: By age group and gender (Pool 1 pivotal trials)

Total exposed population in randomised, blinded trials (PATENT-1 and CHEST-1)				
Age group	**Persons**		**Person-years**	
	M	**F**	**M**	**F**
<65 years	76	260	19.8	63.7
≥65–<75 years	27	83	7.1	21.2
≥75 years	17	27	4.4	7.3
Total	**120**	**370**	**31.3**	**92.2**
Total exposed population in PATENT-1, CHEST-1, and uncontrolled LTEs (PATENT-2 and CHEST-2)				
Age group	**Persons**		**Person-years**	
	M	**F**	**M**	**F**
<65 years	109	343	130.8	441.6
≥65–<75 years	39	111	37.1	131.8
≥75 years	19	30	16.0	20.4
Total	**167**	**484**	**183.9**	**593.8**

< = Less than, ≥ = Greater than or equal to, F = Female, IAS = Integrated analysis of safety, LTE = Long-term extension, M = Male, RMP = Risk Management Plan.
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.3/11 and 12]

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Table Part II SIII-10: By age group and gender (totals in Pool 3 – all riociguat studies)

Total exposed population in all randomised blinded clinical trials (PATENT-1, CHEST-1, PATENT PLUS and LEPHT)				
Age group	**Persons**		**Person-years**	
	M	**F**	**M**	**F**
<65 years	152	285	40.8	70.3
≥65–<75 years	60	85	15.5	21.7
≥75 years	23	29	6.2	7.9
Total	**235**	**399**	**62.5**	**100.0**
Total exposed population in all clinical trials in Pool 3				
Age group	**Persons**		**Person-years**	
	M	**F**	**M**	**F**
<65 years	211	406	209.3	546.7
≥65–<75 years	99	136	69.0	173.1
≥75 years	34	35	30.3	21.2
Total	**344**	**577**	**308.6**	**741.0**

< = Less than, ≥ = Greater than or equal to, F = Female, IAS = Integrated analysis of safety, M = Male, RMP = Risk Management Plan.
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.3/1 and 2]

Table Part II SIII-11: By ethnic or racial origin (by indication – Pool 3)

Ethnic/racial origin	**Persons**	**Person-years**
CTEPH		
White	209	309.5
Black or African American	8	8.4
Asian	52	66.0
Other	11	9.0
Total	**280**	**392.9**
PAH		
White	307	413.0
Black or African American	5	6.0
Asian	130	180.9
Other	22	16.2
Total	**464**	**616.1**

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Table Part II SIII-11: By ethnic or racial origin (by indication – Pool 3)

Ethnic/racial origin	Persons	Person-years
PH-LVD		
White	104	28.7
Black or African American	6	1.7
Asian	17	4.0
Other	6	1.7
Total	**133**	**36.2**
PH-ILD		
White	21	4.3
Total	**21**	**4.3**
PH-COPD		
White	23	0.2
Total	**23**	**0.2**

COPD = Chronic obstructive pulmonary disease, CTEPH = Chronic thromboembolic pulmonary hypertension, IAS = Integrated analysis of safety, ILD = Interstitial lung disease, LVD = Left ventricular disease, PAH = Pulmonary arterial hypertension, PH = Pulmonary hypertension, RMP = Risk Management Plan.
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.4/6, 7, 8, 9 and 10]

Table Part II SIII-12: By ethnic or racial origin (Pool 1 pivotal trials)

Total exposed population in randomised, blinded trials (PATENT-1 and CHEST-1)		
Ethnic/racial origin	**Persons**	**Person-years**
White	314	80.2
Black or African American	12	3.0
Asian	138	33.9
Other	26	6.4
Total	**490**	**123.5**
Total exposed population in PATENT-1, CHEST-1, and uncontrolled LTEs (PATENT-2 and CHEST-2)		
Ethnic/racial origin	**Persons**	**Person-years**
White	423	491.2
Black or African American	13	14.4
Asian	182	246.8
Other	33	25.2
Total	**651**	**777.6**

IAS = Integrated analysis of safety, LTE = Long-term extension, RMP = Risk Management Plan.
[Source: IAS additional analyses for the RMP, PH-37087, Table 2.4/11 and 12]

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Table Part II SIII-13: By ethnic or racial origin (totals in Pool 3 – all riociguat studies)

Total exposed population in all randomised blinded clinical trials (PATENT-1, CHEST-1, PATENT PLUS, and LEPHT)		
Ethnic/racial origin	**Persons**	**Person-years**
White	429	111.7
Black or African American	18	4.7
Asian	155	37.9
Other	32	8.1
Total	**634**	**162.4**
Total exposed population in all clinical trials in Pool 3		
Ethnic/racial origin	**Persons**	**Person-years**
White	664	755.7
Black or African American	19	16.1
Asian	199	250.9
Other	39	26.9
Total	**921**	**1,049.6**

IAS = Integrated analysis of safety, RMP = Risk Management Plan.
[Source: IAS additional analyses for the RMP, PH-37087,Tables 2.4/1 and 2]

Table Part II SIII-14: Special populations (by indication – Pool 3)

CTEPH		
	Persons	**Person-years**
Pregnant women	N/A	N/A
Lactating women	N/A	N/A
Renal impairment (Cockcroft Gault formula):		
<30 mL/min	5	6.8
≥30–<50 mL/min	36	38.7
≥50–<80 mL/min	128	188.5
>80 mL/min	94	136.7
History of hepatic impairment	20	21.3

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Table Part II SIII-14: Special populations (by indication – Pool 3)

PAH		
	Persons	**Person-years**
Pregnant women	N/A	N/A
Lactating women	N/A	N/A
Renal impairment (Cockroft Gault formula):		
<30 mL/min	2	3.3
≥30–<50 mL/min	40	42.8
≥50–<80 mL/min	145	202.2
>80 mL/min	256	354.0
History of hepatic impairment[a]	67	99.3
PH-LVD		
	Persons	**Person-years**
Pregnant women	N/A	N/A
Lactating women	N/A	N/A
Renal impairment (Cockroft Gault formula):		
≥30–<50 mL/min	18	5.5
≥50–<80 mL/min	49	11.9
>80 mL/min	66	18.8
History of hepatic impairment[a]	10	3.2
PH-ILD		
	Persons	**Person-years**
Pregnant women	N/A	N/A
Lactating women	N/A	N/A
Renal impairment (Cockroft Gault formula):		
≥30–<50 mL/min	3	0.7
≥50–<80 mL/min	8	1.4
>80 mL/min	10	2.2
History of hepatic impairment[a]	1	0.2

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Table Part II SIII-14: Special populations (by indication – Pool 3)

PH-COPD		
	Persons	**Person-years**
Pregnant women	N/A	N/A
Lactating women	N/A	N/A
Renal impairment (Cockroft Gault formula):		
<30 mL/min	2	0.0
≥30–<50 mL/min	3	0.0
≥50–<80 mL/min	7	0.1
>80 mL/min	11	0.1
History of hepatic impairment[a]	1	0.0

< = Less than, > = Greater than, ≥ = Greater than or equal to, COPD = Chronic obstructive pulmonary disease, CTEPH = Chronic thromboembolic pulmonary hypertension, IAS = Integrated analysis of safety, ILD = Interstitial lung disease, LVD = Left ventricular disease, mL = Millilitre, min = Minute, MSSO = Maintenance and Support Services Organization, N/A = Not applicable, PAH = Pulmonary arterial hypertension, PH = Pulmonary hypertension, RMP = Risk Management Plan, SMQ = Standardised Medical Dictionary for Regulatory Activities Query.
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.5/6, 7, 8, 9 and 10]
[a] Hepatic impairment was identified by MSSO SMQ "hepatic disorders" excluding sub-SMQs "liver-related investigations, signs and symptoms" and "liver-related coagulation and bleeding disturbances".

Table Part II SIII-15: Special populations (Pool 1 pivotal trials)

Total exposed population in randomised, blinded trials (PATENT-1 and CHEST-1)		
	Persons	**Person-years**
Pregnant women	N/A	N/A
Lactating women	N/A	N/A
Renal impairment (Cockroft Gault formula):		
<30 mL/min	4	1.0
≥30–<50 mL/min	57	14.4
≥50–<80 mL/min	172	44.9
>80 mL/min	233	57.3
History of hepatic impairment[a]	60	14.0

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Table Part II SIII-15: Special populations (Pool 1 pivotal trials)

Total exposed population in randomised, blinded trials (PATENT-1 and CHEST-1)		
	Persons	**Person-years**
Total exposed population in PATENT-1, CHEST-1 and uncontrolled LTEs (PATENT-2 and CHEST-2)		
	Persons	**Person-years**
Pregnant women	N/A	N/A
Lactating women	N/A	N/A
Renal impairment (Cockroft Gault formula):		
<30 mL/min	4	2.5
≥30–<50 mL/min	71	72.8
≥50–<80 mL/min	226	263.6
>80 mL/min	317	411.5
History of hepatic impairment[a]	75	92.6

< = Less than, > = Greater than, ≥ = Greater than or equal to, IAS = Integrated analysis of safety, LTE = Long-term extension, mL = Millilitre, min = Minute, MSSO = Maintenance and Support Services Organization, N/A = Not applicable, RMP = Risk Management Plan, SMQ = Standardised Medical Dictionary for Regulatory Activities Query.
[Source: IAS additional analyses for the RMP, PH-37087, Table 2.5/11 and 12]
[a] Hepatic impairment was identified by MSSO SMQ "hepatic disorders" excluding sub-SMQs "liver-related investigations, signs and symptoms" and "liver-related coagulation and bleeding disturbances".

Table Part II SIII-16: Special populations (totals in Pool 3 – all riociguat studies)

Total exposed population in all randomised blinded clinical trials (PATENT-1, CHEST-1, PATENT PLUS and LEPHT)		
	Persons	**Person-years**
Pregnant women	N/A	N/A
Lactating women	N/A	N/A
Renal impairment (Cockroft Gault formula):		
<30 mL/min	4	1.0
≥30–<50 mL/min	75	19.8
≥50–<80 mL/min	227	58.3
>80 mL/min	304	77.3
History of hepatic impairment[a]	72	17.7
Total exposed population in all clinical trials in Pool 3		
	Persons	**Person-years**
Pregnant women	N/A	N/A

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Table Part II SIII-16: Special populations (totals in Pool 3 – all riociguat studies)

Lactating women	N/A	N/A
Renal impairment (Cockroft Gault formula):		
<30 mL/min	9	10.0
≥30–<50 mL/min	100	87.7
≥50–<80 mL/min	337	404.0
>80 mL/min	437	511.7
History of hepatic impairment[a]	99	124.1

< = Less than, > = Greater than, ≥ = Greater than or equal to, IAS = Integrated analysis of safety, mL = Millilitre, min = Minute, MSSO = Maintenance and Support Services Organization, N/A = Not applicable, RMP = Risk Management Plan, SMQ = Standardised Medical Dictionary for Regulatory Activities Query.
[Source: IAS additional analyses for the RMP, PH-37087, Tables 2.5/1 and 2]
[a] Hepatic impairment was identified by MSSO SMQ "hepatic disorders" excluding sub-SMQs "liver-related investigations, signs and symptoms" and "liver-related coagulation and bleeding disturbances".

An integrated safety analysis with cut-off date MAR 2017 focused on the pivotal studies in Pool 1 (Source: PH-40000). Data on exposure is presented up to Month 84, after which patient numbers are very low, due to the gradual transition from study drug to commercial drug.

Table Part II SIII-17: List of studies for integrated analysis of safety – MAR 2017 update

Study		Indication	Study phase	Number of subjects analysed	Analysis population		
					Phase 3 placebo-controlled studies in PAH or CTEPH	Multi-dose studies in PAH or CTEPH	Riociguat studies
11348	(CHEST-1)	CTEPH	3	261	X	X	X
11349	(CHEST-2)	CTEPH	3	237	X[a]	X	X
12934	(PATENT-1)	PAH	3	443	X	X	X
12935	(PATENT-2)	PAH	3	396	X[a]	X	X

CTEPH = Chronic thromboembolic pulmonary hypertension, PAH = Pulmonary arterial hypertension.
[a] Extension study following on from a placebo-controlled study, but not placebo-controlled itself.
[b] Single-dose study.

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Table Part II SIII-18: Cumulative treatment exposure - Pool 1 pivotal trials (exposed population in PATENT-1, CHEST-1, and uncontrolled LTEs PATENT-2 and CHEST-2)

Treatment exposure (weeks)	BAY 63-2521 (main) N=490 (100%)	Placebo (main) N=214 (100%)	BAY 63-2521 (LTE, main) N=442 (100%)	BAY 63-2521 (LTE, placebo in main) N=191 (100%)	LTE total N=633 (100%)
At least 1 dose	490 (100%)	214 (100%)	442 (100%)	191 (100%)	633 (100%)
At least 2 weeks	478 (97.6%)	208 (97.2%)	442 (100.0%)	190 (99.5%)	632 (99.8%)
At least 4 weeks	474 (96.7%)	205 (95.8%)	438 (99.1%)	189 (99.0%)	627 (99.1%)
At least 6 weeks	466 (95.1%)	203 (94.9%)	435 (98.4%)	188 (98.4%)	623 (98.4%)
At least 8 weeks	461 (94.1%)	201 (93.9%)	433 (98.0%)	186 (97.4%)	619 (97.8%)
At least 12 weeks	419 (85.5%)	174 (81.3%)	428 (96.8%)	185 (96.9%)	613 (96.8%)
At least 16 weeks	130 (26.5%)	71 (33.2%)	426 (96.4%)	183 (95.8%)	609 (96.2%)
At least 20 weeks	0	0	425 (96.2%)	181 (94.8%)	606 (95.7%)
At least 24 weeks	0	0	423 (95.7%)	181 (94.8%)	604 (95.4%)
At least 36 weeks	0	0	417 (94.3%)	179 (93.7%)	596 (94.2%)
At least 48 weeks	0	0	407 (92.1%)	172 (90.1%)	579 (91.5%)
At least 60 weeks	0	0	398 (90.0%)	167 (87.4%)	565 (89.3%)
At least 72 weeks	0	0	393 (88.9%)	166 (86.9%)	559 (88.3%)
At least 84 weeks	0	0	385 (87.1%)	164 (85.9%)	549 (86.7%)
At least 96 weeks	0	0	378 (85.5%)	162 (84.8%)	540 (85.3%)
At least 108 weeks	0	0	361 (81.7%)	152 (79.6%)	513 (81.0%)
At least 120 weeks	0	0	342 (77.4%)	141 (73.8%)	483 (76.3%)
At least 132 weeks	0	0	321 (72.6%)	133 (69.6%)	454 (71.7%)
At least 144 weeks	0	0	292 (66.1%)	127 (66.5%)	419 (66.2%)
At least 156 weeks	0	0	271 (61.3%)	116 (60.7%)	387 (61.1%)
At least 168 weeks	0	0	249 (56.3%)	105 (55.0%)	354 (55.9%)
At least 180 weeks	0	0	220 (49.8%)	96 (50.3%)	316 (49.9%)
At least 192 weeks	0	0	204 (46.2%)	84 (44.0%)	288 (45.5%)
At least 204 weeks	0	0	176 (39.8%)	70 (36.6%)	246 (38.9%)
At least 216 weeks	0	0	161 (36.4%)	62 (32.5%)	223 (35.2%)
At least 228 weeks	0	0	142 (32.1%)	55 (28.8%)	197 (31.1%)
At least 240 weeks	0	0	119 (26.9%)	48 (25.1%)	167 (26.4%)
At least 252 weeks	0	0	93 (21.0%)	39 (20.4%)	132 (20.9%)

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Table Part II SIII-18: Cumulative treatment exposure - Pool 1 pivotal trials (exposed population in PATENT-1, CHEST-1, and uncontrolled LTEs PATENT-2 and CHEST-2)

Treatment exposure (weeks)	BAY 63-2521 (main) N=490 (100%)	Placebo (main) N=214 (100%)	BAY 63-2521 (LTE, main) N=442 (100%)	BAY 63-2521 (LTE, placebo in main) N=191 (100%)	LTE total N=633 (100%)
At least 264 weeks	0	0	74 (16.7%)	30 (15.7%)	104 (16.4%)
At least 276 weeks	0	0	58 (13.1%)	24 (12.6%)	82 (13.0%)
At least 288 weeks	0	0	47 (10.6%)	18 (9.4%)	65 (10.3%)
At least 300 weeks	0	0	37 (8.4%)	15 (7.9%)	52 (8.2%)
At least 312 weeks	0	0	33 (7.5%)	11 (5.8%)	44 (7.0%)
At least 324 weeks	0	0	24 (5.4%)	9 (4.7%)	33 (5.2%)
At least 336 weeks	0	0	18 (4.1%)	6 (3.1%)	24 (3.8%)
At least 348 weeks	0	0	14 (3.2%)	3 (1.6%)	17 (2.7%)
At least 360 weeks	0	0	6 (1.4%)	2 (1.0%)	8 (1.3%)
At least 372 weeks	0	0	4 (0.9%)	0	4 (0.6%)
At least 384 weeks	0	0	1 (0.2%)	0	1 (0.2%)

LTE = Long-term extension.

Computation bases on the entire range between first tablet intake and last documented tablet intake. Treatment interruptions were not deducted. Data cut-off MAR 2017.

Table Part II SIII-19: Study treatment dose titration by visit - actual dose received in uncontrolled LTEs (PATENT-2 and CHEST-2)

Visit	Dose	BAY 63-2521 (LTE, main) (N=442)	BAY 63-2521 (LTE, placebo in main) (N=191)	LTE total (N=633)
LTE baseline/Start of extension	Total number of patients	442	191	633
	0.5 mg TID	6 (1.4%)	0	6 (0.9%)
	1.0 mg TID	12 (2.7%)	191 (100%)	203 (32.1%)
	1.5 mg TID	59 (13.3%)	0	59 (9.3%)
	2.0 mg TID	80 (18.1%)	0	80 (12.6%)
	2.5 mg TID	285 (64.5%)	0	285 (45.0%)

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Table Part II SIII-19: Study treatment dose titration by visit - actual dose received in uncontrolled LTEs (PATENT-2 and CHEST-2)

Visit	Dose	BAY 63-2521 (LTE, main) (N=442)	BAY 63-2521 (LTE, placebo in main) (N=191)	LTE total (N=633)
LTE Day 14	Total number of patients	441	190	631
	0.5 mg TID	7 (1.6%)	7 (3.7%)	14 (2.2%)
	1.0 mg TID	12 (2.7%)	16 (8.4%)	28 (4.4%)
	1.5 mg TID	28 (6.3%)	167 (87.9%)	195 (30.9%)
	2.0 mg TID	106 (24.0%)	0	106 (16.8%)
	2.5 mg TID	288 (65.3%)	0	288 (45.6%)
LTE Day 28	Total number of patients	439	188	627
	0.5 mg TID	6 (1.4%)	4 (2.1%)	10 (1.6%)
	1.0 mg TID	13 (3.0%)	11 (5.9%)	24 (3.8%)
	1.5 mg TID	27 (6.2%)	17 (9.0%)	44 (7.0%)
	2.0 mg TID	78 (17.8%)	156 (83.0%)	234 (37.3%)
	2.5 mg TID	315 (71.8%)	0	315 (50.2%)
LTE Day 42	Total number of patients	435	188	623
	0.5 mg TID	5 (1.1%)	1 (0.5%)	6 (1.0%)
	1.0 mg TID	14 (3.2%)	9 (4.8%)	23 (3.7%)
	1.5 mg TID	28 (6.4%)	12 (6.4%)	40 (6.4%)
	2.0 mg TID	72 (16.6%)	26 (13.8%)	98 (15.7%)
	2.5 mg TID	316 (72.6%)	140 (74.5%)	456 (73.2%)
LTE Day 56	Total number of patients	433	186	619
	0.5 mg TID	3 (0.7%)	3 (1.6%)	6 (1.0%)
	1.0 mg TID	13 (3.0%)	4 (2.2%)	17 (2.7%)
	1.5 mg TID	22 (5.1%)	8 (4.3%)	30 (4.8%)
	2.0 mg TID	41 (9.5%)	18 (9.7%)	59 (9.5%)
	2.5 mg TID	354 (81.8%)	153 (82.3%)	507 (81.9%)
LTE Day 84	Total number of patients	428	185	613
	0.5 mg TID	4 (0.9%)	4 (2.2%)	8 (1.3%)
	1.0 mg TID	7 (1.6%)	5 (2.7%)	12 (2.0%)
	1.5 mg TID	24 (5.6%)	2 (1.1%)	26 (4.2%)
	2.0 mg TID	30 (7.0%)	20 (10.8%)	50 (8.2%)
	2.5 mg TID	363 (84.8%)	154 (83.2%)	517 (84.3%)

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Table Part II SIII-19: Study treatment dose titration by visit - actual dose received in uncontrolled LTEs (PATENT-2 and CHEST-2)

Visit	Dose	BAY 63-2521 (LTE, main) (N=442)	BAY 63-2521 (LTE, placebo in main) (N=191)	LTE total (N=633)
LTE Month 6	Total number of patients	423	181	604
	0.5 mg TID	4 (0.9%)	3 (1.7%)	7 (1.2%)
	1.0 mg TID	7 (1.7%)	3 (1.7%)	10 (1.7%)
	1.5 mg TID	18 (4.3%)	2 (1.1%)	20 (3.3%)
	2.0 mg TID	33 (7.8%)	18 (9.9%)	51 (8.4%)
	2.5 mg TID	361 (85.3%)	155 (85.6%)	516 (85.4%)
LTE Month 12	Total number of patients	405	172	577
	0.5 mg TID	4 (1.0%)	1 (0.6%)	5 (0.9%)
	1.0 mg TID	5 (1.2%)	5 (2.9%)	10 (1.7%)
	1.5 mg TID	17 (4.2%)	3 (1.7%)	20 (3.5%)
	2.0 mg TID	31 (7.7%)	10 (5.8%)	41 (7.1%)
	2.5 mg TID	348 (85.9%)	153 (89.0%)	501 (86.8%)
LTE Month 24	Total number of patients	368	154	522
	0.5 mg TID	3 (0.8%)	1 (0.6%)	4 (0.8%)
	1.0 mg TID	2 (0.5%)	5 (3.2%)	7 (1.3%)
	1.5 mg TID	15 (4.1%)	4 (2.6%)	19 (3.6%)
	2.0 mg TID	33 (9.0%)	12 (7.8%)	45 (8.6%)
	2.5 mg TID	315 (85.6%)	132 (85.7%)	447 (85.6%)
LTE Month 36	Total number of patients	273	113	386
	0.5 mg TID	2 (0.7%)	1 (0.9%)	3 (0.8%)
	1.0 mg TID	4 (1.5%)	3 (2.7%)	7 (1.8%)
	1.5 mg TID	12 (4.4%)	3 (2.7%)	15 (3.9%)
	2.0 mg TID	25 (9.2%)	8 (7.1%)	33 (8.5%)
	2.5 mg TID	230 (84.2%)	98 (86.7%)	328 (85.0%)
LTE Month 48	Total number of patients	170	65	235
	0.5 mg TID	1 (0.6%)	0	1 (0.4%)
	1.0 mg TID	3 (1.8%)	3 (4.6%)	6 (2.6%)
	1.5 mg TID	7 (4.1%)	0	7 (3.0%)
	2.0 mg TID	16 (9.4%)	6 (9.2%)	22 (9.4%)
	2.5 mg TID	143 (84.1%)	56 (86.2%)	199 (84.7%)

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Table Part II SIII-19: Study treatment dose titration by visit - actual dose received in uncontrolled LTEs (PATENT-2 and CHEST-2)

Visit	Dose	BAY 63-2521 (LTE, main) (N=442)	BAY 63-2521 (LTE, placebo in main) (N=191)	LTE total (N=633)
LTE Month 60	Total number of patients	81	33	114
	0.5 mg TID	0	0	0
	1.0 mg TID	0	2 (6.1%)	2 (1.8%)
	1.5 mg TID	3 (3.7%)	1 (3.0%)	4 (3.5%)
	2.0 mg TID	8 (9.9%)	1 (3.0%)	9 (7.9%)
	2.5 mg TID	70 (86.4%)	29 (87.9%)	99 (86.8%)
LTE Month 72	Total number of patients	35	13	48
	0.5 mg TID	0	0	0
	1.0 mg TID	0	2 (15.4%)	2 (4.2%)
	1.5 mg TID	1 (2.9%)	0	1 (2.1%)
	2.0 mg TID	3 (8.6%)	0	3 (6.3%)
	2.5 mg TID	31 (88.6%)	11 (84.6%)	42 (87.5%)
LTE Month 84	Total number of patients	12	2	14
	0.5 mg TID	0	0	0
	1.0 mg TID	0	0	0
	1.5 mg TID	0	0	0
	2.0 mg TID	1 (8.3%)	0	1 (7.1%)
	2.5 mg TID	11 (91.7%)	2 (100.0%)	13 (92.9%)

LTE = Long-term extension, TID = *Ter in die* (three times a day).

A phase IIa study in adult patients with ΔF508 homozygous cystic fibrosis (study 17020) was terminated after completion of cohort 1 with 21 patients, due to lack of efficacy. An abbreviated CSR became available on 20 JUN 2018 (PH-40094). **Study 16277 (RISE SSc Study)** was a randomized, double-blind, placebo-controlled phase II study to investigate the efficacy and safety of riociguat in patients with diffuse cutaneous systemic sclerosis. The study included 121 randomized patients and evaluation of the main phase data showed that the study did not meet its primary and secondary endpoints (PH-39734). Riociguat was well tolerated in both completed studies and no safety concern was detected.

Study 15681 (PATENT-CHILD) was a phase-III, open-label, multicentre, multinational study to investigate the safety, tolerability, and pharmacokinetics of riociguat in children from 6 - <18 years of age with PAH. Efficacy is an exploratory objective. The study enrolled 24 patients and administration of riociguat was adjusted according to body weight (tablets or oral suspension). The trial has started on 29 OCT 2015 (FPFV) and main phase is completed.

Last Patient/Last Visit (LPLV) of the main study phase was 07 MAR 2020. Twenty-four patients were enrolled in the study. Out of those, 18 patients were enrolled in the older age cohort from 12 to <18 years old and 6 patients were enrolled in the age cohort from 6 to <12 years.

Twenty-one subjects completed 24 weeks of treatment, of which 16 subjects were up-titrated to the maximum 2.5 mg TID dose (or body weight equivalent).

The results of the safety analyses (Interim CSR PH-41307) of the main treatment period (up to 24 weeks) of the study indicate that riociguat is safe and well tolerated when given as treatment in subjects from ≥6 to <18 years of age with symptomatic PAH. The safety profile observed in the PATENT-CHILD study is similar to that observed in adults. No bone and/or growth anomalies were reported during the main treatment period of the study.

Riociguat exposure (median of AUC and C_{max}) observed in paediatric subjects was towards the 25^{th} percentile of AUC and C_{max} in adult PAH subjects. Due to the small sample size for paediatric subjects, an exploratory descriptive analysis of the relationship between riociguat exposure and change in response, e.g., 6 Minute Walking Distance (6MWD) and N-terminal-pro hormone B-type Natriuretic Peptide (NT-proBNP), was conducted.
No pharmacokinetics (PK)/ Pharmacodynamic (PD) relationship was found for the change in 6MWD Week 24 to baseline in PATENT-CHILD, similar to the adult data in PATENT-1.
A trend in improvement of 6MWD and other outcome parameters was observed between baseline (last observed value prior to start of riociguat treatment) and Week-24.

A total of 21 patients have completed the main study phase and 21 have entered the optional long term extension phase (LTE). Two patients are still ongoing in the LTE.

<u>Summary of Main Phase and LTE Phase (ongoing) until 31 JAN 2023 (interim safety assessment):</u>

The most frequently reported TEAEs until 31 JAN 2023 by primary SOCs were infections and infestations (75.0%), nervous system disorders (45.8%), and respiratory, and thoracic and mediastinal disorders (33.3%).

At cut-off, 12 subjects reported a serious TEAE. The most frequently reported primary SOCs for TESAEs were respiratory, thoracic, and mediastinal disorders (in 5/24 [20.8%] subjects) and cardiac disorders (in 3/24 [12.5%] subjects; PT: right ventricular failure). PAH and haemoptysis were reported in 2 subjects each (2/24 [8.3%]), all other PTs were reported in individual subjects only. A total of 3 drug-related TESAEs were reported: right ventricular failure, pulmonary arterial hypertension and hypotension (1/24; 4.2% each).

No deaths were reported during main phase and in the LTE phase up to the cut-off date of 31 JAN 2023.

<u>LTE Phase (ongoing) 01 FEB 2023 to 19 SEP 2023</u>:

Data reported for this period is preliminary and manually compiled. In this period 10 TEAEs have been reported in 4 subjects, 3 of those as serious TEAEs (exacerbation of asthmatic bronchitis, COVID-19 infection, and death). The events exacerbation of asthmatic bronchitis

and COVID-19 infection were of moderate intensity, not study drug-related and are reported with an outcome as “recovered/resolved”.

A 22-year-old male patient died on 04 MAY 2023 (reported term: Death). Patient started riociguat on 10 MAY 2018 and experienced progression of underlying disease (idiopathic PAH, start date 20 MAR 2017) during study conduct: Worsening of WHO FC (05 AUG 2020) and AE Abnormal lab test – high NT-proBNP (9671.1 pg/ml), start date 30 JAN 2023. Patient refused qualification for lung transplant without any reason. Qualification was not done, and requirements have not been verified, because the patient did not agree to the procedure. According to the investigator, the patient died suddenly at home. No autopsy was performed. The investigator assessed SAE death as unrelated to study drug.

No treatment-emergent AESIs or AEs leading to discontinuation were reported for this period.

Overall, the LTE data are consistent with what has been observed in the main study phase. No new safety concerns have been identified.

PART II: Module SIV: Populations not Studied in Clinical Trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table Part II SIV-1: Exclusion criteria in pivotal clinical studies

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Pregnant women	Studies in animals have shown reproductive toxicity (see Part II Module SII).	No	Pregnancy is a contraindication, and women of childbearing potential must use effective contraception during treatment with riociguat. Monthly pregnancy tests are recommended.
Clinically relevant hepatic dysfunction (indicated by bilirubin >2 times the upper limit of normal [ULN] at Visit 0, and/or alanine aminotransferase or aspartate aminotransferase >3 times the ULN at Visit 0, and/or signs of severe hepatic insufficiency [e.g., impaired albumin synthesis with albumin <32 g/L, hepatic encephalopathy >Grade 1a] at Visit 0)	To reduce the impact of comorbidities on the homogeneity of the trial population. Patients with PH have a higher than average background rate of abnormal liver enzyme levels predominantly due to hepatic congestion from right-sided heart failure (see section SIV.3.4).	No	Severe hepatic impairment (Child-Pugh C) is a contraindication. The data from the EXPERT study indicated minimal use in CTEPH/PAH patients with hepatic impairment. Increased frequency of hypotension due to increased exposure were not observed in the EXPERT sub-population with hepatic impairment.
Pre-treatment with PAH-specific medication (CTEPH indication only)	ERAs and PCAs were excluded from CHEST because none had been approved for this patient population at time of development. No evidence of clinical efficacy had been shown in patients with CTEPH.	No	Based on combination therapy data from the PATENT study. Riociguat was administered to patients with PAH on stable ERA or PCA therapy. Both of these patient populations demonstrated clear efficacy benefits with no increase in safety signal. No safety concern regarding pre-treatment with PAH-specific medication is expected for CTEPH.

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Table Part II SIV-1: Exclusion criteria in pivotal clinical studies

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Exclusions related to pulmonary disease, such as forced expiratory volume <60%, severe restrictive lung disease, severe congenital abnormalities of the lung. Exclusions related to abnormalities in blood gases (capillary or arterial at rest): SaO_2 <88% at Visit 0 despite supplemental oxygen therapy; PaO_2 <55 mmHg at Visit 0 despite supplemental oxygen therapy; $PaCO_2$ >45 mmHg at Visit 0	Patients with underlying lung disease are classified as having WHO Group 3 PH (1) and were excluded to ensure homogeneity of the target patient population.	No	Addressed in the Indication section of the SmPC. Riociguat is not indicated in patients with PH due to lung disease (WHO Group 3). The subgroup of PH-IIP is contraindicated.
Resting heart rate in the awake patient <50 bpm or >105 bpm at Visit 0 and/or Visit 1 before randomisation	Tachycardia and bradycardia could suggest a pathology driven by underlying cardiovascular disease and not specifically PAH or CTEPH. The limits were chosen based on evidence-based experience.	No	Evaluation of integrated analyses revealed that there were no clinically relevant increases in heart rate and no increase in the incidence of irregular heart rate in patients receiving riociguat.
Atrial fibrillation/flutter within the last 90 days before Visit 1	Patients with atrial fibrillation/flutter within the last 90 days before Visit 1 were excluded from the phase 3 clinical studies in the claimed indication to allow for accurate measurements with right heart catheter.	No	Patients with atrial fibrillation/flutter within the last 90 days before Visit 1 were included in study 14308 (LEPHT, report no. A62512, Module 5.3.5.4). Favourable effects of riociguat on haemodynamics could be demonstrated in the LEPHT study population, which had a prevalence of atrial fibrillation of > 10%.

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Table Part II SIV-1: Exclusion criteria in pivotal clinical studies

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Left-sided heart failure with an ejection fraction <40% within the last 90 days before Visit 1	Patients with underlying LVD are classified as having WHO Group 2 PH (1) and were excluded to ensure homogeneity of the patient population.	No	Patients with left heart failure with an ejection fraction <40% within the last 90 days before start of study medication were excluded from the phase 3 clinical studies in the claimed indication, but that population was investigated in study 14308 (LEPHT; report no. A62512; Module 5.3.5.4) and favourable effects of riociguat on haemodynamics in that population could be demonstrated.
Pulmonary venous hypertension indicated by baseline pulmonary capillary wedge pressure >15 mmHg (if age is 18–75 years at Visit 1) or >12 mmHg (if age is >75 years at Visit 1)	Patients with underlying pulmonary venous hypertension are classified as having WHO Group 2 PH (1) and were excluded to ensure homogeneity of the patient population.	No	Data from a phase 2 study of patients with PH associated with systolic LVD (LEPHT; report no. A62512; Module 5.3.5.4) indicate that this is not a safety concern.
Hypertrophic obstructive cardiomyopathy	Patients with hypertrophic obstructive cardiomyopathy do not have PAH or CTEPH and were excluded to ensure homogeneity of the patient population.	No	Addressed in the SmPC. Left ventricular outflow tract obstruction is a major determinant of symptoms of hypertrophic obstructive cardiomyopathy, and is included as a warning in section 4.4.
Severe proven or suspected coronary artery disease (patients with Canadian Cardiovascular Society Angina Classification class 2-4, and/or requiring nitrates, and/or myocardial infarction within the last 90 days before Visit 1)	Patients with underlying coronary artery disease were excluded to ensure homogeneity of the patient population and to reduce the possibility of patients requiring nitrate therapy during the study.	No	In this population nitrate use is the most relevant safety aspect, which is addressed as a contraindication in the SmPC.

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Table Part II SIV-1: Exclusion criteria in pivotal clinical studies

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Positive for HIV	To reduce the impact of comorbidities on the homogeneity of the trial population. Patients with HIV infection might require anti-retroviral therapy (e.g., ritonavir).	No	Addressed in the SmPC. Potential drug interaction with ritonavir, a strong multi-pathway CYP and P-gp/BCRP inhibitor, is included as a warning in section 4.4.
Clinical evidence of symptomatic atherosclerotic disease (peripheral artery disease with reduced walking distance, history of stroke with persistent neurological deficit etc.)	To achieve a homogenous population of patients with PAH and CTEPH that truly reflected the target disease population.	No	This was an efficacy-driven exclusion criterion, as symptomatic atherosclerotic disease might influence walking distance measurements. The safety of riociguat is not expected to be different in this patient population.
Congenital or acquired valvular or myocardial disease if clinically significant, apart from tricuspid valvular insufficiency due to PH	To achieve a homogenous population of patients with PAH and CTEPH that truly reflected the target disease population.	No	This was an efficacy-driven exclusion criterion. The safety of riociguat is not expected to be different in this patient population.
Evidence of recurrent thromboembolism despite sufficient (documented) oral anticoagulation – also when pulmonary arteries are not affected	To achieve a homogenous population of patients. To ensure that patients with recurrent pulmonary embolism rather than CTEPH and those with extrinsic compression of the pulmonary arteries (e.g., mediastinal disease or fibrosis, primary pulmonary vascular tumours, pulmonary veno-occlusive disease, and large-vessel pulmonary arteritis) that may be indistinguishable from CTEPH were not included.	No	This was an efficacy-driven exclusion criterion. The safety of riociguat is not expected to be different in this patient population.

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Table Part II SIV-1: Exclusion criteria in pivotal clinical studies

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
History of uncontrolled arterial hypertension within the last 90 days before Visit 1 and/or SBP >180 mmHg and/or diastolic blood pressure >110 mmHg at Visit 0 and/or Visit 1 before randomisation.	Uncontrolled systemic hypertension is likely to be due to underlying cardiovascular disease and not directly associated with PAH and CTEPH.	No	Implication for the target population considered to be low; mode of action of riociguat causes blood-pressure-lowering effects. The safety of riociguat is not expected to be different in this patient population

BCRP = Breast cancer resistance protein, bmp = beats per minute, CHEST = Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial, CTEPH = Chronic thromboembolic pulmonary hypertension, CYP = Cytochrome P450, ERA = Endothelin receptor antagonist, EXPERT = EXPosurE Registry RiociguaT in Patients with Pulmonary Hypertension, HIV = Human immunodeficiency virus, IIP = Idiopathic interstitial pneumonia, LEPHT = Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial, LVD = Left ventricular disease, P-gp = P-glycoprotein, $PaCO_2$ = Partial pressure of carbon dioxide, PAH = Pulmonary arterial hypertension, PaO_2 = Partial pressure of oxygen, PCA = Prostacyclin analogue, PH = Pulmonary hypertension, PATENT = Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial, SaO_2 = Oxygen saturation, SBP = Systolic blood pressure, SmPC = Summary of Product Characteristics, ULN = Upper limit of normal, WHO = World Health Organisation.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Table Part II SIV-2: Limitations to detect adverse reactions in clinical trials

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	PAH and CTEPH are orphan diseases (for more details on epidemiology, see Part II Module SI); therefore, the population available to study is relatively small (Pooled PATENT-1 and CHEST-1: n=704).	Rare AEs and those not directly related to the mode of action may not be detectable during the study period.
Due to prolonged exposure	AEs related to the mode of action (e.g., hypotension) are detectable, even during short-term treatment. Other AEs may be identified during the LTE studies. Long-term safety data for more than 10 years are available from clinical trials. Therefore, limitations are minimal.	Additional long-term data is collected in the LTE studies.
Due to cumulative effects	AEs due to accumulation of riociguat are unlikely because of the short half-life of riociguat; therefore, limitations are minimal.	Based on the PK profile of riociguat, the implications for the target population are considered to be limited.

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Table Part II SIV-2: Limitations to detect adverse reactions in clinical trials

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which have a long latency	Standard follow-up time was 30 days. LTE studies increase the likelihood of detection of AEs with a long latency.	Impact on the target population is limited; to date, no adverse reaction with a long latency has been identified.

AE = Adverse event, CHEST = Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial, CTEPH = Chronic thromboembolic pulmonary hypertension, LTE = Long-term extension, PAH = Pulmonary arterial hypertension, PATENT = Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial, PK = Pharmacokinetic.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

SIV.3.1. Children

EMA approval was granted for tablets on 31 MAY 2023: For paediatric PAH patients aged less than 18 years of age and body weight ≥ 50 kg with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists. The recommended starting dose is 1.0 mg three times daily (TID) for 2 weeks. Tablets should be taken TID approximately 6 to 8 hours apart.

However, the safety and efficacy of Adempas in children and adolescents below 18 years of age with chronic thromboembolic pulmonary hypertension and in children with pulmonary arterial hypertension below 6 years has not been established. See also section 4.2 (special populations) of the Summary of Product Characteristics (SmPC).

The incidence of idiopathic pulmonary arterial hypertension (PAH) is lower in children than in adults. By contrast, the incidence of congenital heart disease-associated PAH is much higher in children than in adults; however, there is marked heterogeneity in presentation, which is characterised by highly variable clinical outcomes. Chronic thromboembolic pulmonary hypertension (CTEPH) is extremely rare in children; therefore, children with CTEPH are not a valid target patient population. A waiver has been granted for the evaluation of riociguat in children with CTEPH.

PATENT-CHILD LTE study is still ongoing. Interim analysis of the data indicated, that the LTE data are consistent with what has been observed in the main study phase. No new safety concerns have been identified. Overall, the results of the safety analyses in PATENT-CHILD indicate that the administration of body weight adjusted riociguat (tablets or suspension) is safe and well tolerated when given to subjects between ≥6 and <18 years of age with idiopathic PAH, heritable PAH, or PAH associated with connective tissue disease (CTD) or congenital heart disease (CHD) with shunt closure.

A Paediatric Investigational Plan (PIP) has been agreed (EMEA-000718-PIP01-09-M05) and completed. The study of riociguat in children aged from 6 years to less than 18 years with PAH was initiated in OCT 2015 (NCT02562235) (study 15681, Eudra-CT number

2014-003952-29) and includes paediatric patients with PAH (idiopathic, hereditable, PAH associated with connective tissue diseases and congenital heart disease). The main phase of study was completed on 07 MAR 2020. The long-term extension phase of the study currently ongoing.

SIV.3.2. Elderly

Data for patients aged between 65 (according to the definition of 'elderly' used by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E7) and 80 years are available. Fifty-four (54) patients aged ≥75 years were included in PAH Soluble Guanylate Cyclase–Stimulator Trial 1 (PATENT-1) and CTEPH Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1) combined. Of the 490 patients who received riociguat in PATENT-1 and CHEST-1, 44 (9%) were aged ≥75 years. Patients aged >80 years were excluded from the phase 3 studies in PAH and CTEPH.

PAH was previously considered to be an illness that affects mostly the young, but it is now increasingly recognised in the elderly. Patients aged >80 years have a high probability of co-morbid conditions and multiple medications, leading to variability in outcome. Furthermore, patients aged >80 years are more vulnerable to haemodynamic changes and cardiac structural changes than younger patients. They are likely to have associated heart failure or diastolic dysfunction and may also have left ventricular stiffness. It is considered unethical to perform right heart catheterisation in this patient population in clinical trials, because the risk associated with cardiac catheterisation procedures increases with increasing age (68).

SIV.3.3. Pregnant or Breast-Feeding Women

Pregnant and breast-feeding women were excluded from clinical trials of riociguat. Studies in animals have shown reproductive toxicity. During the clinical trials programme, patients were counselled to use contraception, and regular pregnancy testing was performed. Eight 8 pregnancies have occurred during treatment with riociguat in clinical studies, with the following outcomes:

Table Part II SIV-3: Pregnancies occurring during treatment with riociguat in clinical studies

Source	Age	Study medication	Exposure	Reported event	Outcome
Phase III					
PATENT-2 (study 12935) Mfr control number [redacted]	[redacted]	Continued	1st trimester	Drug exposure during pregnancy Induced abortion	Elective abortion

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Table Part II SIV-3: Pregnancies occurring during treatment with riociguat in clinical studies

Source	Age	Study medication	Exposure	Reported event	Outcome
PATENT-2 (study 12935) Mfr control number [redacted]	[redacted]	Discontinued permanently	N/A	Ectopic pregnancy Note: status after sterilisation procedure with bilateral tubal occlusion	Laparotomy, salpingectomy
PATENT-2 (study 12935) Mfr control number [redacted]	[redacted]	Continued	1st trimester	Drug exposure during pregnancy Induced abortion Abortion	Elective abortion
PATENT-2 (study 12935) Mfr control number [redacted]	[redacted]	Discontinued permanently	1st trimester	Drug exposure during pregnancy, abdominal delivery/Caesarean section, premature delivery	Live male baby delivered *via* caesarean section at 32 weeks gestation, weight 1.59 kg and height 38 cm.[a]
PATENT-2 (study 12935) Mfr control number [redacted]	[redacted]	Discontinued permanently	1st trimester	Exposure during pregnancy Cardiac failure Abortion	Hysterotomy abortion at 19 weeks after LMP due to heart failure in the mother. A dead male foetus (normal appearance, clear amniotic fluid, no cord entanglement) was extracted. No autopsy was performed. Five (5) weeks later the mother died of PAH aggravation and cardiac shock assessed as unrelated to riociguat
PATENT-2 (study 12935) Mfr control number [redacted]	[redacted]	Discontinued	1st trimester	Maternal exposure during pregnancy Abortion induced	Abortion was induced since physical condition of mother would not allow continuation of

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Part II: Module SIV - Populations not studied in clinical trials

Table Part II SIV-3: Pregnancies occurring during treatment with riociguat in clinical studies

Source	Age	Study medication	Exposure	Reported event	Outcome
					pregnancy and delivery. No intra-uterine abnormalities detected. Stillbirth with no foetal post-natal abnormalities.
CHEST-2 (study 11349) Mfr control number [redacted]	[redacted]	Continued	1st trimester	Pregnancy	Spontaneous abortion around 4.5 weeks
Phase II					
RISE-SSC (study 16277) Mfr control number [redacted]	[redacted]	Interrupted	1st trimester	Vomiting Exposure during pregnancy (Elective abortion)	Elective abortion

CHEST = Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial, cm = Centimetre, Kg = Kilogram, LMP = Last menstrual period, Mfr = manufacturer, N/A = Not applicable, PAH = Pulmonary arterial hypertension, PATENT = Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial.
[a] The investigator initially reported congenital heart disease temporarily specified as atrial septal defect awaiting results of re-examination when baby is 6 months old and indicated that the baby might have patent foramen ovale at birth, which may close in the future and then would not be considered heart defect. Cardiac ultrasound scan performed at 3 months showed a patent foramen ovale, which was considered as no significant impact to the baby by the local physician. The investigator agreed with the conclusion and re-assessed the event as non-serious.

Pregnancies were not suspected to be due to an interaction between riociguat and the contraceptive measures. Lack of interaction with ethinyl estradiol and levonorgestrel was shown in study 17309 (PH-38786).

In the SmPC, riociguat is contraindicated during pregnancy; monthly pregnancy tests are recommended, and it is stated that women of childbearing potential must use effective contraception. Breast-feeding is included in section 4.6 of the SmPC.

SIV.3.4. Patients with Hepatic Impairment

Patients with clinically relevant hepatic dysfunction (indicated by bilirubin >2 times the upper limit of normal [ULN] at Visit 0, and/or alanine aminotransferase or aspartate aminotransferase >3 times the ULN at Visit 0, and/or signs of severe hepatic insufficiency [e.g., impaired albumin synthesis with albumin <32 g/L, hepatic encephalopathy >Grade 1a] at Visit 0) were excluded from the PATENT and CHEST phase 3 clinical studies. The reason for this was to reduce the impact of comorbidities on the homogeneity of the trial population.

Patients with pulmonary hypertension (PH) have a higher than average background rate of abnormal liver enzyme levels predominantly due to hepatic congestion from right-sided heart failure.

The pharmacokinetics (PK), safety and tolerability of a single dose of riociguat (1 mg) were assessed in patients with hepatic impairment (Child-Pugh class A or B) and in age-, weight- and gender-matched healthy controls in a single-centre, non-randomised, non-controlled, and non-blinded observational study with group stratification. This study has been completed and reported (study 11916; PH-36317), and an extension of the study including only non-smoking patients has also been completed (study 15001; PH-36744). There was no clinically relevant change in exposure in cirrhotic patients with mild hepatic impairment (Child-Pugh A). The PK profile in Child-Pugh B hepatic impairment showed increased exposure of riociguat still overlapping with ranges in healthy controls. The application of the riociguat individual dose titration scheme is adequate to balance efficacy and safety in patients with moderate hepatic impairment (Child-Pugh B).

Hepatic impairment is addressed in the SmPC in sections 4.2, 4.3, and 4.4.

SIV.3.5. Patients with Renal Impairment

Patients with creatinine clearance <30 mL/min were excluded from the PATENT and CHEST phase 3 studies. This was because limited data on the clearance and exposure of riociguat in patients with severe renal impairment were available at the time of planning the phase 3 studies.

The PK, safety, and tolerability of a single dose of riociguat (1 mg) were investigated in patients with renal impairment and age- and weight-matched healthy controls in a single-centre, non-randomised, non-controlled, non-blinded observational study with group stratification. This study has been completed and reported (study 11915; PH-36285), and an extension of the study including only non-smoking patients has also been completed (study 15000; PH-36745). Riociguat is not expected to be dialyzable, and patients with a creatinine clearance <15 mL/min were not included in the phase 1 trials.

The phase 1 data suggest that exposure is increased in all patients with renal impairment, and does not increase proportionally with decreasing renal function as expected. In the phase 3 studies in PAH and CTEPH (Pool 1), more than 35% of patients receiving riociguat had mild renal impairment at baseline (based on the Cockroft Gault formula; 189/490 [39%] in the randomised controlled studies and 210/557 [38%] in the long-term extensions [LTEs]) and approximately 20% had moderate renal impairment (101/490 [21%] in the randomised controlled studies and 106/557 [19%] in the LTEs). The trial protocol excluded patients with a creatinine clearance <30 mL/min at baseline, but despite this, 4 such patients were included in the Pool 1 randomised controlled studies, 2 of whom continued in the LTE studies. All of these patients were included in the safety population and were analysed in the subgroup of patients with a creatinine clearance of <30 mL/min.

Event rates for treatment-emergent adverse events (AEs), treatment-emergent serious AEs and most of the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms did not substantially increase with decreasing renal function in the riociguat treatment group when compared with placebo. The rate of the preferred term hypotension showed an increase

with decreasing renal function when compared with placebo. This can be explained by the different PK profile in renal impairment; exposure is increased but still overlaps with ranges in healthy controls.

The safety and efficacy data from the studies in the applied indications did not indicate the need for dose adjustment in patients with mild to moderate renal impairment. The application of the riociguat individual dose titration scheme is adequate to balance efficacy and safety in this population.

Renal impairment is addressed in the SmPC in sections 4.2, 4.4, and 5.2.

SIV.3.6. Patients with Other Relevant Co-Morbidity

Patients with PH subtypes other than PAH (World Health Organisation [WHO] Group 1) and CTEPH (WHO Group 4 (1)) were not included in the phase 3 studies PATENT and CHEST, to achieve a homogenous population of patients with PAH and CTEPH that truly reflected the target disease population. However, they were investigated in several phase 2 studies.

The SmPC addresses this topic in the Indication section. The riociguat indication is restricted to the PH groups studied.

SIV.3.7. Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population

Disease severity in patients with PH is based on individual classification according to WHO functional class (I–IV, with IV being the most severe). Patients in functional class IV were included in both PATENT and CHEST. However, in both studies, patients were excluded if their baseline 6-minute walk distance was less than 150 m. Thus, patients with functional class IV (severe disease) were included in the study only if they were able to walk more than 150 m in 6 minutes at baseline.

SIV.3.8. Sub-Populations Carrying Known and Relevant Polymorphisms

Genetic studies in familial PAH (FPAH) have revealed heterozygous germline mutations in the bone morphogenetic protein type II receptor (BMPR2), a receptor for the transforming growth factor/bone morphogenetic protein superfamily (69). Mutations in the *BMPR2* gene have been found in approximately 70% of families with FPAH. In addition, up to 25% of patients with apparent idiopathic PAH have been found to harbour similar mutations. There are no data available suggesting that patients with the *BMPR2* germline mutation respond differently to PAH therapy from those without the mutation. Diagnosis of PAH does not require genetic testing. Genetic testing for known mutations in *BMPR2* is available from several laboratories in North America and Europe, but not all patients undergo screening. Patients with symptomatic FPAH were eligible for inclusion in PATENT, but no analyses of gene mutations have been performed with regard to efficacy or safety outcomes.

SIV.3.9. Patients of Different Racial and/or Ethnic Origin

Riociguat has been examined in 4 studies in Japanese men: 2 bioequivalence studies (study 14769; report no. A51270; study 14845; report no. A51271), 1 single dose escalation study [study 12639; MRR-00304], and 1 multiple dose escalation study [study 12640; report

no. A43125]. In the multiple dose escalation study, healthy Japanese men received riociguat 1.0 mg and riociguat 1.5 mg three times daily (TID) for 7 days. Riociguat was fairly well tolerated in these healthy men at a dose of 1.0 mg TID, but not at a dose of 1.5 mg TID. For this reason, the planned dose of 2.5 mg TID was not tested in healthy Japanese men.

The Phase I development program consists of a total of 36 clinical pharmacology studies performed world-wide, including 32 studies in healthy white, black, Hispanic, and Asian (Chinese and Japanese) subjects as well as in patients with renal or hepatic impairment.

A basic phase 1 dose escalation study was undertaken in healthy Chinese males to investigate the safety and PK effects of riociguat after single and multiple oral doses of 1.0 mg and 2.0 mg tablets TID over 7 days using a randomised, double-blind, placebo-controlled, group comparison design (study 14361; report no. A57942). In total, 139 healthy individuals were enrolled; 36 (mean age 36.3 years, range 23–44 years) were randomised and completed the study without major deviations from the protocol. In the phase 3 clinical trial programme, black or African American patients accounted for fewer than 2% of the patient population in PATENT-1 and approximately 5% of the study population in CHEST-1.

PK data revealed no relevant differences due to ethnicity in the exposure to riociguat (integrated analysis of PK in volunteers [healthy and special populations]; PH-36936).

PART II: Module SV: Post-authorisation Experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, patient exposure is estimated at the time of product distribution, not at the time of product consumption. There is a delay between the times a medication is distributed until it is consumed by a patient. Patient exposure has been estimated by calculation from company distribution data. In addition, especially in the initial phase there may be a higher percentage of Adempas in stock, thus not yet taken by patients. This has to be taken into account when reviewing patient exposure and the calculation of reporting rate. From the rate of spontaneously reported side effects it is not possible to conclude an incidence rate (the true frequency) of side effects as the denominator (exposed patients) is unknown. An unknown number of patients will not have used Adempas for the whole period, either because they initiated after its start date or because they stopped before its end date. Due to the recommended titration scheme, an estimation of the number of patients exposed to Adempas based on different dose strengths administered is considered difficult. Instead, a crude patient time exposure can be estimated based on the assumption that three tablets are taken as the total daily dose. In order to present an overall estimate of exposed patients to all approved dosages, person-months (30 treatment days) and person-years were calculated independent of the different dosing schedules.

SV.1.2 Exposure

The cumulative worldwide exposure to Adempas since the start of marketing authorization until 19 SEP 2024 is estimated at 2,350,952 patient-months or approximately 195,913 patient-years, excluding interventional clinical studies.

PART II: Module SVI: Additional EU Requirements for the Safety Specification

SVI.1. Potential for misuse for illegal purposes

Limited pack sizes for riociguat and availability only on prescription will limit any potential risk of misuse for illegal purposes. At present, no potential for misuse or illegal use has been identified.

Part II: Module SVII - Identified and potential risks

SVII.1. Identification of safety concerns in the initial Risk Management Plan submission

Not applicable. According to the European Medicines Agency (EMA) guidance on the format of the risk management plan (RMP) in the European Union (EU) (Good Pharmacovigilance Practices [GVP]) Module V, Revision 2, effective since 31 MAR 2017, section 1 of Module SVII is expected to be submitted only for initial marketing authorisation applications.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

With the update of the RMP to version 8.4, “Bone safety in patients <18 years old” was included as a new “Important Potential Risk” according to the regulatory request following the application for indication in children <18 years of age with PAH (EMEA/H/C/002737/II/0037). Non-clinical data was taken into consideration (Part II SII) which described bone changes in juvenile and adolescent animals at supratherapeutic doses. However, due to species differences in skeletal development and bone turnover and the very rapid bone growth in rats, a direct transfer of this pre-clinical evidence to children is not deemed possible.

In addition, the PATENT-CHILD study investigated potential bone changes in children aged 6 to <18 years of age. The study enrolled 24 patients, of which 18 patients belonged to the age 12 to <18 years age group and 6 patients were in the 6 to <12 years age group. No bone and/or growth anomalies were reported during the main treatment period of the study. The available clinical evidence was considered too limited by EMA to conclude on this potential safety concern. The long-term extension phase of this study is still ongoing.

Following the update to RMP version 7.3, all safety concerns were removed. The list of safety concerns was re-evaluated based on the experience obtained during 5 years of marketing authorization and evaluation of the recently finalized post-authorisation safety study (PASS) **EXP**osur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension (EXPERT). EXPERT was a global, multicentre, prospective, uncontrolled non-interventional cohort study documenting data from patients with pulmonary hypertension (PH) treated with Adempas where 1,348 patients were enrolled. The analysis set comprised 1,330 patients, since 18 patients either had withdrawn consent or had no information about riociguat dosing at the time of data cut-off. Among the 1,330 patients, 326 patients had pulmonary arterial hypertension (PAH), 956 patients had chronic thromboembolic pulmonary hypertension (CTEPH), and 48 patients had other forms of PH. The re-evaluation of the list of safety concerns was based on the safety analysis of the 1,282 patients with PAH/CTEPH, except for the risk of “Off-label use in patients with idiopathic interstitial pneumonias (IIP)” which was evaluated by an analysis of the 5 patients with PH-IIP.

The EXPERT PASS study was used as a main tool for routine pharmacovigilance to collect case reports and relevant safety data for riociguat in a real world setting in order to further characterize and re-evaluate the list of safety concerns for Adempas. For each potential and

identified risk, the incidence of treatment-emergent adverse events (TEAEs) per topic was compared between the EXPERT safety data for the PAH/CTEPH indications and the pooled integrated analysis of safety (IAS) data set from the long-term extension (LTE) studies PATENT-2 and CHEST-2 with a data cut-off in 2012. This comparison was chosen, since the 2012 LTE IAS was used for the last updated of the safety specification in RMP version 6.2 and since the mean treatment duration during EXPERT (541 days) was closest to the mean treatment duration of the 2012 LTE IAS safety cut-off (423 days). (Source: IAS 2012 Table 1.3.1/1: Treatment duration [in days] - all pivotal studies [safety analysis set] EXPERT: Part I, Table 1.10.1).

In addition, all safety concerns were reanalysed to evaluate whether or not they meet the new definition of important potential/identified risks or missing information as per GVP Module V, Revision 2 by specifying whether additional PV activities or additional risk minimization activities are ongoing or considered needed, according to the recommendation in Procedure No. EMEA/H/C/002737/II/0030.

The following safety concerns were removed with the submission of the RMP version 7.3:

Important identified risks:

- Hypotension

  including hypotension due to drug interactions with:

  - organic nitrates
  - phosphodiesterase-5 inhibitors
  - strong multi-pathway cytochrome P450 (CYP) and
  - P-glycoprotein (P-gp)/breast cancer resistance protein (BCRP) inhibitors
  - strong CYP1A1 inhibitors and strong P-gp/BCRP inhibitors
- Upper gastrointestinal motility disorders
- Worsening of pulmonary venous occlusive disease (PVOD)
- Serious haemoptysis/pulmonary haemorrhage
- “Off-label use in patients with idiopathic interstitial pneumonias (IIP), with or without pulmonary hypertension (PH)”

Important potential risks:

- Medication error
- Renal failure
- Treatment of patients with pre-existing atrial fibrillation
- Bone changes and fractures
- Concomitant smoking (induction of cytochrome P450 [CYP]1A1)

- Bleeding
- Embryo–foetal toxicity
- Off-label use in patients aged <18 years

Missing information

- Patients with systolic blood pressure <95 mmHg/arterial hypotension
- Patients with severe hepatic impairment/hepatic dysfunction
- Patients with creatinine clearance <30 mL/min or dialysis
- Patients with CTEPH or PAH in World Health Organization (WHO) functional class IV
- Long-term safety in clinical practice
- Patients with uncontrolled hypertension
- Pregnancy and lactation
- Patients aged <18 years

Justification for the removal of safety concerns

Table Part II SVII-1: Justification for the removal of safety concerns

Safety concern	Justification

Important identified risks
• Hypotension, including hypotension due to drug interactions with:
  • organic nitrates
  • phosphodiesterase-5 inhibitors
  • strong multi-pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp)/breast cancer resistance protein (BCRP) inhibitors
  • strong CYP1A1 inhibitors and strong P-gp/BCRP inhibitors
• Worsening of pulmonary venous occlusive disease (PVOD)
• Serious haemoptysis/pulmonary haemorrhage
• Upper gastrointestinal motility disorders
• “Off-label use in patients with idiopathic interstitial pneumonias (IIP), with or without pulmonary hypertension (PH)”
	• To align with the guidance of GVP module V, Revision 2.
	• No additional activities beyond routine risk minimisation measures are in place and there is no reasonable expectation that any additional pharmacovigilance activity can further characterise the risks.
	• Risk minimisation activities recommending specific clinical measures to address the risk have become fully integrated into standard clinical practice.
	• According to the recommendation in Procedure No. EMEA/H/C/002737/II/0030

Important potential risks • Bleeding • Embryo–foetal toxicity	• To align with per guidance of GVP module V, Revision 2. • No additional activities beyond routine

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Part II: Module SVII - Identified and potential risks

Table Part II SVII-1: Justification for the removal of safety concerns

Safety concern	Justification
• Off-label use in patients aged <18 years • Medication error • Renal failure • Treatment of patients with pre-existing atrial fibrillation • Bone changes and fractures • Concomitant smoking (induction of cytochrome P450 [CYP]1A1)	risk minimisation measures are in place and there is no reasonable expectation that any additional pharmacovigilance activity can further characterise the risk. • According to Procedure No. EMEA/H/C/002737/II/0030
Missing information • Patients with systolic blood pressure <95 mmHg/arterial hypotension • Patients with severe hepatic impairment/hepatic dysfunction • Patients with creatinine clearance <30 mL/min or dialysis • Patients with CTEPH or PAH in World Health Organization (WHO) functional class IV • Long-term safety in clinical practice • Patients with uncontrolled hypertension • Pregnancy and lactation • Patients aged <18 years	• To align with per guidance of GVP module V, Revision 2 • No additional activities beyond routine risk minimisation measures are in place and there is no reasonable expectation that any additional pharmacovigilance activity can further characterise

BCRP = Breast cancer resistance protein, CTEPH = Chronic thromboembolic pulmonary hypertension, CYP = Cytochrome P450, GVP = Good pharmacovigilance practice, EMEA = Europe, Middle East and Africa, IIP = Idiopathic interstitial pneumonias, mL = Millilitre, min = Minute, mmHG = Millimetre of Mercury, No. = Number P-gp = P-glycoprotein, PAH = Pulmonary arterial hypertension, PH = Pulmonary hypertension, PVOD = Pulmonary venous occlusive disease, WHO = World Health Organization

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

SVII.3.1.1. Important Potential Risk: Bone safety in patients <18 years old

HLGT: Bone disorders (excluding congenital and fractures)

PT's: Body height abnormal; Body height above normal; Body height below normal; Growth failure; Growth disorder; Growth accelerated; Growth retardation; Acral overgrowth.

Potential mechanisms:

Riociguat restores the NO-sGC-cGMP pathway and leads to increased intracellular levels of cGMP. It is known that cGMP has an effect on proliferation, differentiation, and function of cartilage and bone cells, either regulated by the NO-sGC-cGMP or the C-type natriuretic

peptide–particulate guanylate cyclase–cGMP signalling pathway. The thickening of growth plates and hyperostotic cortical remodelling seen in pre-clinical studies are considered to be secondary to the pharmacological mechanism of riociguat. The clinical relevance remains hypothetical.

Evidence source(s) and strength of evidence:

Non-clinical data:

PH-36257 (2-week toxicology study) and PH-36659 (13-week tox study), (M4.2.3.5.4)

Clinical trial data:

PH-41307 (PATENT-CHILD study, main phase),

PH-42339 (PATENT-CHILD study, technical report, including LTE (cut-off 19 SEP 2024))

The inclusion of bone changes as an important potential risk was based on pre-clinical data. The available clinical evidence was considered too limited to conclude on this potential safety concern. The LTE phase of the clinical study is still ongoing.

Characterisation of the risk:

Pulmonary Arterial Hypertension in paediatrics is a rare disease. The estimated incidence and prevalence of PAH are 0.5-2.2 cases per million children-years and 2–16 cases per million children, respectively (34-36). The frequency of bone changes in patients <18 years old with PAH is unclear.

In pre-clinical studies, morphological changes of the bones in rapidly growing juvenile and adolescent rats were observed at supratherapeutic exposures (at ten times the unbound AUC in the paediatric population) secondarily to the effects of the NO-sGC-cGMP pathway on bone homeostasis. The bone findings were identified in juvenile rats in the pilot juvenile toxicity study with riociguat at similar exposure levels to those observed in adolescent rats in the 4-week repeat-dose toxicity studies, therefore indicating no increased susceptibility of juvenile animals. There was a trend for reversibility for the bone alterations in the general 4-week repeat-dose toxicity study in rats after 2 weeks of recovery. This is in line with published data showing partial reversibility of bone effects in male Sprague-Dawley rats that were treated for 7 days with an sGC stimulator after a recovery period of 2 weeks and full reversibility after 5 weeks of recovery (Homer *et al.,* 2015). In addition, no comparable bone findings were seen in full-grown rats after life-long treatment in the rat carcinogenicity study with riociguat despite comparable age of the rats at study start (i.e., during adolescence and therefore within the period of rapid bone growth) and similar exposures as in the shorter duration studies. Therefore, there is indication for full normalization despite continuous treatment after the cessation of rapid bone growth.

In the PATENT-CHILD study, 24 subjects were treated, with 6 subjects ≥6 to <12 years old (4 females, 2 males) and 18 subjects ≥12 to <18 years old (7 females, 11 males). The study included monitoring of bone growth and morphology by means of X-ray of the left hand and wrist, performed at baseline and after 24 weeks of treatment. This was continued during the LTE phase every 12 months. Bone age and bone morphology were assessed centrally by a specialist. In addition, assessment of height, pubertal development using Tanner scale as well

as chronological age were included to evaluate the subject's overall development. No bone and/or growth anomalies were reported during the main phase of the study nor for the LTE phase with cut-off date 19 SEP 2024.

Risk factors and risk groups:

No particular risk factors or risk groups are known for the population of patients <18 years old with PAH.

Preventability:

There are no specific measures known to prevent bone changes in patients <18 years old with PAH.

Impact on the risk-benefit balance of the product:

Available PATENT-CHILD data do not show any bone and/or growth anomalies during the main treatment period of the study. The LTE phase is ongoing. Until cut-off for this RMP no case of bone and/or growth anomalies were shown. The actual and expected impact on the benefit-risk balance is considered to be low.

Public health impact:

PAH is a rare disease, and the PATENT-CHILD clinical data did not reveal any bone changes inpatients <18 years old, therefore the public health impact is considered to be low.

SVII.3.2. Presentation of the missing information

No missing information has been identified for Adempas.

PART II: Module SVIII: Summary of the Safety Concerns

Table Part II SVIII-1: Summary of safety concerns

Important identified risks	• None
Important potential risks	• Bone safety in patients <18 years old
Missing information	• None

PART III: Pharmacovigilance Plan

III.1 Routine pharmacovigilance activities

The objective of the routine pharmacovigilance activities for Adempas is surveillance to identify and evaluate changes in reporting frequency, severity, or other event characteristics.

Routine pharmacovigilance activities include adverse reactions reporting, signal detection, and evaluations in Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR).

III.1.1. Specific Adverse Reaction Follow-up Questionnaires

A specific follow-up questionnaire is in place for case reports pertaining to the following safety concern (see Annex 4):

Important potential risks

- Bone safety in patients <18 years old

III.1.2. Other forms of routine pharmacovigilance activities

For each PBRER/PSUR, a review of the cases reported during the reporting period is conducted for the following safety concern

Important potential risks

- Bone safety in patients <18 years old

III.2 Additional pharmacovigilance activities

A tabulated summary of completed pharmacovigilance study programme is provided in **Annex 2**.

PASS PATENT-CHILD LTE summary

Study short name and title:

PATENT-CHILD Phase III Study – Long term Extension (SN 15681)

Rationale and study objectives:

PATENT-CHILD was a 24-participant trial designed to evaluate PK, safety, and tolerability with exploratory efficacy endpoints over a time period of 24 weeks (main phase). The LTE phase is ongoing. The primary safety outcome of this study was incidence of Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs) as well as discontinuations from the study. Also, part of the primary safety outcome was the analysis of the change of bone age from baseline to the Week 24 compared to chronological age, and changes in bone morphology. This was done by means of X-ray of the left hand and wrist.

PATENT-CHILD LTE: Bone age and bone morphology assessment is continued during the LTE at 12 months intervals until growth velocity has plateaued and growth plates are closed.

In addition, any bone changes as assessed by the investigator are to be reported as Adverse Events of Special Interest (AESI).

Study design:

This is an open-label, single arm study with individual dose titration.

Study population:

The study population includes all patients previously enrolled in the main phase of the PATENT-CHILD study and who continued in the LTE phase.

Subjects from 6 years to less than 18 years of age with PAH and WHO FC I-III were included in the main phase of the PATENT-CHILD study. Pulmonary Arterial Hypertension had to be diagnosed by right heart catheterization (RHC), and patients had to be on standard of care PAH medications, allowing Endothelin Receptor Antagonist (ERA) and/or Prostacyclin Analogue (PCA), for at least 12 weeks prior to baseline visit.

Milestones:

Data collection started with First Subject First Visit (FSFV) in the LTE on 19 APR 2016[2]. The LTE phase is still ongoing.

The technical report (PH-42339) was submitted to the EMA in AUG 2022 (EMEA/H/C/002737/II/0037).

III.3 Summary table of additional pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities (EMA)				
PATENT-CHILD (SN 15681): safety, tolerability, and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with pulmonary arterial hypertension (PAH) - LTE				
On-going	To evaluate safety, tolerability, and pharmacokinetics of oral riociguat treatment in children 6 to <18 years of age with PAH.	Bone safety in patients <18 years old	Final report	Six months after LPLV (EOS as per protocol)

EMA: European Medicine Agency; EOS: End of Study; LPLV: Last Patient Last Visit

[2] First Visit date for LTE corresponds to last visit of main phase, after which subject continued in LTE phase

PART IV: Plans for Post-Authorisation Efficacy Studies

Table Part IV-1: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study, Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstance				
None				

Based on available data, there are no identifiable gaps in knowledge about efficacy in the target population and there is no need at this time for further post-authorisation efficacy studies.

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(including evaluation of the effectiveness of risk minimisation activities)

PART V: Risk Minimisation Measures

Risk Minimisation Plan

No additional risk minimisation measures beyond routine are ongoing or considered needed for Adempas.

V.1 Routine risk minimisation measures

The routine risk minimisation measures for Adempas comprise:

- Routine risk communication messages to communicate the risks to healthcare professionals and patients, so that an informed decision can be made *via* package leaflet and SmPC.
- Routine risk communication messages recommending specific clinical measures to address the risks *via* package leaflet and SmPC.
- Other routine measures beyond risk communication: prescription-only status.
- No safety concerns were identified for Adempas which require additional risk minimization measures beyond routine.

Table Part V-1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization measures
Bone safety in patients <18 years old **(Important potential risk)**	**Routine risk communication for informed decision-making:** • SmPC section 4.2 (Special Populations/ Paediatric population) and 5.3 (Pre-clinical safety data) **Routine risk communication recommending specific clinical measures to address the risk:** • None. **Other routine risk minimization measures beyond the Product Information:** • Prescription-only medicine status • Treatment initiated and monitored by a physician experienced in the treatment of PAH.

PAH = Pulmonary arterial hypertension; SmPC = Summary of product characteristics

V.2 Additional risk minimisation measures

Not applicable.

V.3 Summary of risk minimisation measures

Not applicable.

PART VI: Summary of risk management plan

Summary of Risk Management Plan for Adempas

This is a summary of the risk management plan (RMP) for Adempas. The RMP details important risks of Adempas, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) associated with Adempas.

Adempas' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Adempas should be used.

This summary of the RMP for Adempas should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Adempas RMP.

I. The medicine and what it is used for

Adempas is authorised for (see SmPC for the full indication):

- **Chronic thromboembolic pulmonary hypertension (CTEPH)**

  Adempas is indicated for the treatment of adult patients with World Health Organisation (WHO) Functional Class (FC) II-III with

  - inoperable CTEPH,
  - persistent or recurrent CTEPH after surgical treatment to improve exercise capacity.

- **Pulmonary arterial hypertension (PAH) in adults**

  - Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with PAH with WHO FC II to III to improve exercise capacity.

- **Pulmonary arterial hypertension (PAH) in children and adolescents**

  - Adempas is indicated for the treatment of PAH in paediatric patients aged 6 to less than 18 years of age with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists.

Adempas contains riociguat as the active substance and it is given by oral administration.

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Further information about the evaluation of Adempas' benefits can be found in the Adempas' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/adempas#assessment-history-section

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Adempas, together with measures to minimise such risks and the proposed studies for learning more about Adempas' risks, are outlined below.

Routine risk minimization measures for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of the medicinal product. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table Part VI-1: Important identified risks, important potential risks, and important missing information associated with Adempas

Important identified risks	None
Important potential risks	Bone safety in patients <18 years old
Missing information	None

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II.B Summary of important risks

Table Part VI-2 : Important potential risk: Bone safety in patients <18 years old

Evidence for linking the risk to the medicine	The inclusion of bone safety in patients <18 years old as an important potential risk was based on pre-clinical data. The available clinical evidence was considered too limited to conclude on this potential safety concern. The long-term extension phase of the clinical study is still ongoing.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk minimisation measures
Additional pharmacovigilance activities	PATENT-CHILD Long Term Extension study

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Adempas.

II.C.2 Other studies in post-authorisation development plan

PATENT-CHILD Phase III Study – Long term Extension (SN 15681)

Purpose of the study:

PATENT-CHILD was a 24-participant trial designed to evaluate PK, safety, and tolerability with exploratory efficacy endpoints over a time period of 24 weeks (main phase). The LTE phase is ongoing. The primary safety outcome of this study was incidence of TEAEs and TESAEs as well as discontinuations from the study. Also, part of the primary safety outcome was the analysis of the change of bone age from baseline to the Week 24 compared to chronological age, and bone morphology. This was done by means of X-ray of the left hand and wrist.

PATENT-CHILD LTE:

Bone age and bone morphology assessment is continued during the LTE at 12 months intervals until growth velocity has plateaued and growth plates are closed. In addition, any bone changes as assessed by the investigator are to be reported as Adverse Events of Special Interest (AESI).

PART VII: Annexes

Table of Content

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table-1: Planned and ongoing studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
PATIENT CHILD Long Term Extension study Category 3 Ongoing	To evaluate safety and tolerability of ricoiguat, incidence of adverse events, serious adverse events and adverse events of special interest in paediatric patients aged 6 to <18 years of age with PAH.	• Long term safety • Bone safety in patients <18 years old	Study Protocol: Module 5.3.5.2, Report PH-41307, Section 16.1.1 Interim report: Technical report (Module 5.3.5.2, Report PH-42339) Final study report: Six months after LPLV (EOS as per protocol)

Table-2: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report

EXPosur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension (EXPERT)
(riociguat exposure registry)
Category 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:
		  ○ organic nitrates
		  ○ phosphodiesterase-5 inhibitors
		  ○ strong multi-pathway CYP and P-gp/BCRP inhibitors
		  ○ strong CYP1A1 inhibitors and strong P-gp/BCRP inhibitors
		• Serious haemoptysis/ pulmonary haemorrhage
		• Off-Label Use in patients with Idiopathic Interstitial Pneumonia (IIP) with or without Pulmonary hypertension
		Important potential risks:
		• Bleeding
		• Embryo–foetal toxicity
		• Renal failure
		• Off-label use in patients aged
			Available data presented in each PBRER/PSUR
			Final report on 26 JUL 2019

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Table-2: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
		<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 CTEPH or PAH in WHO functional class IV • Long-term safety in clinical practice • Patients with uncontrolled hypertension	
In vitro studies to determine the M-1 potential to inhibit renal efflux transporters MATE1 and MATE2K Category 3	To further define drug-drug interaction potential of riociguat and M-1	Unknown potential for drug-drug interactions	MAY 2014

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Table-2: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
In vitro studies to determine the substrate characteristics of riociguat and metabolite M-1 towards human transporters Category 3	To further define drug-drug interaction potential of riociguat and M-1	N/A	DEC 2014

< = Less than, BCRP = Breast cancer resistance protein, CTEPH = Chronic thromboembolic pulmonary hypertension, CYP = Cytochrome P450, EXPERT = Exposure Registry riociguat in patients with pulmonary hypertension, IIP = Idiopathic Interstitial Pneumonia, M-1 = Main metabolite, MATE1 = Multidrug and toxin extrusion protein 1, MATE2K = Multidrug and toxin extrusion protein 2K, min = Minute, mL = Millilitre, NA = Not applicable, P-gp = P-glycoprotein, PAH = Pulmonary arterial hypertension, PBRER = Periodic benefit-risk evaluation report, PSUR = Periodic safety update report, WHO = World health organization

Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan.

Part A: **Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP**

Not Applicable

Part B: **Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP**

Not Applicable

Part C: **Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority**

Approved protocols: Module 5.3.5.2 (PH-41307)

Category 3 – PATENT-CHILD LTE

Procedure number: EMEA/H/C/002737/II/0037

Sequence eCTD: 0097

Annex 4 – Riociguat FU Questionnaire Bone safety in patients <18 years old

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SECTION I- REFERENCE ID		
BAYER CASE ID:	**STUDY ID:**	**PATIENT ID:**
SECTION II- REPORTER/PATIENT INFORMATION		
REPORTER: ☐ **Physician** ☐ **Nurse** ☐ **Other (specify):** _____		
REPORTER CONTACT INFORMATION		
Name:		**Institution/Practice Name:**
Address:		
ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**
PATIENT INFORMATION:		
Age at onset of event:	**Gender at birth:** ☐ **Male** ☐ **Female**	**Weight:** **unit:** / **Height:** **unit:**
SECTION III- BAYER PRODUCT INFORMATION Riociguat		
Therapy from *(dd/mm/yyyy)*: **to** *(dd/mm/yyyy)*: ☐ **ongoing**		
Lot/Batch Number:		**Model/Serial #** *(applicable for medical devices only)*:
Indication:		**Diagnosed on:**
Route of Administration:		

SECTION IV- ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	**Start date** *(dd/mm/yyyy)*:	**Stop date** *(dd/mm/yyyy)*:	**Outcome** *(e.g., recovered, recovered with sequelae, not recovered, improved, fatal)*

TREATMENT PROVIDED FOR EVENT		
Treatment such as any surgery, radiation therapy, immunotherapy etc.	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*

Is the reported event related to Riociguat?

☐ Yes

☐ No *(specify alternative explanation/other contributing factors below)*

Alternative explanation (e.g., underlying disease / other concomitant medication/ condition predisposing to the event):

Is the reported event a complication of the underlying condition? ☐ Yes ☐ No

Action taken with Riociguat			
☐ Dose not changed			
☐ Dose reduced	From:	To:	New dose:

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☐ Dose increased	From:	To:	New dose:
☐ Interrupted	From:	To:	
☐ Drug Withdrawn	From:		
☐ Unknown			
Did the adverse event abate/stop after treatment stopped? ☐ Yes ☐ No ☐ Unknown ☐ N/A		Did the event reoccur upon resuming the treatment ☐ Yes ☐ No ☐ Unknown ☐ N/A	

SECTION IV A- RELEVANT CLINICAL SYMPTOMS *(to AE of Interest)*	
Symptom	**Details** *(e.g., provide values or frequency if available and description of development of symptom over time if possible)*
Body height above normal	
Body height below normal	
Growth failure	
Growth accelerated	
Epiphyses premature fusion	
Epiphyses delayed fusion	
Bone deformities (specify)	
Bone pain (specify location)	
Joint pain (athralgia) (specify location)	
Other (specify):	
Other (specify):	

Additional Questions:
Was the symptom observed before start of treatment with Riociguat?

Have there been any other abnormalities in the overall physical development of the child observed (e.g. height, weight, pubertal development)?

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS

Laboratory Data	**Units / referenc erange**	**Before start of drug**	**Last values before event**	**After onset of event**			
		Date *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** (dd/mm/yyyy)	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*
☐ Hemoglob							

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in							
☐ Serum creatinine							
☐ Estimated GFR							
☐ Potassium							
☐ Sodium							
☐ Blood Glucose							
☐ Blood alkaline phosphatase							
☐ Bone alkaline phosphatase							

Laboratory Data	**Units / reference range**	**Before start of drug**	**Last values before event**	**After onset of event**			
		Date *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** (dd/mm/yyyy)	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*	**Date** *(dd/mm/yyyy)*
☐ ALT/ SGPT							
☐ AST/SGOT							
☐ Gamma GT							
☐ Phosphate							
☐ Calcium							
☐ Albumin							
☐ HbA1c							
☐ CRP							
☐ Magnesium							
☐ TSH							
☐ fT3 (Tri-iodothyronine free)							
☐ fT4 (Thyroxine free)							
☐ Calcitonin							
☐ Osteocalcin							
☐ Vit D							

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(Blood 25-hydroxycholecalciferol)							
☐ Vit D (Blood 1,25-dihydroxycholecalciferol)							
☐ PTH (parathyroid hormone)							
☐ Somatotropin (Growth hormone)							

Further investigations	**Test date** *(dd/mm/yyyy)*	**Short summary of the result**
☐ X-ray (specify body part): _____		
☐ MRI (specify technique and body part): _____		
☐ CT scan (specify technique and body system) _____		
☐ Bone densitometry (e.g DEXA scan)		
☐ Ultrasound (specify technique and body part)		
☐ Biopsy: Specify:		
☐ Other *(specify technique, site)*:		

SECTION V - RELEVANT CONCOMITANT MEDICATION						
Concomitantly administered medications given at any time point during Adempas (riociguat) treatment.						
Concomitant product name	**Route of administration**	**Indication for use**	**Dose / Frequency**	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Possible cause for the event?**
Sexual hormones (specify: Estrogen, testosterone, gestagenes, GnRH analoga): _____						
Growth hormones (specify) _____						
Corticosteroids (specify) _____						

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Tetracyclines (Specify)						
Vitamin D						
Hormonal contraceptives (specify)						
Cancer therapy (specify)						
Other (specify)						
Other (specify)						

SECTION VI - MEDICAL HISTORY / RISK FACTORS				
Relevant medical history / Concurrent conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details (e.g., specify location)**
☐ Prematurity at birth				
☐ Congenital musculoskeletal disorders				
☐ Extremity deformities (specify)				
☐ Obesity				
☐ Malnutrition				
☐ Bone disorders (specify)				
☐ Bone neoplasm (specify)				
☐ Fracture (specify)				
☐ Bone and joint therapeutic procedures (e.g., surgery) (specify)				
☐ Renal disease (specify)				
☐ Coeliac disease				
Relevant medical history / Concurrent conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details (e.g., specify location)**
☐ Inflammatory bowel disease				
☐ Diabetes mellitus (Type I and II)				
☐ Thyroid disorder (specify)				
☐ Cushing's Syndrome				
☐ Atopy/ Atopic skin disease (specify)				
☐ Previous tetracycline therapy				
☐ Other (specify):				
☐ …				

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SECTION VII- FAMILY HISTORY RELEVANT TO REPORTED EVENT	
Condition	**Family member(s) and approximate age(s) at onset**
Familial acromegaly	
Familial short stature	
Genetic disorders (specify) _____	
Other:	

SECTION VIII: ADDITIONAL INFORMATION (COMMENTS) *(if any): This section can also be used to provide information on any of the sections above. Please note the relevant section number below.*

Cause of death *(If selected outcome was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *(Continue with SECTION IV)*

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document like hospital discharge letters, histopathology report for confirmation of new malignancy diagnosis, if available.

Please sign here: If your signature is not yet configured on your device, please follow the instructions that appear when you click in the Signature field	**Signature:**

Annex 5 – Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 6 – Details of proposed additional risk minimisation activities

Not applicable

Annex 7 – Other supporting data (including referenced material)

Annex 7.1 – Literature References

Annex 7.1 – Literature reference

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Annex 8 – Summary of changes to the risk management plan over time

Table 1: Summary of Changes to the Risk Management Plan over Time

Version	Approval date Procedure number	Change
1.1	EMEA/H/C/002737	Initial RMP submission, Day 120 response
1.2	EMEA/H/C/002737	response
2.1	EMEA/H/C/002737/II/0001	response
3.0	23 OCT 2014 EMEA/H/C/002737/II/0001	Unknown potential for drug-drug interactions: Non-clinical study confirmed that riociguat's main metabolite is no inhibitor of MATE1 and MATE2K at relevant therapeutic concentrations.
3.1	23 OCT 2014 EMEA/H/C/002737/II/0001	Correction of formal aspects. Update of wordings referring to actions and activities in all Modules. In that context Part II Module SV populated.
4.0	EMEA/H/C/002737/II/0006 26 FEB 2015	Pharmacovigilance Plan milestone update. Non-clinical studies revealed that the risk of clinically relevant drug-drug interactions by riociguat and its metabolite on the studied human transporters MATE, OAT and OCT is regarded as low.
6.1	EMEA/H/C/2737/II/0014	Initial RMP submission Off-label use in patients with IIP, with or without PH.
6.2	EMEA/H/C/0002737/II/0014 23 FEB 2017	Potential for off-label use: A feasibility study on differentiating clinical classes of PH based on medical claims data was completed. Pharmacovigilance Plan: four studies have been completed.
7.1	EMEA/H/C/002737/II/0030 AUG 2019	Updated RMP format according to Guideline on good pharmacovigilance practices (GVP) Module V–Risk management systems (Rev 2) Revision of list of safety concerns based on EXPERT study results and according to (GVP) Module V (Rev 2). Update of details of important identified and important potential risks based on EXPERT study results
7.2	EMEA/H/C/002737/II/0030 DEC 2019	Change to Part II Module SVII based on a post-hoc analysis.
7.3	EMEA/H/C/002737/II/0030 MAR 2020	Revision of list of safety concerns according to (GVP) Module V (Rev 2) and recommendations in the Procedure EMEA/H/C/002737/II/0030.
8.1	EMEA/H/C/002737/II/0037	Changes to Part I, Part II (SI, SII, SIII and SIV) and Part VI to align with paediatric PAH indication
8.2	EMEA/H/C/002737/II/0037	Updates following RfSI in the Procedure EMEA/H/C/002737/II/0037
8.3	EMEA/H/C/002737/II/0037	Updates following CHMP/PRAC AR in the Procedure EMA/CHMP/934374/2022
8.4	EMEA/H/C/002737/II/0037	Updates following CHMP/PRAC AR

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Table 1: Summary of Changes to the Risk Management Plan over Time

Version	Approval date Procedure number	Change
9.1	EMEA/H/C/002437/X/0041	Updates to Part I, Part II SI and Part VI to align with submission for line extension for children < 50 kg (paediatric PAH indication). All document: editorial correction of erroneous typos
9.2	EMEA/H/C/002437/X/0041	Responses to CHMP D120 LoQ; Updates of data for PATENT Child LTE in: Part II SIII Clinical trial exposure Part II SIV Populations not studied in clinical trials Part II SV Post marketing exposure and Part II SVII Important Potential Risk: Bone safety in patients <18 years old
9.3	EMEA/H/C/002437/X/0041	Responses to CHMP D150 LoQ; Update of: Part I alignment with proposed SmPC Part VI alignment with proposed SmPC

CHMP = The Committee for Medicinal Products for Human Use, EMEA = Europe, Middle East and Africa, EXPERT = Exposure registry riociguat in patients with pulmonary hypertension, GVP = Good pharmacovigilance practices, MATE1 = Multidrug and toxin extrusion protein 1, MATE2K = Multidrug and toxin extrusion protein 2K, OAT = Organic anion transporter, OCT = Organic cation transporter, PRAC = Pharmacovigilance risk assessment committee, PH = Pulmonary hypertension, RMP = Risk management plan