26 April 2023
EMA/229554/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Adempas

International non-proprietary name: riociguat

Procedure No. EMEA/H/C/002737/II/0037

Marketing authorisation holder (MAH) Bayer AG

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

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List of abbreviations

6MWD	6-minute walking distance
6MWT	6-minute walking test
ACCP	American College of Clinical Pharmacy.
ADMA	Asymetric dimethyl arginine
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
APAH	Associated PAH
AUC	Area under the plasma concentration vs time curve from zero to infinity for total (bound and unbound) drug after a single dose
BCRP	Breast cancer resistance protein
BNP	B-type natriuretic peptide
CD	Capped dose
cGMP	Cyclic guanosine monophosphate
CHD	Congenital heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum total (bound and unbound) drug concentration in plasma after single dose administration
CTD	Common technical document
CTEPH	Chronic thromboembolic pulmonary hypertension
C_{trough}	Drug concentration in plasma immediately before administration of the next dose
CW	Clinical worsening
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DLP	Data lock point
DMC	Data monitoring committee
EC	European Commission
ECG	Electrocardiogram
EMA	European Medicines Agency
EQ-5D	European Quality of Life 5 Dimensions
ERA	Endothelin receptor antagonist

ESC	Euopean Society of Cardiology
ERS	European Respiratory Society
EU	European Union
FC	Functional class
FDA	Food and Drug Administration
FPAH	Familial PAH
HIV	Human immunodeficiency virus
HPAH	Hereditable PAH
IASAP	Integrated analysis statistical analysis plan
ICH	International Council on Harmonization
IDT	Individual dose titration
IPAH	Idiopathic PAH
IR	Immediate release
LLOQ	Lower limit of quantification
LTE	Long-term extension
MA	Marketing Application
MAH	Marketing Authorization Holder
MoA	Mode of action
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
MSD	Merck Sharp & Dohme
NA	Not applicable
NO	Nitric oxide
NT-proBNP	N-terminal pro–B-type natriuretic peptide
PAH	Pulmonary arterial hypertension
PBPK	Population physiology-based
PBRER	Periodic benefit-risk evaluation report)
PCA	Prostacyclin analogue
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamics
PDCO	Paediatric Committee
PDE	Phosphodiesterase
PDE5(i)	Phosphodiesterase 5 (inhibitor)

PedsQL	Paediatric Quality of Life Inventory
PH	Pulmonary hypertension
PI	Patient information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
popPK	Population pharmacokinetic
PSUR	Periodic safety update report
PT	Preferred Term
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
QoL	Quality of life
SAE	Serious adverse event
SAF	Safety analysis set
SBP	Systolic blood pressure
SD	Standard deviation
sGC	Soluble guanylate cyclase
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SoC	Standard of care
ss	Steady state
SVR	Systemic vascular resistance
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TID	Three times daily
TTCW	Time to clinical worsening
UK	United Kingdom
USA	United Stetes of America
WHO	World Health Organization
WSPH	World Symposium on Pulmonary Hypertension
WU	Wood unit

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bayer AG submitted to the European Medicines Agency on 29 August 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 6 to less than 18 years of age with WHO Functional Class (FC) I to III in combination with endothelin receptor antagonists with or without prostanoids for ADEMPAS, based on results from pivotal study PATENT-CHILD (Study 15681); this is a Phase III, Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with PAH; As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0289/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0289/2016 was completed.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	29 August 2022
Start of procedure	17 September 2022
CHMP Rapporteur Assessment Report	16 November 2022
PRAC Rapporteur Assessment Report	18 November 2022
PRAC members comments	23 November 2022
Updated PRAC Rapporteur Assessment Report	24 November 2022
PRAC Outcome	1 December 2022
CHMP members comments	05 Dec 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 December 2022
Request for supplementary information (RSI)	15 December 2022
CHMP Rapporteur Assessment Report	28 March 2023
PRAC Rapporteur Assessment Report	24 March 2023
PRAC members comments	4 April 2023
PRAC Outcome	14 April 2023
CHMP members comments	17 April 2023
Updated CHMP Rapporteur Assessment Report	20 April 2023
CHMP Opinion	26 April 2023
The CHMP adopted a report on similarity of Adempas with Opsumit (Appendix 1)	26 April 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

This application for Adempas (riociguat) is a Type II variation for adding an indication in paediatric patients aged 6 to less than 18 years with pulmonary arterial hypertension (PAH). PAH is a rare disease where pulmonary arterial pressure is elevated and can affect both adults and children.

Epidemiology

PAH in paediatrics is a rare disease. The estimated incidence and prevalence of PAH is 0.5–2.2 cases per million children-years and 2–16 cases per million children, respectively (Fraisse et al. 2010, Moledina et al. 2010, van Loon et al. 2011). An evaluation of the Tracking Outcomes and Practice in Paediatric Pulmonary Hypertension Registry (TOPP) and the Registry to Evaluate Early and Long-Term Pulmonary Hypertension Disease Management (REVEAL) has shown that 57% of the children with pulmonary hypertension had either idiopathic or familial disease and 36% had an underlying CHD (Barst et al. 2012, Berger et al. 2012, Zijlstra et al. 2014).

Aetiology and pathogenesis

The distribution of PAH etiologies in children is slightly different from that in adults, with a larger proportion of PAH associated with congenital heart disease (CHD) in children, whereas in both populations, the majority of patients have idiopathic PAH (IPAH). According to different paediatric registries and surveys, IPAH and CHD-PAH account for about 90% of all paediatric PAH cases and thus present far the most important patient groups (Beghetti 2009). In PATENT-CHILD, 75% of subjects had a primary diagnosis of IPAH, and 16.7% had a diagnosis of CHD-PAH, while in PATENT-1 61.4% had a primary diagnosis of IPAH, followed by 25.1% diagnosed with connective tissue disease-associated PAH. These findings are consistent with major registries such as TOPP and REVEAL-CHILDREN (Barst et al. 2012, Berger et al. 2012).

PAH is a group of diseases characterized by an imbalance between vasodilator and vasoconstrictor activities, leading to increased vasoconstriction and remodelling of the pulmonary vasculature (National Pulmonary Hypertension Centres of the and Ireland 2008). The process of remodelling being accompanied by a worsening of endothelial function also includes intimal proliferation, which may result in complete occlusion of some vessels and is complicated by the development of thrombi in the small pulmonary arteries (Widlitz and Barst 2003).

A number of mediators and growth factors have been shown to be involved in driving the cellular changes (Galie et al. 2004, Giaid et al. 1993). Increased circulating and local expression of endothelin-1 as well as serotonin is observed in subjects with PAH, while vasodilator pathways are deficient. Subjects with PAH produce less endothelial-derived prostacyclin and have a reduced expression of NO synthase and an increased production of vasoconstrictive thromboxane (Morrell et al. 2009), which has provided the rationale for therapies (Humbert et al. 2004, Humbert and Ghofrani 2016).

Children have more pulmonary vascular medial hypertrophy, less intimal fibrosis and fewer plexiform lesions at presentation, and RH failure is less frequent than in adults. However, the variability in the phenotype is not necessarily indicative of a different primary mechanism but likely multifactorial and associated with epigenetic changes, gender and other factors such as inflammation. There are more similarities than differences in the characteristics of PAH in children and adults, resulting in guidelines recommending similar diagnostic and therapeutic algorithms in children and adults (Rosenzweig et al. 2019). Specifically, the amenability of the NO-sGC-cGMP pathway to therapeutic interventions using riociguat has been demonstrated in multiple adult studies in PAH and CTEPH (Ghofrani et al. 2013a, Ghofrani et al. 2013b, Rubin et al. 2015, Simonneau et al. 2015). The vasoactive effects of cGMP-enhancing therapies is reflected by hemodynamic parameters (PVRI and CI) that are predictive of outcome.

Clinical presentation, diagnosis

Historically, the definition of PH in children has been the same as in adults, i.e. mPAP ⩾25 mmHg. However, due to variability in pulmonary hemodynamics during the post-natal transition, paediatric PH has been defined as mPAP ≥25 mmHg after 3 months of age. This was the definition applied in the paediatric PATENT-CHILD study conducted with riociguat.

The 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018 proposed to modify the definition for PH in adults as mPAP >20 mmHg and to include PVR ≥3 Wood units (WU) to identify pre-capillary PH (Rosenzweig et al. 2019). The new definition is meanwhile recognized and is applied to paediatric subjects. However, paediatric patients having a mPAP ≥ 25 mmHg at rest were included in the PATENT-CHILD study based on the previous definition in place at the start of the study in 2015 (Galie et al. 2009). Considering the different distribution of PH etiologies in children compared to adults (see below), PATENT-CHILD enrolled paediatric PAH patients 6 to <18 years suffering from idiopathic PAH, hereditary PAH, and congenital heart disease-associated PAH after shunt closure (CHD-PAH).

The symptoms of PAH include dyspnea on exertion, fatigue, palpitation, chest pain, syncope and cough, which are rarely present in the early stage. The disease is progressive and has a poor prognosis. When the subject presents with these symptoms, the conditions have often already advanced. Causes of elevated pulmonary arterial pressure are diverse, with the clinical classifications most recently updated in 2018 at the 6th WSPH. Basically, the pathologic processes that characterize PAH are similar for adults and children (Barst et al. 2011).

PAH remains an important cause of mortality and morbidity in adults and children.

There is still a high unmet medical need despite the availability and use of targeted therapies. The 1-, 3- and 5-year transplant-free survival (survival free from transplantation) in children with IPAH has been reported to be 89%, 76% and 54%, respectively. Overall survival was 89%, 84% and 74%, respectively, with 1 of 4 paediatric IPAH subjects dying within 5 years of presentation (Moledina et al. 2010). In a comparison between 3 referral centres with different populations of paediatric PAH subjects, unadjusted 1-, 3-, and 5-year transplantation-free rates were 100%, 96% and 90% for New York; 95%, 87%, and 78% for Denver; and 84%, 71%, and 62% for the Netherlands, respectively (Zijlstra et al. 2014). In the paediatric PAH cohort in the REVEAL registry in the US, 5-year survival from diagnosis for the overall cohort was 74 ±6%, with no significant difference between idiopathic/familial PAH and APAH-CHD cohorts (Barst et al. 2012).

PH-related hospitalizations appear to have increased over the past decade; however, because of uncertain factors, such as earlier recognition of the disease, diagnosis of PH in more diverse settings, or improved care, hospital mortality has decreased during this period (Frank et al. 2015, Maxwell et al. 2015).

Management

PAH in children is a progressive disease for which no cure is available. The most current approach in the management of paediatric PAH promotes the identification of appropriate targets for goal-oriented therapy. Determinants of paediatric idiopathic/heritable PAH risk allow for a risk stratification into two categories (lower risk and higher risk of poorer outcomes) (Rosenzweig et al. 2019). It can serve for example, to determine the need for additional therapy. As in adult subjects, determinants of higher risk in children include clinical evidence of right ventricular failure, progression of symptoms, WHO FC III or IV, significantly elevated or rising brain natriuretic peptide/N terminal pro type brain natriuretic peptide (BNP/ NT proBNP) levels, severe right ventricular enlargement or dysfunction and pericardial effusion.

Additional hemodynamic parameters that predict higher risk include mPAP/mSAP ratio >0.75, mRAP >10 mmHg, cardiac index <2.5 L/min/m2, and pulmonary vascular resistance index (PVRI) >20 WU*m2.

Currently, the PDE5-inhibitor sildenafil (Revatio) and the endothelin receptor antagonist (ERA) ambrisentan (Volibris) are the only drugs approved for the treatment of paediatric PAH in Europe (**Table 1**). The ERA bosentan (Tracleer) is recommended for paediatric use in guidelines and has information regarding PK and posology in the EU PI, but the indication does not specify use in paediatric age groups. The use of other ERAs and prostanoids in the treatment of paediatric PAH is common but off-label.

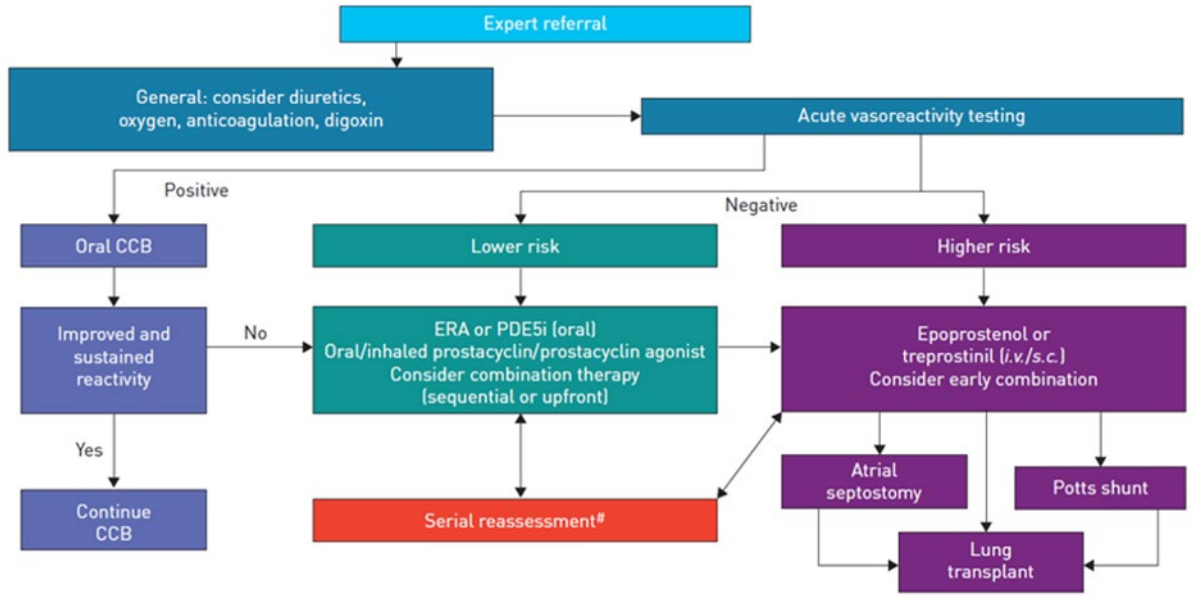
Table 1. Overview of major therapies/drugs currently used in the intended patient population

	Indication / Use	Benefits	Limitations/uncertainties
Sildenafil (Revatio®)	Treatment of PAH in paediatric patients aged 1 to 17 years with WHO FC I to III	Efficacy (CPET) shown in PPH and CHD-PAH	- Efficacy shown in treatment-naïve patients only - No consistent dose trend
Ambrisentan (Volibris®)	Treatment of PAH in adolescents and children (aged 8 to <18 years) with WHO FC II to III	Efficacy (6MWD) has been shown in IPAH, familial, corrected congenital heart disease and in PAH associated with connective tissue disease	- No dose trend observed for 6MWD - Not approved for children <8 years of age
Bosentan (Tracleer®)	Treatment of PAH to improve exercise capacity and symptoms in patients with WHO FC III	Based on PK results, dosing recommendation for children ≥1 year of age	- No paediatric indication but paediatric posology information
Tadalafil (Adcirca®)	Not yet approved for paediatric s	not known	not known

PAH = pulmonary arterial hypertension, PPH = primary pulmonary hypertension, IPAH = idiopathic pulmonary arterial hypertension, CHD-PAH = PAH associated with congenital heart disease, FC = functional class, 6MWD = 6-minute walking distance, PK = pharmacokinetic, CPET = Cardiopulmonary Exercise Test

Recent guidelines recommend a treatment algorithm based on risk status as outlined in the **Figure 1.**

Figure 1. Paediatric idiopathic/familial PAH treatment algorithm



* deterioration or not meeting treatment goals
CCB = calcium channel blocker, ERA = endothelin receptor antagonist, PDE5i = phosphodiesterase type 5 inhibitor

There is a high medical need for additional treatment options for PAH in light of the poor life expectancy and impact on the daily life of children and their relatives, and to provide treating physicians with suitable instructions and appropriate formulations for paediatric use.

2.1.2. About the product

Mode of action

Riociguat (Adempas) is a direct soluble guanylate cyclase (sGC) stimulator. sGC is a key enzyme in the cardiopulmonary system and the receptor for NO. It catalyses the generation of the signalling molecule cGMP, which plays a pivotal role in regulating cellular processes such as vascular tone, proliferation, fibrosis, and inflammation. Its dual mode of action riociguat directly stimulates sGC and synergizes with NO, restoring the NO-sGC-cGMP pathway. Importantly, riociguat exerts its biological effects independently of NO, which is present in low levels in some patients with CTEPH and PAH.

Adempas that is currently approved in the EU in 2014 for the treatment of adult patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

The **current** indication for Adempas as 0.5, 1.0, 1.5, 2.0, 2.5 mg film-coated tablets is as follows:

Chronic thromboembolic pulmonary hypertension (CTEPH)

Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with

• inoperable CTEPH,

• persistent or recurrent CTEPH after surgical treatment,

to improve exercise capacity (see section 5.1).

Pulmonary arterial hypertension (PAH)

Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity.

Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease (see section 5.1).

The indication for Adempas **proposed** by the MAH is as follows:

Chronic thromboembolic pulmonary hypertension (CTEPH)

Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with

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

to improve exercise capacity (see section 5.1).

Pulmonary arterial hypertension (PAH)

Adults

Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity.

Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease (see section 5.1).

Paediatrics

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) I to III in combination with endothelin receptor antagonists with or without prostanoids.

The study establishing use included aetiologies of idiopathic PAH or hereditable PAH and PAH associated with congenital heart disease after surgical correction (see section 5.1).

The posology **proposed** by the MAH for the paediatric indication is:

Paediatric patients:

Adempas is available for paediatric use as a tablet for those with body weight ⩾50 kg.

Titration of Adempas 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 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 and the patient has no signs or symptoms of hypotension, the dosage should be increased by 0.5 mg every 2 weeks to a maximum dose of 2.5 mg TID.

If systolic blood pressure falls below these specified levels the dosage 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 the specified levels or the patient shows signs and symptoms of hypotension the current dose should be decreased by 0.5 mg TID.

5.1.3 The development programme/compliance with guidance/scientific advice

The paediatric program was designed to support two paediatric populations based on weight. Existing riociguat tablets (0.5, 1.0, 1.5, 2.0, 2.5 mg) support dosing in children with a body weight ≥50 kg, while new granules for oral suspension formulation was developed to support dosing in children with a body weight <50 kg. The MAH decided to separate the submission of type II variation to add a paediatric indication to tablets (for children ≥50 kg) from that of the granules for oral suspension submission. Information for use in children with bodyweight ≥50 kg is included in the posology section.

This application is based on the data obtained from the clinical program in the paediatric population comprising data from the 24-week main phase of the pivotal Phase 3 study PATENT-CHILD (Study 15681), conducted in subjects ≥6 years to <18 years in the PAH indication. The study included children who received both tablets and granules for oral suspension formulations. Because the small size of PATENT-CHILD, the clinical experience for both formulations is presented in its totality to support the evaluation. This is considered acceptable as the dosing regimens for both formulations were designed to achieve systemic exposures in the range seen in adults.

A waiver had been granted to exclude study in children from birth to <6 years because the specific medicinal product is likely to be unsafe due to the observation of bone effects in juvenile and adolescent rats.

Compliance with CHMP guidance

The most relevant CHMP guidelines applied:

- Paediatric addendum to CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (EMA/CHMP/213972/2010)
- Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018)
- ICH guideline E11A on paediatric extrapolation Step2b 2022

Scientific Advice

- Pre-submission meeting with EMA held on Aug 26th 2020, to discuss:
    - Acceptability of the approach to extrapolation from adults
    - Adequacy of safety and risk minimization procedures

Paediatric investigation plan (PIP)

The application is based on the results of the completed paediatric development program in line with the approved EU PIP, EMEA-000718-PIP01-09-M06 (PIP decision number P/0289/2016) and with the completed full compliance check (EMA/PDCO/533423/2020).

Table 2. Overview of measures included in EU Paediatric Investigation Plan

Area	PIP measure	Description	PIP compliance check
Quality related	Study 1	Development of an oral liquid age appropriate formulation.	*18 April 2016*
Non-clinical studies	Study 2	Report PH-36257: 2-week repeat-dose toxicity study in juvenile rats.	*7 Dec 2012*
	Study 3	Report PH-36659: 13-week repeat-dose toxicity study in juvenile rats.	*7 Dec 2012*
Clinical studies	Study 5	Study 14986 (Phase 1): Open-label, randomised, single dose, study to assess pharmacokinetics and investigate the relative bioavailability and food effect of the oral liquid formulation of riociguat in healthy adults.	*7 Dec 2012*
	Study 6	Study 15681 (Phase 3): Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with pulmonary arterial hypertension (PAH).	*11 Dec 2020*
	Study 7	Deleted in procedure EMEA-000718-PIP01-09-M04.	
Extrapolation, modelling and simulation studies	Study 4	Study 15463 (Phase 1): Physiologically based pharmacokinetic (PBPK) modelling study to predict the pharmacokinetic properties of riociguat in the pediatric population.	*7 Dec 2012*
Other studies		Not applicable.	
Other measures		Not applicable.	

*Article 46 requires for pediatric clinical studies submission of the completed study report within 6 months of the last patient's last visit.
EU = European Union; PIP = Paediatric Investigation Plan

The paediatric development program for riociguat was designed to address the following objectives:

- Develop a dosing regimen for children aged between 6 and <18 years that results in riociguat exposures similar to levels observed in adult PAH patients dosed with 1 to 2.5 mg tablets TID.
- Demonstrate that PK/PD relationship are similar between children and adults.
- Demonstrate the safety and tolerability of riociguat use for paediatric PAH

The applicability of this extrapolation approach from adult data for the treatment of paediatric PAH has been accepted by EMA (EMEA-000718-PIP01-09-M06, September 2016).

2.2. Non-clinical aspects

2.2.1. Toxicology

Reproductive and developmental toxicity

At the initial MAA, two juvenile toxicity studies in rats have been assessed. In juvenile rats treated at doses of >10 mg/kg/day (10 times intended human exposure) with riociguat treatment starting at postnatal day (PND) 6 (corresponding to a human neonate age of <1 month) over a treatment period of about 3 weeks, thickening of trabecular bone and hypercellularity consisting of activated osteoblasts and osteoclasts were observed, and in addition hyperostosis and remodelling in the metaphyseal and diaphyseal bone was found. In contrast, in juvenile rats treated for 14 weeks starting at PND 6 with riociguat doses of up to 3 mg/kg/day (1 – 2 times the human exposure), no histopathological observations were made in the femur. Since it was expected that the Riociguat-induced bone lesions observed in juvenile rats might have relevance for the therapeutic application of riociguat in children, treatment of the paediatric population with riociguat was thought not to be justified at that moment.

2.2.2. Ecotoxicity/environmental risk assessment

Riociguat is already used in existing marketed products and no significant increase in environmental exposure is anticipated with the extension to paediatric use.

Therefore, riociguat is not expected to pose a risk to the environment.

2.2.3. Discussion on non-clinical aspects

At the initial MAA, two juvenile toxicity studies in rats have been assessed. In juvenile rats treated at doses of >10 mg/kg/day (10 times intended human exposure) with riociguat treatment starting at postnatal day (PND) 6 (corresponding to a human neonate age of <1 month) over a treatment period of about 3 weeks, thickening of trabecular bone and hypercellularity consisting of activated osteoblasts and osteoclasts were observed, and in addition hyperostosis and remodelling in the metaphyseal and diaphyseal bone was found. In contrast, in juvenile rats treated for 14 weeks starting at PND 6 with riociguat doses of up to 3 mg/kg/day (1 – 2 times the human exposure), no histopathological observations were made in the femur. Since it was expected that the Riociguat-induced bone lesions observed in juvenile rats might have relevance for the therapeutic application of riociguat in children, treatment of the paediatric population with riociguat was thought not to be justified at that moment.

During a Pre-Submission in 2020, the Rapporteurs commented that safety data are very limited, especially for events that may take longer than 24 weeks (e.g. bone effects) but up to now comparable to adults, which is reassuring and asked if long-term safety data (from clinical LTE part of the study) will be submitted. The MAH responded that no bone findings up to that point had been seen in the main part and in the ongoing LTE. The MAH informed that case of a grouped submission of extension of indication and line extension in Q3 2022 more data from LTE would be included in the dossier. The Rapporteurs

commented that use in children <6 y should not be suggested since the waiver below 6 y was based on the pre-clinical bone safety findings. This may lead to a contraindication.

Now, the MAH has discussed that increased susceptibility of juvenile animals has not been observed, the bone findings were observed in the juvenile toxicity study at systemic exposure levels 10-fold higher than the AUC in the paediatric population, and the very rapid bone growth in rats compared to human childhood cannot directly be transferred to children due to species-specific differences in skeletal development and bone turnover. In line with this, in the PATENT-CHILD study in children of 6 years and older, no effects on bone growth or morphology were described.

Riociguat is already used in existing marketed products and no significant increase in environmental exposure is anticipated with the extension to paediatric use.

2.2.4. Conclusion on the non-clinical aspects

From a non-clinical point of view, the MAH sufficiently justified the safe use of riociguat in humans >6 years old.

Riociguat is not expected to pose a risk to the environment as no significant increase in environmental exposure is anticipated with the extension to paediatric use.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

The studies included in the agreed PIP EMEA-000718-PIP01-09-MO6 (P/0289/2016) are presented below.

Table 3. Overview of measures included in EU Paediatric Investigation Plan

Area	PIP measure	Description	PIP compliance check
Quality related	Study 1	Development of an oral liquid age appropriate formulation.	*18 April 2016*
Non-clinical studies	Study 2	Report PH-36257: 2-week repeat-dose toxicity study in juvenile rats.	*7 Dec 2012*
	Study 3	Report PH-36659: 13-week repeat-dose toxicity study in juvenile rats.	*7 Dec 2012*
Clinical studies	Study 5	Study 14986 (Phase 1): Open-label, randomised, single dose, study to assess pharmacokinetics and investigate the relative bioavailability and food effect of the oral liquid formulation of riociguat in healthy adults.	*7 Dec 2012*
	Study 6	Study 15681 (Phase 3): Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with pulmonary arterial hypertension (PAH).	*11 Dec 2020*
	Study 7	Deleted in procedure EMEA-000718-PIP01-09-M04.	
Extrapolation, modelling and simulation studies	Study 4	Study 15463 (Phase 1): Physiologically based pharmacokinetic (PBPK) modelling study to predict the pharmacokinetic properties of riociguat in the paediatric population.	*7 Dec 2012*
Other studies		Not applicable.	
Other measures		Not applicable.	

*Article 46 requires for paediatric clinical studies submission of the completed study report within 6 months of the last patient's last visit.
EU = European Union; PIP = Paediatric Investigation Planatric

2.3.2. Pharmacokinetics

This application is based on the extrapolation of efficacy and safety in adults to the paediatric population based on comparable exposure.

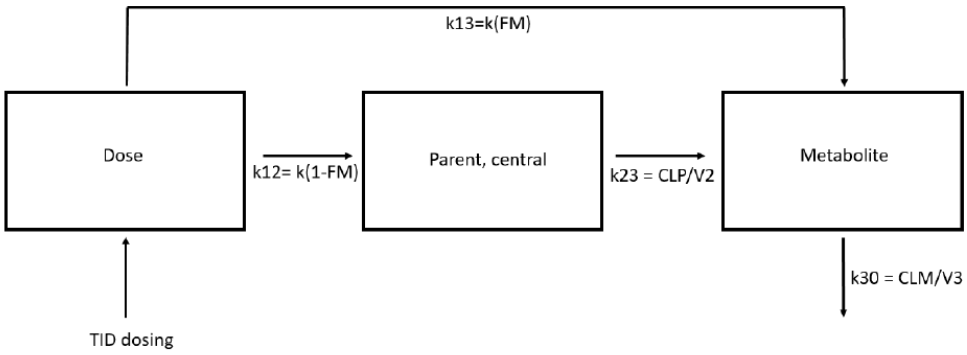
In relation to the pharmacokinetic support of this variation to include the paediatric population 6-<18 years of age with PAH, results of the bioavailability Study 14986 and PK results of the Phase 3 paediatric Study 15681 (PATENT-CHILD) clinical study in paediatric PAH patients were provided.

Bioanalytical methods. Plasma samples were analysed for riociguat and M-1 with analytical method SBQ-14004 method, which was used in the package in support of the adult indication of Adempas.

The stability of all analytes were established for the original marketing application for adult PAH and CTEPH. The stability was determined under sample handling and storage conditions and covered the interval from sampling to analysis. All analytes were stable under those conditions. Incurred sample reanalysis demonstrated the robustness of the analytical method.

PopPK model. A PopPK model was developed in order to describe the PK in paediatric patients based on data from PATENT-CHILD Study 15681, in which paediatric patients received either the oral formulation of the tablet. The initial population PK model was a one-compartment model for riociguat, coupled to a one-compartment model for major metabolite M-1.

Figure 2



CLP: clearance parent compound; CLM: clearance metabolic compound. V2; volume of the central parent compartment. V3; volume of the central metabolite compartment. FM: fraction of metabolite generated pre-systemically. k12: absorption rate constant parent compound into central compartment.

The number of subjects and PK samples in PATENT-CHILD Study 15681 was sparse and, therefore, the pre-existing adult data from PATENT-I/II were used to enrich the data set and as prior knowledge. The final popPK model included a description of metabolite M-1 formation from the parent drug in the central riociguat compartment, in combination with a direct appearance from the dose compartment. The model further included estimated allometric scaling that adequately described the data from both adult and paediatric PAH patients. Parameter estimates of the final popPK model is shown in Table 3

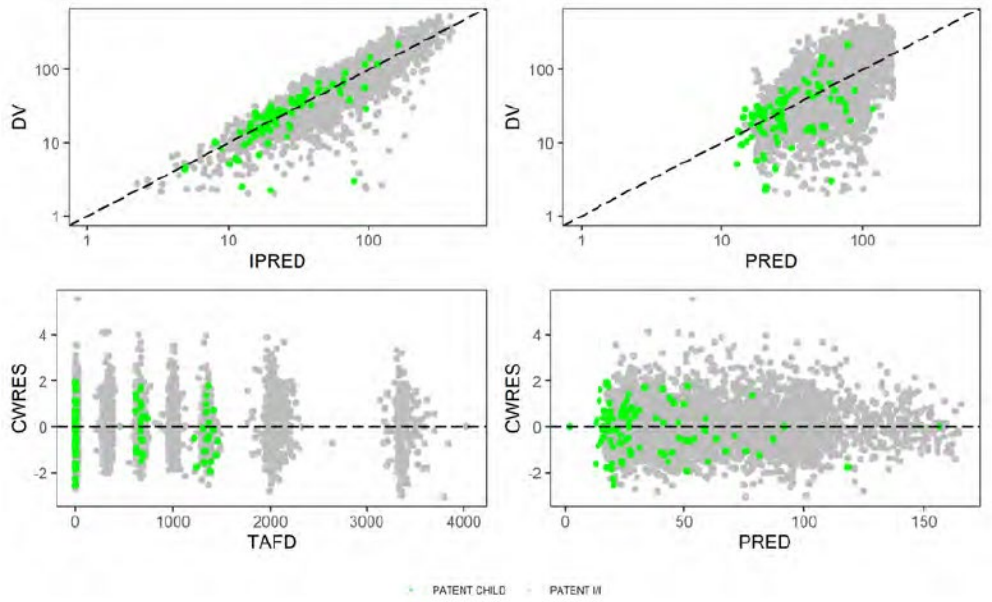
Table 4. Parameter estimates obtained with the final PK model E for riociguat and M-1.

Parameter Name	Estimate	SE	RSE (%)	95% CI
FM	0.208	0.0222	10.7	(0.164-0.251)
CLP (L/h)	1.73	0.0639	3.68	(1.61-1.86)
CLM (L/h)	3.25	0.0678	2.09	(3.12-3.38)
V2 (L)	26.1	0.986	3.77	(24.2-28.1)
V3 (L)	67.5	3.73	5.52	(60.2-74.8)
WGHT on CLP	0.157	0.0999	63.8	(-0.0392-0.353)
WGHT on CLM	0.425	0.0750	17.7	(0.278-0.572)
WGHT on V2	0.376	0.0768	20.4	(0.226-0.526)
WGHT on V3	0.329	0.118	35.8	(0.0980-0.0.560)
Inter-individual variability	**Estimate**	**SE**	**RSE (%)**	**95% CI**
ω^2_{CLP}	0.274	0.0232	8.45	(0.229-0.320)
ω^2_{CLM}	0.153	0.0131	8.61	(0.127-0.178)
$\text{cov}(\omega_{CLM}, \omega_{CLP})$	0.0302	0.0109	36.1	(0.0084-0.052)
ω^2_{V2}	0.0762	0.0133	17.5	(0.0500-0.102)
$\text{cov}(\omega_{V2}, \omega_{CLP})$	0.0845	0.0133	15.7	(0.0579-0.111)
$\text{cov}(\omega_{V2}, \omega_{CLM})$	0.0296	0.0852	28.8	(0.126-0.466)
ω^2_{V3}	0.229	0.0288	12.6	(0.173-0.286)
$\text{cov}(\omega_{V3}, \omega_{CLP})$	-0.0721	0.0177	-24.6	(-0.108-(-0.0367))
$\text{cov}(\omega_{V3}, \omega_{CLM})$	0.0924	0.0152	16.5	(0.0620-0.123)
$\text{cov}(\omega_{V3}, \omega_{V2})$	0.0220	0.0172	78.1	(-0.0124-0.0564)
Residual Error	**Estimate**	**SE**	**RSE (%)**	**StDev**
σ^2 prop error riociguat	0.125	0.00547	4.36	0.354
σ^2 prop error M1	0.111	0.00586	5.29	0.333

Abbreviations: CLP; Clearance of parent compound (riociguat). CLM, Clearance of metabolite (M-1). V2; volume of the central parent compartment. V3; volume of the central metabolite compartment.
RSE (%) is calculated as SE/Estimate*100; 95% CI is calculated as Estimate +/- 1.96*SE; for back-transformed parameters 95% CI is back-transformed values of 95% CI; %CV is calculated as sqrt(exp(ω2)-1)*100; ; StDev is calculated as sqrt(prop error): in this case, prop error is defined already as StDev, therefore StDev is the same as the estimated σ.
In NONMEM the individual value for CLP was calculated with Equation (6.4-1). In the NONMEM code, the scaling was accidentally applied twice for CLM, V2 and V3. Therefore, the values of the estimates reported for WGHT on CLM, WGHT on V2 and WGHT on V3 are twice the NONMEM output.

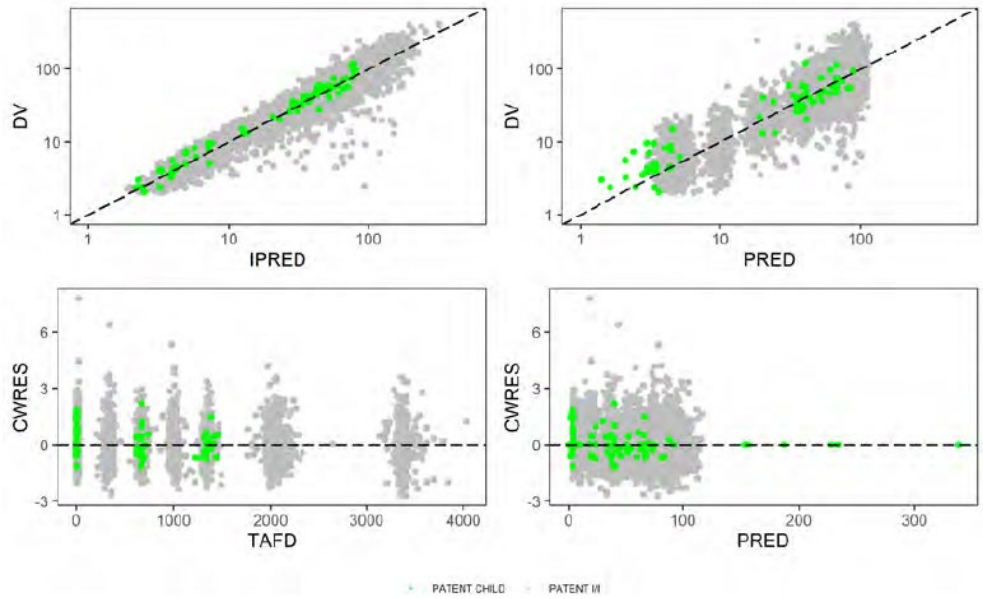
The model was developed in an adequate manner, and, based on the provided GoF plots and pcVPC plots (Figure 3, Figure 4, Figure 5 and Figure 6), yielded an adequate description of the riociguat and M-1 PK data, both in adults and in children.

*Figure 3. GoF plot final model after allometric scaling (final Model E) - **Riociguat**.*



The subjects from PATENT-I/II are coloured grey and subjects from PATENT-CHILD are coloured green. Upper left panel: Observations versus individual fitted values. Upper right panel: Observations versus population fitted values. Lower left panel: Conditional weighted residual versus time (in hours). lower right panel: Conditional weighted residuals versus population fitted values. Dashed line: line of identity (upper panels) or line indicating 0 (lower panels).

*Figure 4. GoF plot final model after allometric scaling (final Model E) - **M-1**.*



The subjects from PATENT-I/II are coloured grey and subjects from PATENT-CHILD are coloured green. Upper left panel: Observations versus individual fitted values. Upper right panel: Observations versus population fitted values. Lower left panel: Conditional weighted residual versus time (in hours). lower right panel: Conditional weighted residuals versus population fitted values. Dashed line: line of identity (upper panels) or line indicating 0 (lower panels).

Figure 5. Prediction-corrected Visual Predictive Check (pcVPC): PK of riociguat obtained with the final PK model (Model E) identified on PK data from PATENT-I/II and PATENT-CHILD.

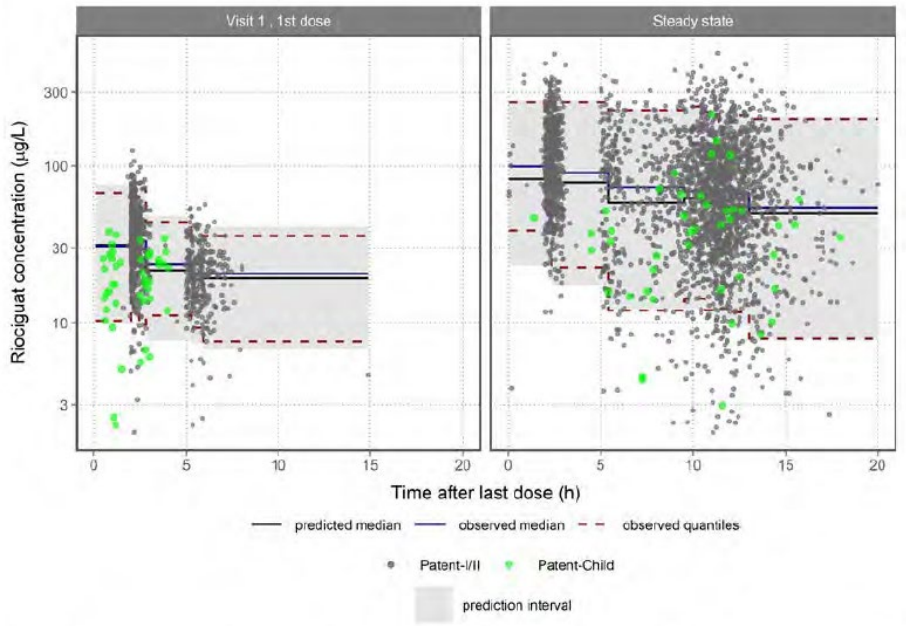
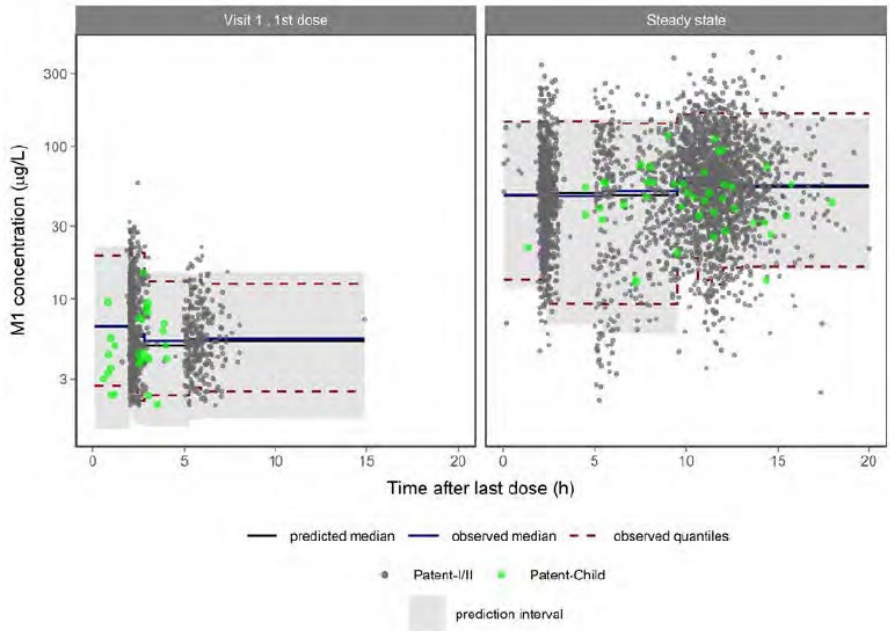


Figure 6. Prediction-corrected Visual Predictive Check (pcVPC): PK of M-1 obtained with the final population PK model (Model E) identified on PK data from PATENT-I/II and PATENT-CHILD.



Separate GoF plots were provided for children with the tablet formulation and children with the suspension. The model performed equally for both situations and for riociguat and for M-1. Therefore, the PK data generated by the developed popPK model are considered to provide an adequate estimation of the PK for riociguat and M-1 in the paediatric population in the PATENT-CHILD Study 15681, and confirm bioequivalence of the oral suspension and tablet formulations.

PBPK model

Using PBPK modelling, a dose scaling of riociguat from adult subjects to paediatric subjects with PAH has been performed, resulting in body weight-adjusted dosing for patients below 50 kg receiving oral liquid formulation. For paediatric subjects of body weight above 50 kg, the adult doses using the IR tablets was administered.

ADME in paediatric population

No data on riociguat plasma protein binding specific to children is available. Steady-state volume of distribution (Vss) estimated via popPK modelling in children (age range 6 to <18 years) following oral administration of riociguat is 26 L on average, comparable to the volume of distribution in adults (30 L). No new data were provided regarding excretion and metabolism characteristics; the characteristics in adults are also considered applicable for the requested 6-<18 years patient population.

In total, 76% (16/21) of the paediatric patients included in the PATENT-CHILD Study 15681 at week 24 ended up at the maximum 2.5 mg dose or the dose equivalent to that dose.

Overall, the riociguat and M-1 PK profile was considered to be similar in children as in adults by the MAH.

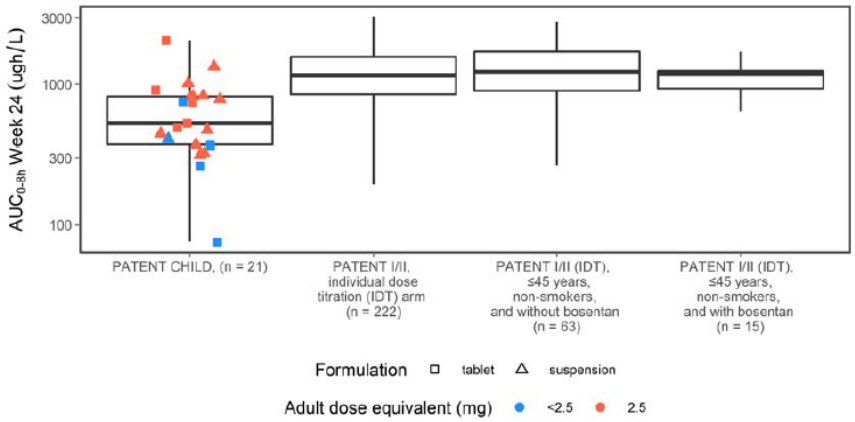
Comparison exposure in paediatric vs adult patients. Riociguat exposure in paediatric subjects with PAH was compared with the observed exposure in adult subjects with PAH included in the individual dose titration (IDT) arm in PATENT-1/2 studies. The observed plasma concentrations in paediatric subjects (PATENT-CHILD) overlapped with the observed concentrations in adult subjects with PAH (PATENT-1 and PATENT-2).

For the comparison of PK parameters between adult subjects and paediatric subjects, adult reference groups were defined that closely resembled the paediatric PAH population with respect to age, background treatment, and being smokers or non-smokers. Smoking and concomitant administration of bosentan with riociguat alter riociguat plasma concentrations. In adult subjects, cigarette smoke reduced riociguat exposure by 2.3-fold on average. The effect of cigarette smoke on riociguat exposure showed high variability due to induction of CYP1A1 via polycyclic aromatic. CYP1A1 catalyses the formation of riociguat's main metabolite M-1 in liver and lungs. Coadministration of bosentan, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in adult subjects with PAH by 27% on average.

The selected adult subgroups were therefore non-smoking subjects with PAH below 45 years, with or without concomitant intake of bosentan during riociguat treatment. PATENT-CHILD includes only subjects on stable PAH therapy excluding smokers whereas PATENT-1 includes in addition to pre-treated subjects also naïve subjects and allowed smoking.

The 75th percentile of riociguat area under the curve at steady state AUC(0-8h)ss in paediatric subjects is comparable to the lowest 25th percentile of adult subjects AUC for all comparison groups. Paediatric subjects receiving 2.5 mg (adult dose equivalents) showed higher exposures, thereby more resembling the values observed in adult subjects (**Figure 7**).

Figure 7. Comparison riociguat AUC(0-8h)ss at week 24 (visit 9)



Whiskers (black vertical lines): range between lowest and highest observation. Box: range between 25th and 75th percentile. Black horizontal line: median of observations. Symbols: individual observations; shape determines formulation, color determines TID dosing level (dose equivalents).

The median $AUC(0\text{-}8h)_{ss}$ in paediatrics subjects (525 µg·h/L) was 55% lower at week 24 than in adult subjects with PAH of the IDT arm in the PATENT-1/2 study (1163 µg·h/L). Factors that contributed to the lower exposure in paediatric subjects are the lower average maintenance dose of riociguat in PATENT-CHILD compared to the average dose in PATENT-1/2 and the higher than predicted riociguat clearance in some paediatric subjects with PAH, who were mostly adolescent.

Among the 24 paediatric subjects with PAH analysed in the population PK analysis, nine (37.5%) showed an estimated apparent riociguat plasma clearance that was above the 95th percentile predicted clearance by the PBPK model for the given age or body weight. The reason for the high clearance of these mostly adolescent paediatric subjects with PAH remains unknown but did not correlate with clinical worsening.

The observed geometric means of estimated C_{max} and C_{trough} values were lower in paediatric subjects compared to adult subjects, respectively (**Table 6**).

Table 5. Summary statistics of riociguat exposure measures at week 24.

Parameter	PATENT-CHILD (n=22) geo.mean/geo.SD (range)	PATENT-1/2, individual dose titration (IDT) arm (n=222) geo.mean/geo.SD (range)	PATENT-1/2I(IDT), ≤45 years, non-smokers, without bosentan (n=63) geo.mean/geo.SD (range)	PATENT-1/2(IDT), ≤45 years, non-smokers, with bosentan (n=15) geo.mean/geo.SD (range)
AUC (µg·h/L)	550 / 2.00 (75.5 – 2071)	1124 / 1.67 (194 – 3065)	1180 / 1.57 (264 – 2817)	1064 / 1.34 (640 – 1716)
C_{max} (µg/L)	86.4 / 1.88 (14.6 – 289)	168 / 1.57 (30.3 – 418)	175 / 1.49 (48.1 – 392)	162 / 1.25 (103 – 237)
C_{trough} (µg/L)	48.7 / 2.24 (4.58 – 222)	108 / 1.88 (9.48 – 342)	115 / 1.72 (18.1 – 304)	99.1 / 1.53 (36.8 – 187)

In addition, adult subjects with PAH showed higher riociguat exposure in comparison to adult healthy subjects (PK/PD Study 13817, Report PH-36960 in initial MAA dossier]). Paediatric patients included in PATENT-CHILD study were on stable treatment and PAH condition at baseline, and could be placed between healthy subjects and adult PAH patients from disease severity perspective. At baseline, most paediatric subjects in PATENT-CHILD had WHO functional class I or II (n=19, 79.2%), whereas most adult subjects in PATENT-1/2 had a WHO functional class of III (n=140, 55.1%). According to the MAH, this provides a potential explanation for the lower exposure in paediatric patients in comparison to adult PAH patients.

Bioequivalence. Dose normalized comparable bioavailability of riociguat and M-1 in terms of AUC and C_{max} was demonstrated between each paediatric (0.15 mg, 0.3 mg and 2.4 mg) suspensions and the immediate-release tablet. Bioequivalence was demonstrated between the 2.4 mg and 0.3 mg suspensions as well. Therefore, using the oral suspension or the tablet at the same dose is expected to yield comparable exposure. Inclusion of the paediatric PK data obtained with the suspension as well as the tablet, despite the fact that only registration of the tablet for the new paediatric indication is requested, is therefore considered acceptable. This procedure is expected to increase the, though still limited, amount of paediatric PK data in support of this variation.

Food. The food effect observed for the 0.15 mg/mL paediatric HC suspension was comparable to results reported for the currently registered IR tablet. Both the tablet as the suspension can be given regardless of food.

Special patient populations. Due to the limited PK data available from paediatric patients, the influence of intrinsic factors on riociguat exposure could not be fully investigated. As an outcome of the exploratory covariate analyses, body weight, race or gender did not show a relevant impact of riociguat exposure in paediatric subjects. The same effects of intrinsic factors observed in adults should be considered for children and adolescents

2.3.3. Pharmacodynamics

Mechanism of action

Riociguat is a direct soluble guanylate cyclase (sGC) stimulator. sGC is a key enzyme in the cardiopulmonary system and the receptor for NO. It catalyses the generation of the signalling molecule cGMP, which plays a pivotal role in regulating cellular processes such as vascular tone, proliferation, fibrosis, and inflammation. Its dual mode of action riociguat, directly stimulates sGC and synergizes with NO, restoring the NO-sGC-cGMP pathway. Importantly, riociguat exerts its biological effects independently of NO, which is present in low levels in some patients with CTEPH and PAH.

Exposure-Efficacy

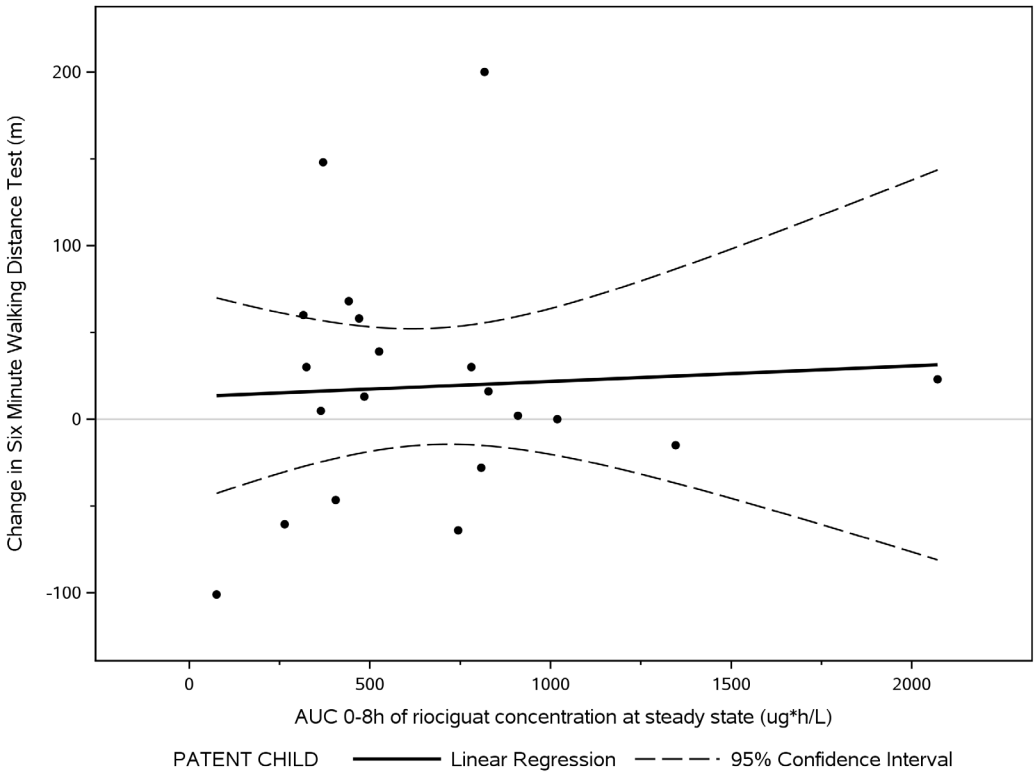
Paediatric population

Right heart catheterization (RHC) to assess and follow up hemodynamic parameters in paediatric subjects with PAH enrolled in the PATENT-CHILD study was not indicated in the Clinical Study Protocol. This was consistent with RHC not being recommended in paediatric studies due to the high rate of serious complications (Ollivier et al. 2019). Since hemodynamic parameters measured via RHC were not obtained in PATENT-CHILD, a PK/PD analysis for hemodynamic parameters, e.g. pulmonary vascular resistance (PVR), cardiac index, etc, was not applicable.

In the paediatric population, PK/PD relationships were investigated for the exercise capacity test 6-minute walking distance test (6MWD) and the biomarker NT-proBNP, a diagnostic biomarker for the presence of heart failure. For 6MWD, the change at week 24 (n=20) compared to baseline did not correlate with riociguat exposure (slope estimate [95 % CI]: 0.0070 m/(µg/L) [-0.685 to 0.699]) (**Figure 8**). For NT-proBNP, the absolute decrease at week 24 showed a weak correlation with riociguat exposure (n=13) (slope estimate [95% CI]: -7.32 (pg/mL)/(µg/L) [-13.6 to -1.00]), but this correlation was mainly driven by three subjects with large absolute NT-proBNP changes in either the positive or negative direction (**Figure 9**). The ratio of NT-proBNP at week 24 to baseline showed no relationship to C_{trough}, as the 95%

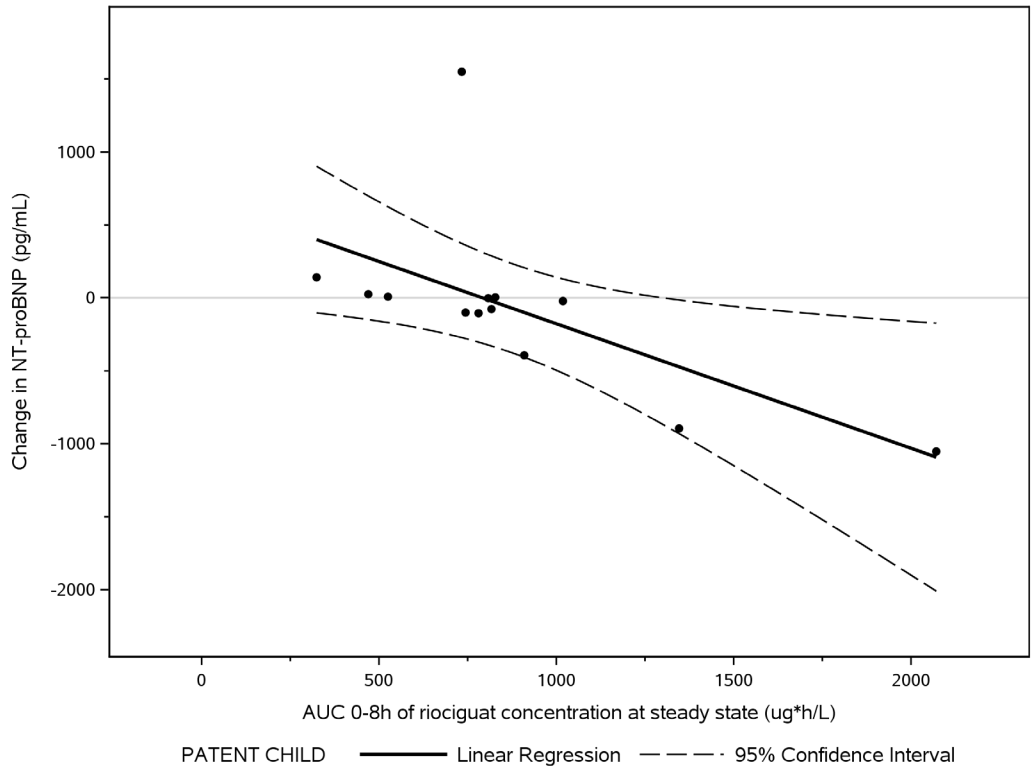
CI of the ratio included 0 (slope estimate [95% CI]: -0.0031 (pg/mL)/(µg/L) [-0.0076 to 0.0015])(**Figure 10**).

Figure 8. Change in Six Minute Walking Distance Test as a function of AUC(0-8h)ss of Riociguat Concentration at steady state for PATENT-CHILD



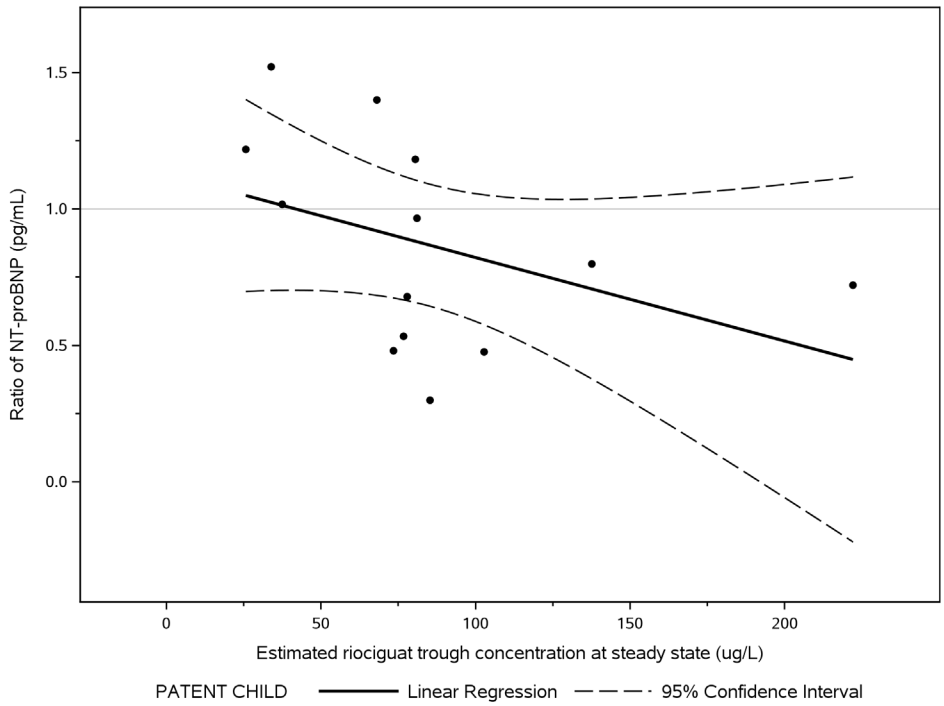
Change was derived as measure taken at visit 9 (week 24) minus the baseline measure. Circles: paediatric subjects with PAH. Solid line: linear regression. Dashed lines 95% confidence interval.

Figure 9. Change in NT-proBNP as a function of AUC(0-8h)ss of riociguat concentration at steady state for PATENT-CHILD



Change was derived as measure taken at visit 9 (week 24) minus the baseline measure. Circles: paediatric subjects with PAH. Solid line: linear regression. Dashed lines: 95% confidence interval

Figure 10. Ratio of NT-proBNP as a function of estimated riociguat trough concentration at steady state for PATENT-CHILD



Adults

In healthy subjects and PH patients, there is a close and direct relationship between riociguat plasma concentrations and hemodynamic effects such as a decrease in systemic and pulmonary vascular resistance, a decrease in systolic blood pressure and an increase in cardiac output after administration of a wide range of single doses (0.5 – 5 mg) or at steady state (1.0 – 2.5 mg tid).

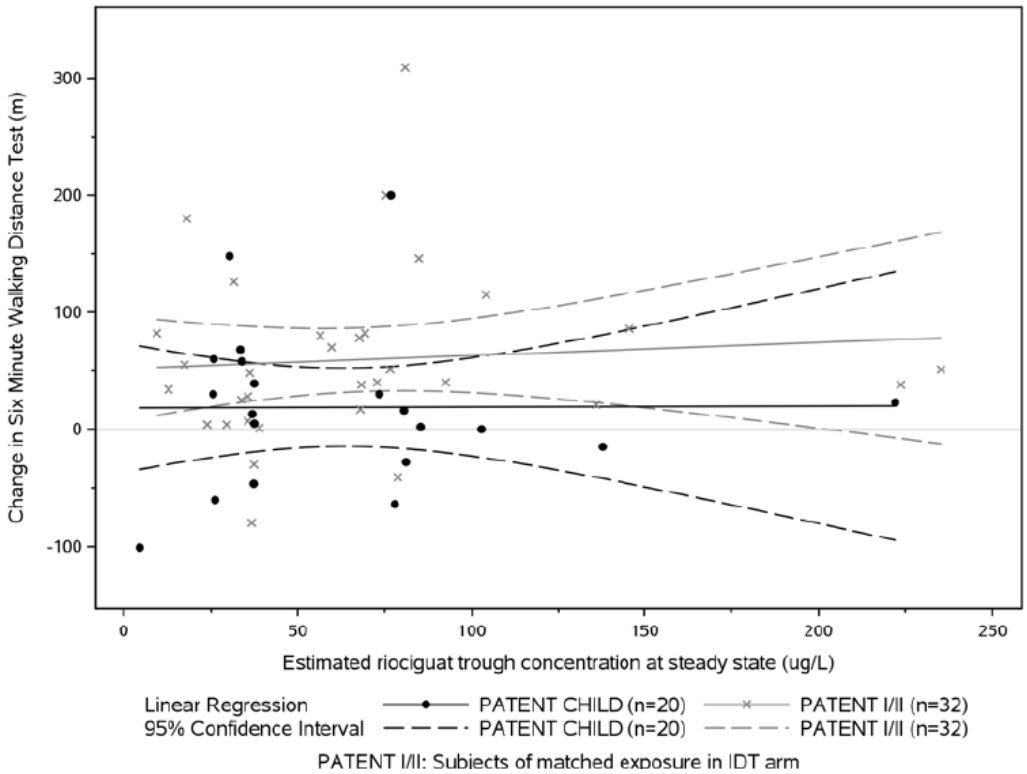
In the adult PAH studies PATENT-1 (pivotal) and PATENT-2 (long-term extension), a negative relationship was found between the change in NT-proBNP and riociguat trough concentrations. The observed increase in 6MWD was not related to riociguat trough concentrations (PK/PD Study 18069).

Comparisons of PK/PD relationship in paediatric subjects and adults with PAH

The PK/PD relationships in paediatric subjects with PAH were compared with adult subjects with PAH. For the comparison, a 'matched exposure' subgroup was selected from PATENT-1/2 studies. This subgroup consists of adult subjects showing individual PK exposure ($AUC(0\text{-}8h)_{ss}$) similar to the observed individuals' PK exposure ($AUC(0\text{-}8h)_{ss}$) in paediatric subjects regardless of their background therapy or smoking status.

The PK/PD data for 6MWD in paediatric PAH subjects were consistent with the data in adult subjects with PAH, as the increase in 6MWD was not related to riociguat trough concentrations (slope estimate [95% CI]: PATENT-CHILD: 0.0070 m/(µg/L) [-0.685 to 0.699]; "matched exposure" adults: 0.111 m/(µg/L) [0.406 to 0.628])(**Figure 11**).

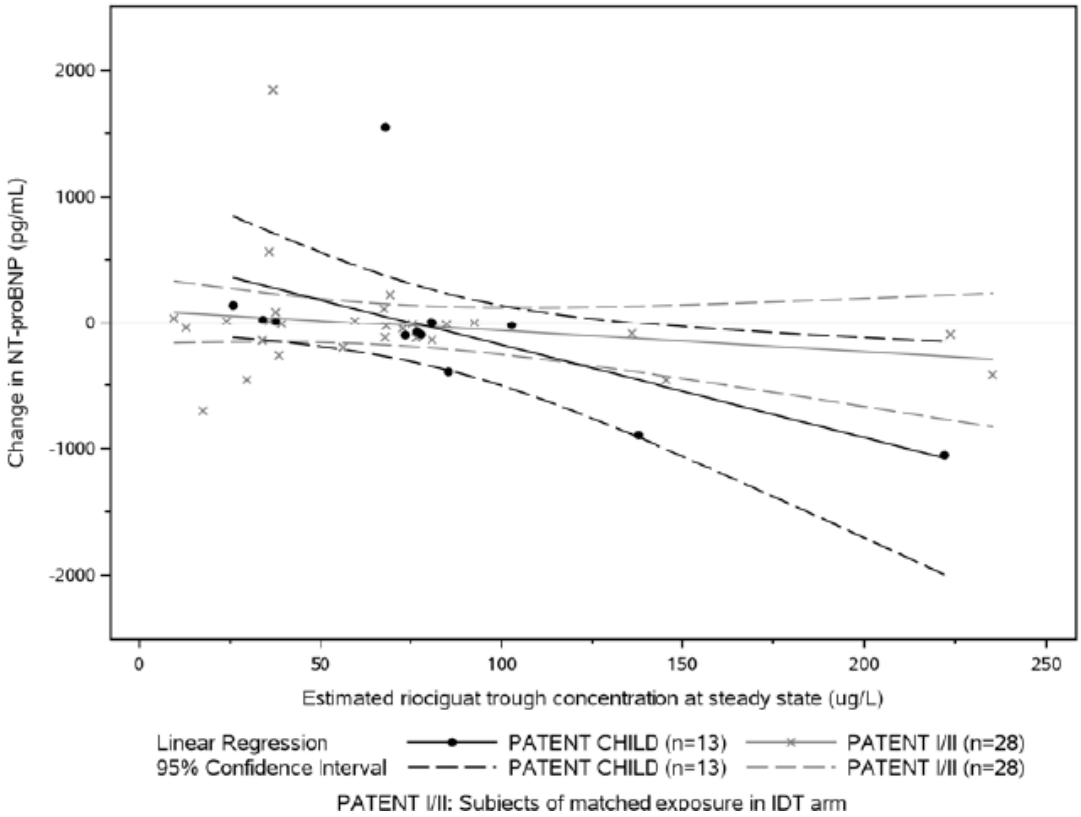
Figure 11. Change in 6MWD Test as a function of estimated riociguat trough concentration at steady-state for PATENT-CHILD and PATENT-1/2 (IDT, matched exposure group)



Change was derived as measure taken at visit 9 (week 24) minus the baseline measure for PATENT CHILD. For PATENT-1/2, change from baseline was derived for Long Term Extension Day 84. Circles: paediatric subjects with PAH. Crosses: adult subjects with PAH (IDT, matched exposure group). Solid lines: linear regression. Dashed lines: 95% confidence interval.

The PATENT-CHILD PK/PD data for NT-proBNP are consistent with the data in adult PAH patients. A negative relationship was found between the change in NT-proBNP and riociguat trough concentrations in PATENT-CHILD (slope estimate [95% CI]: -7.32 (pg/mL)/(µg/L) [-13.6 to -1.00]). However, this relationship was mainly driven by three subjects with large absolute NT-proBNP changes. In the "exposure-matched" adult reference group, no relationship between change in NT-proBNP and riociguat trough concentrations was found (slope estimate [95% CI]: -1.68 (pg/mL)/(µg/L) [-4.75 to 1.39])(**Figure 12**).

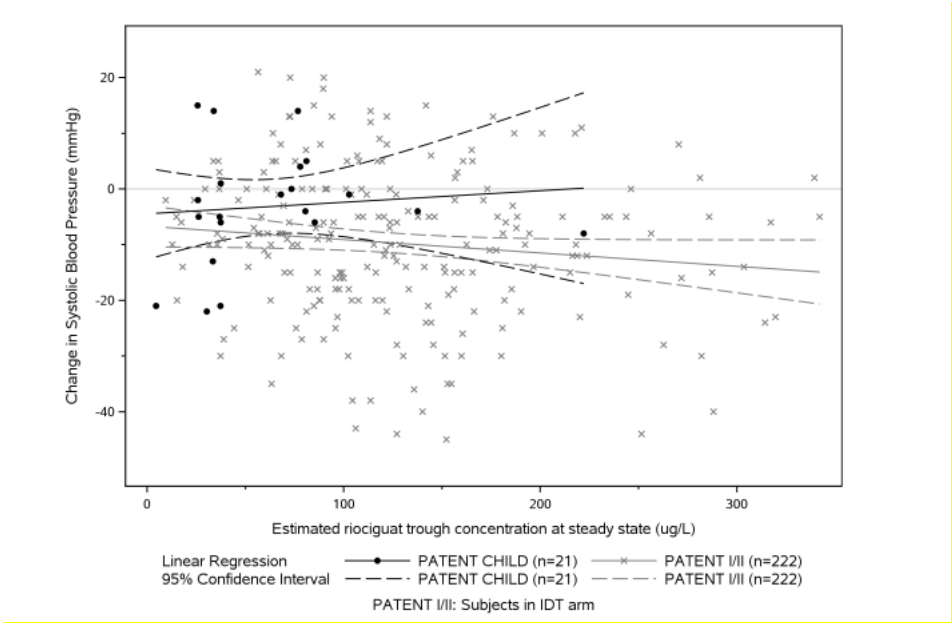
Figure 12. Change in NT-proBNP (pg/mL) as a function of estimated riociguat trough concentration at steady-state for PATENT CHILD and PATENT-1/2 (IDT, matched exposure group)



Change was derived as measure taken at visit 9 (week 24) minus the baseline measure for PATENT-CHILD. For PATENT-1/2, change from baseline was derived for the Long Term Extension Day 84. Circles: paediatric subjects with PAH. Crosses: adult subjects with PAH (IDT, matched exposure group). Solid lines: linear regression. Dashed lines: 95% confidence interval.

Furthermore, no correlation can be seen between PK (Ctrough) and the change in systolic or diastolic blood pressure in the PATENT CHILD study nor in PATENT ½ (**Figure 13** and **Figure 14**). There is a high interpatient variability for the PK of riociguat. The titration scheme has been established to adapt the dose to the individual tolerability of riociguat. Although a relatively high proportion (16/21, 76%) of the pediatric PAH subjects reached the maximum 2.5 mg dose, it cannot be concluded that a higher dose may lead to higher exposure and consequently a clinically significant decrease in blood pressure.

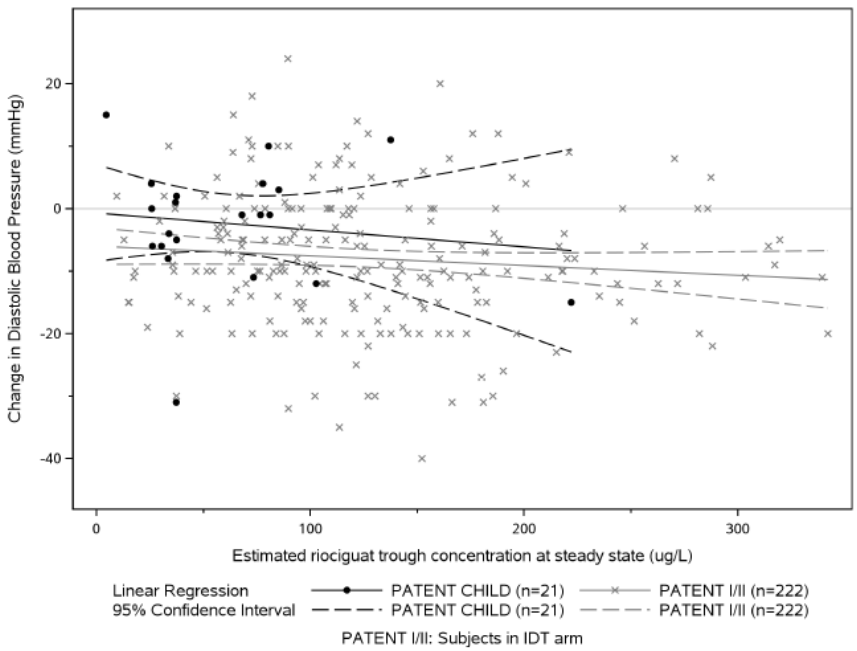
Figure 13. Change in SBP as a function of estimated riociguat trough concentration at steady state for PATENT-CHILD and PATENT 1/2 (IDT)



IDT = individual dose titration, SBP = systolic blood pressure

Encircled subjects are the 3 subjects who experienced hypotension and completed 24 weeks of treatment

Figure 14. Change in DBP as a function of estimated riociguat trough concentration at steady state for PATENT-CHILD and PATENT 1/2 (IDT)



IDT = individual dose titration, DBP = diastolic blood pressure

Encircled subjects are the 3 subjects who experienced hypotension and completed 24 weeks of treatment

2.3.4. Discussion on clinical pharmacology

This application is based on the extrapolation of efficacy and safety in adults to the paediatric population based on comparable exposure.

Bioanalytical methods. Plasma samples were analysed for riociguat and M-1 with the analytical method SBQ-14004 method, which was used in the package in support of the adult indication of Adempas.

The bioanalytical method appears sufficiently validated. The distribution of the QCs is not in line with the requirements stated in the EMA Guideline on bioanalytical validation; however, in light of the requirements concerning QC distribution in the new ICH M10 guideline on bioanalytical method validation, this issue will not be pursued.

PBPK model. Information on the development and validation of the PBPK model was only sparsely provided. However, since this PBPK study was used only to estimate the needed dose to obtain comparable exposure in the PATENT-CHILD Study 15681 (with actual concentration determined later and used for further analysis), the impact of the PBPK model is considered limited. It is expected only to have affected internal decision-making by the MAH. Therefore, the lack of information on the PBPK model will not be further pursued.

The mean exposure obtained in the paediatric population in the PATENT-CHILD Study 15681 was somewhat lower due to a larger clearance in the actual study than predicted by the PBPK model. Without detailed validation data on the PBPK model, these differences remain unexplained. This issue will not be further pursued. However, the reported lower exposure obtained in the paediatric population as compared to the adult population was further discussed concerning the expected efficacy in this population as detailed below.

ADME in the paediatric population. Overall, the MAH considered the riociguat and M-1 PK profiles similar in children and adults. However, although the riociguat $AUC_{(0\text{-}8h)ss}$ exposure in paediatric subjects is within the range of the observed exposure in adult subjects with PAH, the mean exposure in paediatric subjects is lower than in adult PAH patients, i.e., towards the 25th percentile for all comparison groups. It was shown that for a major part of the paediatric subjects (9/24) dosed in the PATENT-CHILD Study 15681, clearance was higher than predicted from the PBPK model. Population PK analysis showed a comparable PK profile in paediatric subjects after administration of oral tablets or granules for suspension (popPK/PD Study 18069); therefore, this is not expected to contribute to the observed differences between paediatric and adult exposure.

Part of the observed difference in exposure appears to be caused by the lower dose-equivalents for children in the maintenance phase of PATENT-CHILD than for the adult population. In the adult individual dose titration reference group the average dose administered was 2.36 mg TID, while for children the average dose equivalent was 2.10 mg TID, and therefore 11% lower. It is agreed that this may partially contribute to the lower exposure observed in the paediatric population as compared to adults in the overall population. In line with this finding, comparing exposure in paediatric patients receiving the 2.5 mg adult equivalent dose and adults receiving the 2.5 mg maximum adult dose indeed yields a somewhat less reduced exposure in the paediatric population than upon comparing the full paediatric and full adult population.

However, the difference in received (dose-equivalent) dose does not explain the difference in exposure between adult and paediatric patients completely. For the remainder of the decreased exposure in the paediatric population, the MAH argues that this is largely caused by a subgroup of paediatric patients (9 out of 24, of which 2 patients terminated the study in the titration phase) with noticeable increased clearance. Since 7 of the 9 paediatric patients with increased clearance were 13 years of older (and two

were 6 and 7 years old), the MAH hypothesizes that this may be caused by exposure of these adolescents to enzyme-inducing tobacco smoke that may be encountered by these subjects. This argumentation is not fully agreed. It is agreed that induction of CYP1A2 may lead to reduced exposure to riociguat. However, in such case one would also expect an increase in metabolite M1 in these subjects. However, exposure to M-1 does not appear to be increased as compared to that in adults. Instead, also for M-1, exposure appears to be low in the paediatric population as compared to adults. Therefore, induction of CYP1A2 is expected not to provide an explanation for the reduced exposure to riociguat in the paediatric population.

As proposed by the MAH, different WHO functional classes in paediatric and adult patients, and the already known differences in exposure between healthy subjects and adult patients may provide a potential explanation for the lower exposure in paediatric patients in comparison to adult PAH patients. It is notable that the WHO functional class was not included as a covariate in the popPK model. Upon request by CHMP, the MAH discussed the option to include this as a covariate in the model. A trend for increased exposure in more severe WHO functional classes was observed in adult patients, with mean exposure in WHO FC2 and FC3 increased by 10% and 25% as compared to that in adult WHO FC1 patients. The paediatric population consisted almost exclusively of WHO FC2 patients (21 out of 24). In the paediatric WHO FC2 group, exposure was markedly lower (estimated appr 50%) than that observed in the adult WHO FC2 group, whereas exposure in the FC3 group was roughly comparable to that in the adult FC3 group. However, CHMP agreed that the number of subject in the paediatric FC3 group is too small (i.e. n=3) to allow drawing firm conclusions on a potential FC dependency of the difference in riociguat exposure between paediatric and adult patients. Since the observed trend of a lower exposure in the paediatric population is indicated not to affect efficacy the potential FC dependency of the difference in exposure between paediatric and adult patients will not be pursued further.

Nevertheless, the observed, and as yet not fully explained reduced exposure in the paediatric population as compared to adults does not appear to result in reduced efficacy, when comparing the efficacy (6-minute walking distance) of the paediatric patients with that in adults and with the other paediatric patients. More specifically, 5 of the 7 patients with unexpectedly high riociguat clearance showed an increase in 6MWD of > 20 meter, which is considered clinically relevant.

In conclusion, based on sparse sampling, riociguat and M-1 PK data in the paediatric population aged 6-<18 years of age has been provided. Although the PK appears roughly comparable, the mean riociguat and M-1 exposure in paediatric subjects are clearly lower than in adult PAH patients, i.e., towards the 25th percentile for all comparison groups. Nevertheless, the observed, and as yet not fully explained reduced exposure in the paediatric population as compared to adults does not appear to result in reduced efficacy, when comparing the efficacy (6-minute walking distance) of the paediatric patients with that in adults and with the other paediatric patients. More specifically, 5 of the 7 patients with unexpectedly high riociguat clearance showed an increase in 6MWD of > 20 meter, which is considered clinically relevant. These findings are consistent with the corresponding PK/PD profiles in adult subjects with PAH, i.e. no clear relationship between changes in 6MWD and riociguat trough concentrations (see also below).

Exposure-efficacy. In the paediatric PAH population, PK/PD relationships were investigated for the 6MWD and NT-proBNP. No PK/PD relationship was observed between riociguat exposure and 6MWD. Further, a weak negative relationship was found between the change in NT-proBNP and riociguat exposure, but this relationship was mainly driven by three subjects with large absolute NT-proBNP changes in either the positive or negative direction. The ratio of NT-proBNP at week 24 to baseline showed no relationship to riociguat exposure.

The PK/PD relationships in paediatric subjects with PAH were compared with adult subjects with PAH using the "matched exposure" subgroup of the PATENT-1/2 studies. Overall, the PK/PD profiles for 6MWD and NT-proBNP at week 24 in paediatric subjects are consistent to the corresponding PK/PD profiles in

adult subjects with PAH, i.e. no relationship between changes in NT-proBNP nor 6MWD and riociguat trough concentrations were observed. Additionally, no correlation can be seen between riociguat exposure and the change in systolic or diastolic blood pressure both in adults and in the paediatric population. Nevertheless, in adults, a PK/PD relationship was established for hemodynamic parameters such as pulmonary vascular resistance (PVR) and cardiac output (CO) obtained via right heart catheterization (RHC). In contrast, in PATENT-CHILD a RHC for assessing and following up hemodynamic parameters was not performed because it is not recommended for pediatric studies (Ollivier et al. 2019). As such, the justification that similar exposures result in similar pharmacodynamic effects is limited (see "Clinical efficacy" for further discussion).

2.3.5. Conclusions on clinical pharmacology

Based on sparse sampling, riociguat and M-1 PK data in the paediatric population aged 6-<18 years of age appears roughly comparable, although the mean riociguat and M-1 exposure in paediatric subjects are clearly lower than in adult PAH patients, i.e., towards the 25th percentile for all comparison groups. This effect is only partially explained by the lower dose-equivalents for children in the maintenance phase of PATENT-CHILD than for the adult population and the presence of increased riociguat clearance in a part of the paediatric population. Nevertheless, the observed, and as yet not fully explained, reduced exposure in the paediatric population as compared to adults does not appear to result in reduced efficacy, when comparing the efficacy (6-minute walking distance) of the paediatric patients with that in adults and with the other paediatric patients. More specifically, 5 of the 7 patients with unexpectedly high riociguat clearance showed an increase in 6MWD of > 20 meters, which is considered clinically relevant. These findings are consistent with the PK/PD profiles in both the adult and the paediatric population, i.e. no relationship between changes in NT-proBNP nor 6MWD and riociguat trough concentrations were observed. Therefore, the justification that similar exposures result in similar pharmacodynamic effects is limited. Nevertheless, the extrapolation of data is acceptable given the favourable trend in 6MWD in the direction of the adult population and the similar safety profiles between adults and the paediatric population.

2.4. Clinical efficacy

It is widely accepted that it is often not feasible to perform statistically powered clinical studies for efficacy in children, as is done for adults; this is particularly valid for PAH, which is considered to be a rare disease in adults and has an even lower incidence in children (Barst et al. 2011). The EMA guideline regarding clinical investigations for medicinal products targeting pediatric PAH allows for extrapolation when the benefit-risk has been characterized in adults. In these cases, the development program focuses on defining the therapeutic dose and collecting data on short- and long-term safety (EMA 2012). Therefore, the application assumes that similar exposures and pharmacodynamic effects in children, as compared to adults, will result in similar efficacy in children. In this respect, a physiologically based pharmacokinetic (PBPK) modelling study (study 15463) has been conducted to predict the pharmacokinetic properties of riociguat in the pediatric population. Additionally, the MAH had conducted a Phase 3 open-label, individual dose titration Study 15681 (PATENT-Child) to assess the PK, safety and exploratory efficacy in paediatric PAH patients aged 6-18 years (**Table 7**). Further, to allow clinical comparisons, paediatric data are displayed side-by-side with pooled data from the phase 3 studies in adults (PATENT-1 and PATENT-2), within the first 24 weeks of treatment.

Table 6. Overview of study 15681 (PATENT-Child)

Type of Study Clinical Phase	Study No. (Report No.)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Numbers of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status Type of Report
Safety, III	15681 (PH-41307)	PK, Safety, exploratory efficacy in paediatric PAH 6-18 years	Multicenter, open-label, single-arm, uncontrolled	Riociguat 0.5 mg tid 1.0 mg tid 1.5 mg tid 2.0 mg tid 2.5 mg tid Or bodyweight adjusted dose Individual dose titration Oral administration	24	Paediatric PAH	Main phase complete
	Technical report (PH-42339)						Long term extension ongoing

Extrapolation concept

Two studies in adult PAH subjects were used for the purposes of extrapolation. PATENT-1 was a 12-week safety and efficacy study of riociguat, while PATENT-2, its companion long-term extension study, continued treatment and efficacy evaluations. PATENT-2 includes an efficacy evaluation after additional 12 weeks of treatment that can be aligned with the 24-week endpoint from PATENT-CHILD.

There are several considerations that justify the overall approach to extrapolate efficacy from adults. These considerations are consistent with those expressed in the EMA reflection paper on extrapolation (EMA 2018) as well as in the current draft ICH E11A guideline on paediatric extrapolation (EMA 2022). Development of a paediatric extrapolation concept requires an understanding of the factors that influence the similarity of disease, the pharmacology of the drug and the response to therapy as well as the safety of use in all the relevant populations.

- The pathophysiology of PAH is similar among children enrolled in PATENT-CHILD (6 to <18 years) and adults (Barst et al. 2011).
- The hemodynamic mechanism of action of riociguat as an sGC stimulator is responsible for PAH efficacy is expected to be similar in adults and children.
- PK exposures in paediatric subjects in PATENT-CHILD are within the range of exposures observed in adult PAH subjects. Adult PAH clinical studies have shown a direct relationship between riociguat plasma concentrations and invasively obtained hemodynamic parameters such as SVR, SBP, PVR, and cardiac output.
- The safety and exploratory efficacy endpoints of the paediatric PATENT-CHILD study allow for comparison to the results from adult riociguat PAH studies. In addition, positive clinical outcomes were observed in the target paediatric population.

The comparison is considered valid because the adult PATENT-1/2 and PATENT-CHILD consist of similar patient populations who were being treated consistent with existing guidelines.

Therefore, the paediatric development program for riociguat was designed to address the following objectives:

- Develop a dosing regimen for children aged between 6 and <18 years that results in riociguat exposures similar to levels observed in adult PAH patients dosed with 1 to 2.5 mg tablets TID.
- Demonstrate that PK/PD relationships are similar between children and adults.
- Demonstrate the safety and tolerability of riociguat use for paediatric PAH

The applicability of this extrapolation approach from adult data for the treatment of paediatric PAH has been accepted by EMA (EMEA-000718-PIP01-09-M06, September 2016).

5.4.2 Dose-response studies

Paediatric dose selection for PATENT-CHILD was based on:

- A relative bioavailability study 14986 comparing the paediatric granules for oral suspension formulation to the approved film-coated tablets showing that the tablets and granules for oral suspension formulations have comparable bioavailability; and
- A population physiology-based PK (PBPK) modeling study (15463) to identify a paediatric dosing regimen that would result in paediatric exposures similar to adult exposures. The doses selected for PATENT-CHILD were calculated based on predicted PK exposure in paediatric patients. This resulted in decision to use already available tablet strengths 0.5, 1, 1.5, 2 and 2.5 mg for children with bodyweight ≥50 kg and a granules for oral suspension formulation for children with bodyweight <50 kg.

The dosing regimens for both tablet and granules for oral suspension formulations were aimed at achieving systemic exposures in the range of that seen in adult PAH patients.

5.4.3 Main study

Study 15681- Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with pulmonary arterial hypertension (PAH)(PATENT-CHILD)

Methods

Study Participants

Eligible subjects were children from 6 years to less than 18 years of age with idiopathic PAH (IPAH), hereditable PAH (HPAH), PAH associated with connective tissue disease and PAH associated with congenital heart disease.

Key inclusion/exclusion criteria are presented in the table below.

Table 7. Key inclusion/exclusion criteria

Study 15681 (PATENT-CHILD)
Inclusion Criteria
- Children from 6 years to less than 18 years of age with pulmonary arterial hypertension (PAH)
- Diagnosed with PAH: o Idiopathic (IPAH) o Hereditable (HPAH)

○ PAH associated with (APAH) ▪ Connective tissue disease ▪ Congenital heart disease with shunt closure more than 6 months ago (no open shunts, confirmed by RHC no less than 4 months after surgery) Regardless of the type of PAH, the following findings were not exclusionary: Patent foramen ovale (PFO) and asymptomatic, isolated, ostium secundum atrial septal defect (OS-ASD) ≤1 cm (both confirmed by echocardiogram) and not associated with hemodynamic alterations indicative of significant shunt, e.g. Qp/Qs ratio less <1.5:1 were not exclusionary
- PAH, diagnosed by right heart catheterization (RHC) at any time prior to enrollment (for patients with closed shunts – RHC no less than 4 months after surgery), with mean pulmonary artery pressure (PAPmean) ≥25 mmHg at rest, pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg, and pulmonary vascular resistance (PVR) >240 dyn·sec·cm-5 (i.e., ≥3.0 wood units·m2)
- Patients must be on standard of care PAH medications, allowing endothelin receptor antagonists (ERA) and/or prostacyclin analogues (PCA), for at least 12 weeks prior to baseline visit. Two groups of patients were included: ○ Prevalent: Patients currently on PAH medication (allowing ERA and/or PCA) who need additional treatment (discretion of the investigator) ○ Incident: Treatment naïve patients initiated on PAH medication (allowing ERA and/or PCA) and then riociguat added once patients are stable on standard of care
- WHO functional class I-III
Exclusion Criteria
- Concomitant use of the following medications: phosphodiesterase (PDE) 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific phosphodiesterase (PDE) inhibitors (theophylline, dipyridamole), nitrates or NO donors (such as amyl nitrite) in any form 1 • Pretreatment with NO donors (e.g. nitrates) within the last 2 weeks before visit 1. The use of any drug including NO acutely for testing during catheterization is not an exclusion criterion.
- Active state of hemoptysis or pulmonary hemorrhage, including those events managed by bronchial artery embolization or any history of bronchial artery embolization or massive hemoptysis within 3 months prior to screening
- Systolic blood pressure (SBP) more than 5 mmHg lower than the age-, sex- and height-adapted level of the 50th SBP percentile
- History of left-sided heart disease, including valvular disease or heart failure
- Pulmonary hypertension related to conditions other than specified in the inclusion criteria
- WHO functional class IV
- Pulmonary veno-occlusive disease
- Screening aspartate transaminase (AST) and/ or alanine transaminase (ALT) more than 3 times the upper limit of normal (ULN)
- Non-stable disease status, e.g., signs and symptoms of decompensated right heart failure
- Severe bronchial asthma
- Severe restrictive lung disease
- Severe congenital abnormalities of the lung, thorax, and diaphragm
- Clinically relevant hepatic dysfunction (especially Child Pugh C)
- Renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73m2 e.g. calculated based on Schwartz formula

Treatments

Study 15681 was composed of two parts:

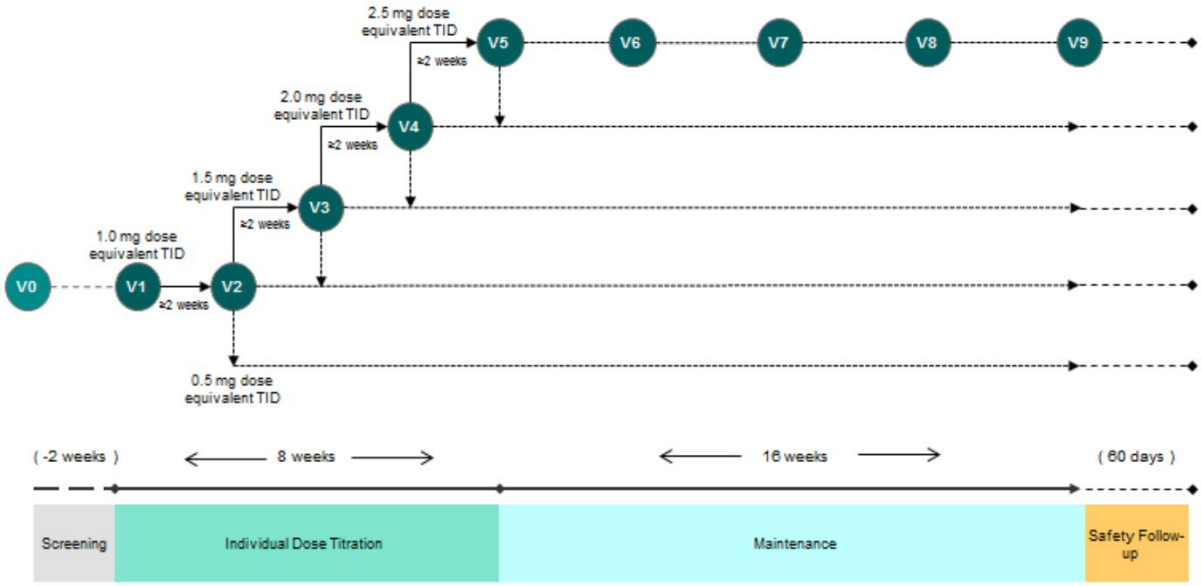
- Main study part (**Figure 15**):
    - A pre-treatment screening period up to 2 weeks to identify potential eligibility of subjects who had been diagnosed with PAH. This visit was to take place up to 2 weeks before Visit 1 (baseline visit).
    - A 24-week main period that included an 8-week titration phase and a 16-week maintenance phase
    - Follow-up period: safety follow-up visit to be performed 60 (±8) days after last study medication intake for all subjects who did not enter the LTE part or who stopped the study medication prematurely. Serious adverse events were to be followed up for at

least 60 days (only for subjects who did not enter the LTE part or who stopped the study medication prematurely).

- Long-term extension (LTE) part
    - Extension phase to allow participants to continue to receive riociguat until market approval of riociguat for the paediatric population or until a subjects turns 18 years of age (whichever came first).
    - Follow-up period: safety follow-up visit to be performed 60 (+8) days after last study medication intake for all subjects stopping study medication either at the end of the LTE or prematurely discontinuing the study at any time.

    The LTE phase is still ongoing. For this submission, data until the cut-off date 07 Jan 2022 are included.

Figure 15. Main study part design



Dosing regimen

All subjects received body-weight-adjusted dose of riociguat to achieve a similar exposure as that observed in adults treated for PAH. The dose titration and maintenance dose was based on bodyweight, systolic blood pressure, and whether the participant showed signs of hypotension.

Subjects <50 kg at baseline received riociguat oral suspension during the initial 24-week main treatment period. Subjects ⩾50 kg at baseline received oral tablets. If the BW decreased below 50 kg, then the IxRS delivered the oral suspension.

The starting dose was the body weight-adjusted equivalent of the 1.0 mg dose in adults (**Table 9**). The individual titration phase comprised 4 visits which were 2 weeks (±2 days) apart. The last dose administered at Visit 4 (Week 8) was regarded as an individual optimal dose, and subjects received that treatment during the 16-week maintenance phase. Down-titration was permitted at all times for safety reasons.

Table 8. Body weight-adjusted riociguat dosing schedule

Body weight (kg)	0.5 mg equivalent TID (mg)/	equivalent volume of suspension TID (mL)*	1.0 mg equivalent TID (mg)	equivalent volume of suspension TID (mL)*	1.5 mg equivalent TID (mg)	equivalent volume of suspension TID (mL)*	2.0 mg equivalent TID (mg)	equivalent volume of suspension TID (mL)*	2.5 mg equivalent TID (mg)	equivalent volume of suspension TID (mL)*
≥12<14	0.12	1.0	0.25	1.75	0.37	2.50	0.50	3.25	0.62	4.25
≥14 <16	0.14	1.0	0.28	1.75	0.42	2.75	0.56	3.75	0.70	4.75
≥16 <18	0.15	1.0	0.31	2.00	0.46	3.00	0.62	4.25	0.77	5.00
≥18 <20	0.17	1.0	0.33	2.25	0.50	3.25	0.67	4.50	0.83	5.50
≥20 <25	0.19	1.25	0.38	2.50	0.57	3.75	0.75	5.00	0.94	6.50
≥25 <30	0.22	1.50	0.44	3.00	0.66	4.25	0.87	6.00	1.09	7.50
≥30 <35	0.25	1.75	0.50	3.25	0.74	5.00	0.99	6.50	1.24	8.50
≥35 <40	0.28	1.75	0.56	3.75	0.84	5.50	1.12	7.50	1.41	9.50
≥40 <50	0.33	2.25	0.66	4.50	1.00	6.50	1.33	9.00	1.66	11.00
≥ 50	0.50	3.25	1.00	6.50	1.50	10.00	2.00**	13.50	2.50**	16.50

Abbreviations: TID = three times daily

* For facilitation of administration of a proper body-adjusted dose, the volumes of suspension are provided with increments of 0.25 mL (for 1-5 mL) and 0.5 ml (for over 5 ml)

** For change in weight category from 40-<50 kg to ≥ 50 kg, IXRS will administer intermediate dose to adjust to 0.5 mg increment (e.g. intermediate dose for 2.0 mg equivalent is 1.50 mg /10.00 mL; for 2.5 mg equivalent is 2.00 mg / 13.50 mL).

Formulations

Two formulations were used in the PATENT-CHILD study:

- Immediate release (IR) tablet formulation (0.5, 1, 1.5, 2, 2.5-mg strengths) was used for children with bodyweight ⩾50 kg, and is identical to the formulation used in the clinical studies that supported riociguat approval for PAH and CTEPH in the adult population.
- Granules-for-oral-suspension (0.15 mg/mL) was a new paediatric formulation created to fulfil the PIP requirement to develop an oral liquid age-appropriate formulation. Study 14986 demonstrated the bioavailability of riociguat and its main metabolite (BAY 60-4552). AUC and Cmax were comparable between the paediatric formulation and the standard IR tablet. The granules-for-oral-suspension formulation was used to support bodyweight-adjusted dosing in children with a bodyweight below 50 kg using a dosing regimen based on pharmacokinetic modelling.

Participants were able to switch between oral suspension and tablet formulations due to bodyweight changes.

Objectives

The *primary* objective of this study was to evaluate safety, tolerability and pharmacokinetics of oral riociguat treatment.

The *secondary* objectives of this study were evaluation of exploratory efficacy outcomes to evaluate the pharmacodynamic profile of riociguat.

Outcomes/endpoints

The secondary outcomes were the assessment of:

- the change from baseline to end of treatment (Week 24) of the following variables:
    - 6-Minute Walking Distance (6MWD)
    - WHO functional class
    - NT-proBNP or BNP (when both tests are available, NT-proBNP was to be chosen over BNP)

- Quality of life scores (parent questionnaire and in subjects able to understand questions): child health-related questionnaire (SF-10) and PedsQL Generic Core scales self-report
- Echocardiographic parameters including:
  - pulmonary arterial systolic pressure (PASP),
  - right ventricular pressure by tricuspid regurgitant jet velocity,
  - tricuspid annular plane systolic excursion (TAPSE),
  - pericardial effusion,
  - left ventricular eccentricity index,
  - estimated right atrial pressure,
  - acceleration time of the pulmonary flow,
  - right heart dimensions,
  - cardiac output.

  Central reading of the echocardiographic parameters were added with the integrated protocol amendment 5 (dated 31 MAY 2016).

and

- time to clinical worsening defines as:
  - Hospitalization for right heart failure
  - Death
  - Lung transplantation
  - Pott's anastomosis and atrioseptostomy
  - Worsening of PAH symptoms, which must include either:
    - an increase in WHO FC, or
    - appearance/worsening symptoms of right heart failure, and need for additional PAH therapy.

Other outcome was assessed as a change in right heart catheterization (RHC) parameters (if available) obtained from RHC performed before study enrollment and during study conduct. The above efficacy variables were collected at baseline and Week 24 in the main study part and were to be collected every 3 to 4 months in the LTE part.

Sample size

At least 20 subjects on treatment with bosentan or other ERAs had to be enrolled in the study. The sample size did not originate from a formal sample size calculation but was based on an evidence-based feasibility assessment. Based on the results of the evidence-based feasibility survey (Davie, 2014) and the proposed PK evaluation, 20 subjects would permit an accurate PK evaluation and feasibility of the study in a reasonable time frame. Every effort was to be made to enroll equal numbers of patients in both age cohorts.

Randomisation and blinding (masking)

The pivotal study concerned a single arm, open-label study.

Statistical methods

All efficacy outcomes were evaluated in an exploratory manner based on the safety analysis set (SAF), i.e. subjects who were assigned to receive study medication and had received at least one dose of the study medication. Unless otherwise specified, baseline was the last available non-missing value prior and up to the time of the first intake of study medication, i.e. first dose of riociguat. Change from baseline was calculated as the value at the post-baseline time point minus the baseline value. Subgroup analyses were performed by age cohort (≥6 to <12 years and ≥12 to <18 years) and by concomitant PAH medication (ERA only, ERA+PCA, PCA only) specified at screening.

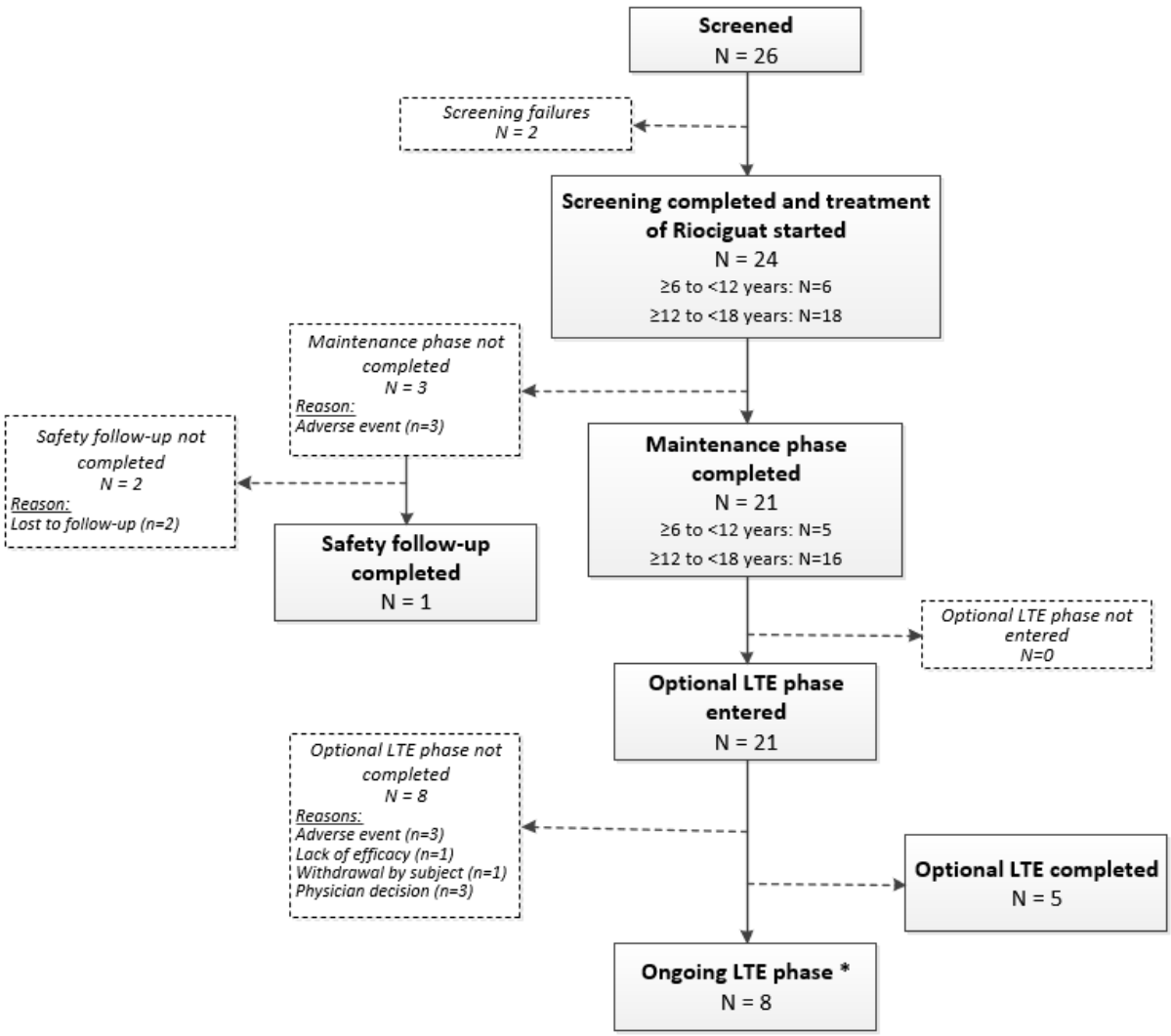
Results

Participant flow

Twenty-four subjects (6 subjects in the ≥6 to <12 years and 18 subjects in the ≥12 to <18 years cohort) entered the main treatment period and received the study drug (riociguat), also known as the safety analysis set (SAF), of which 21 (87.5%) subjects completed the 24-week main treatment period and entered the optional LTE part (**Figure 16**). Three (12.5%) subjects did not complete the main treatment period and the reason for non-completion was adverse events. Of these 3 subjects, 1 subject completed the safety follow-up visit and 2 subjects did not complete the safety follow-up visit due to being lost to follow-up.

Of the 21 subjects entering the LTE part, 8 were still in the study at the data cut-off date (07 JAN 2022). Thirteen subjects terminated the LTE part, 5/13 (38.5%) completed the LTE treatment period per protocol as they reached the age of 18 years, and 8/13 (61.5%) did not complete the LTE treatment period. The main reasons for non-completion were adverse events and physician’s decision (3 subjects [23.1%], each). It is to be noted that the 3 subjects who were withdrawn by physicians' decision continued on commercial Adempas. No Covid-19 pandemic-related reasons for non-completion were reported. No clinically relevant differences for non-completion were reported by age cohort or by concomitant PAH medication.

Figure 16. Subjects disposition chart



* Data cut-off 07 JAN 2022
LTE = long-term extension
Note: The technical report PH-42339 shows the data from children receiving both tablet and oral suspension formulations, comprising the main and the LTE part up to the cut-off date 07 JAN 2022.
For one subject, the end-of-treatment CRF page was erroneously filled-in. It was confirmed by the investigator that the subject was not discontinued by the CDB date of 07 JAN 2022. In consequence, the number of subjects still in the LTE part at that date was 8 (instead of 7). The number of subjects having not completed the LTE phase was 8 (instead of 9), accordingly.

Formulations

A total of 16 children started the study on suspension, while 8 started on riociguat tablets. Of the 16 who started on suspension, 6 switched to tablets at some point during their participation. All switches happened at Week 24 or later. At the time of the data cut-off for the LTE (07 JAN 2022), of the 8 children still in the study, only 3 remained on suspension, while the remaining 5 were receiving tablets. One child who switched to tablets briefly switched back to suspension due to bodyweight fluctuation. There were no instances where a child started on tablets and switched to granules for oral suspension.

Drug dose

At the end of the 8-week titration phase (Visit 5), 16 (72.7%) subjects were on the highest riociguat dose of 2.5 mg or the body-weight equivalent, 1 (4.5%) subject each was on 2.0 mg, on 1.5 mg, and on 1.0 mg, and 3 (13.6%) subjects were on 0.5 mg or the respective body-weight equivalent.

Protocol deviations

In the SAF, a total of 9 (37.5%) subjects were reported with important protocol deviations (**Table 10**). Six (25.0%) subjects did not meet all the inclusion criteria or met at least one exclusion criterion but entered treatment. Three (12.5%) subjects had procedure deviations and 3 (12.5%) subjects had treatment deviations.

Table 9. Number of subjects with important protocol deviations by age group and

	Age group		Concomitant PAH medication		Total
Protocol Deviation Category	Riociguat ≥6 to <12 years N=6 (100%)	Riociguat ≥12 to <18 years N=18 (100%)	Riociguat ERA only N=15 (100%)	Riociguat ERA+PCA[a] N=9 (100%)	Riociguat N=24 (100%)
Subjects with any important protocol deviation	2 (33.3%)	7 (38.9%)	8 (53.3%)	1 (11.1%)	9 (37.5%)
In/Ex criteria not met but subject entered treatment	1 (16.7%)	5 (27.8%)	5 (33.3%)	1 (11.1%)	6 (25.0%)
Procedure deviations	1 (16.7%)	2 (11.1%)	3 (20.0%)	0	3 (12.5%)
Treatment deviations	1 (16.7%)	2 (11.1%)	3 (20.0%)	0	3 (12.5%)

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
In source tables the number of subjects in the concomitant PAH medication subgroup of PCA only is shown as "0". Therefore, the subgroup of PCA only is not shown in this table.
Subjects may have more than one protocol deviation but are only counted once within each deviation category.
a. "PCA" includes prostacyclin analogues and receptor agonists
ERA = endothelin receptor antagonists; In/Ex = inclusion/exclusion; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
In source tables the number of subjects in the concomitant PAH medication subgroup of PCA only is shown as "0". Therefore, the subgroup of PCA only is not shown in this table.
Subjects may have more than one protocol deviation but are only counted once within each deviation category.
a. "PCA" includes prostacyclin analogues and receptor agonists
ERA = endothelin receptor antagonists; In/Ex = inclusion/exclusion; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue

Recruitment

A total of 26 subjects were screened in 16 study centres in 9 countries or regions: Colombia (n=1), Germany (n=5), Hungary (n=2), Italy (n=3), Japan (n=6), Mexico (n=4), Poland (n=2), Taiwan (n=2) and Turkey (n=1). Two subjects did not pass the screen of inclusion/exclusion criteria. 24 subjects entered the main treatment period and received the study drug (riociguat)

The first subject's first visit was on 29 October 2015, and the last visit (main study part) was on 7 March 2020.

Conduct of the study

A total of 14 amendments (6 global and 8 local) to the original protocol (finalized on 13 Mar 2015) has been made. Key efficacy changes appear to have been made in Amendment 3 "*Pharmacodynamics was deleted from primary objective*". Nevertheless, a description of the modification revealed that the original protocol described PD as a primary and secondary objective but elsewhere in the protocol PD was described as secondary/other objective. To keep consistency, the PD is deleted from the primary objective.

Baseline data

Of the 24 subjects in the SAF, 13 (54.2%) were male. The mean age was 12.8 years. Mean weight was 46.44 kg and mean height was 155.06 cm. Demographics and baseline characteristics were generally balanced across concomitant PAH medications groups (**Table 11**). In the younger cohort, the proportion of male subjects was 33.3%, while in the older cohort, it was 61.1%. Concomitant PAH medication at baseline was comparable in the two age-cohorts, with about two-third of subjects receiving ERA only and one-third receiving ERA and PCA.

In the younger cohort, all 6 subjects had a body-weight <50 kg; in the older cohort, 10 subjects had a body-weight ⩾50 kg, and 8 subjects had a body weight <50 kg. Fifteen subjects(62.5%) were on ERA-only at screening, and 9 (37.5%) subjects were on ERA+PCA. No subjects were on PCA only.

The most common type of PAH was idiopathic PAH (18 [75.0%] subjects)(

Table *12*). Idiopathic PAH was the primary diagnosis for 15/18 subjects aged ⩾12 to <18 years compared to 3/6 subjects aged ⩾6 to <12 years. In the younger cohort, PAH associated with congenital heart disease was reported for 2/6 subjects (33.3%) vs 2/18 subjects (11.1%) in the older cohort.

At baseline, a majority of subjects (18 [75.0%]) had a WHO functional class of II with no notable differences across age- and concomitant PAH medication subgroups, which is consistent with the TOPP registry (Berger et al. 2012). The mean 6MWD (SD) was 442.12 (109.67) m. The median NT-proBNP level was 202.00 pg/mL (range: 22.0 to 4440.0 pg/mL). The SF-10 physical and psychosocial summary scores were similar across age and concomitant PAH medication subgroups. The bone age for a majority of subjects was in accordance with the chronological age (12 [50.0%]) or advanced (10 [41.7%]) compared to the chronological age. The results of bone morphology for all 23 subjects who were assessed at baseline were normal.

Table 10. Demographics by age group and concomitant PAH medication (SAF)

	Age group		Concomitant PAH medication		Total
	Riociguat ≥6 to <12 years N=6 (100%)	**Riociguat ≥12 to <18 years N=18 (100%)**	**Riociguat ERA only N=15 (100%)**	**Riociguat ERA+PCA[a] N=9 (100%)**	**Riociguat N=24 (100%)**
Sex					
Female	4 (66.7%)	7 (38.9%)	7 (46.7%)	4 (44.4%)	11 (45.8%)
Male	2 (33.3%)	11 (61.1%)	8 (53.3%)	5 (55.6%)	13 (54.2%)
Age (years)					
n	6	18	15	9	24
Mean (SD)	9.0 (2.3)	14.1 (1.6)	12.5 (3.0)	13.2 (2.5)	12.8 (2.8)
Median (Min-Max)	9.5 (6-11)	13.5 (12-17)	13.0 (6-17)	14.0 (8-17)	13.0 (6-17)
History of cigarette smoking					
Never	6 (100%)	18 (100%)	15 (100%)	9 (100%)	24 (100%)
Baseline weight (kg)					
n	6	18	15	9	24
Mean (SD)	31.77 (13.82)	51.33 (13.63)	48.46 (17.34)	43.07 (13.51)	46.44 (15.93)
Median (Min-Max)	34.10 (12.4-46.5)	48.30 (34.2-80.9)	48.60 (12.4-80.9)	38.90 (33.4-77.0)	45.50 (12.4-80.9)
Baseline height (cm)					
n	6	18	15	9	24
Mean (SD)	132.95 (18.70)	162.43 (9.75)	153.89 (20.81)	157.01 (12.02)	155.06 (17.79)
Median (Min-Max)	138.00 (107.0-154.0)	163.15 (146.0-178.5)	162.00 (107.0-178.5)	156.00 (134.0-177.0)	158.55 (107.0-178.5)
Baseline heart rate (beats/min)					
n	6	18	15	9	24
Mean (SD)	91.7 (34.9)	82.2 (10.3)	83.3 (23.1)	86.7 (10.0)	84.5 (19.0)
Median (Min-Max)	83.0 (55-150)	84.0 (65-104)	79.0 (55-150)	84.0 (76-104)	83.5 (55-150)

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
There were no subjects in the PCA only subgroup. Therefore, this subgroup is not shown.

a. "PCA" includes prostacyclin analogues and receptor agonists

ERA = endothelin receptor antagonists; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue; SD = standard deviation, SAF = safety analysis set

Table 11. Primary diagnosis and indication-specific characteristics at baseline by age group and concomitant PAH medication (safety analysis set)

	Age group		Concomitant PAH medication		Total
	Riociguat ≥6 to <12 years N=6 (100%)	Riociguat ≥12 to <18 years N=18 (100%)	Riociguat ERA only N=15 (100%)	Riociguat ERA+PCA[a] N=9 (100%)	Riociguat N=24 (100%)
Primary diagnosis of PH					
n	6 (100%)	18 (100%)	15 (100%)	9 (100%)	24 (100%)
Idiopathic PAH	3 (50.0%)	15 (83.3%)	10 (66.7%)	8 (88.9%)	18 (75.0%)
Hereditable PAH [b]	0	1 (5.6%)	0	1 (11.1%)	1 (4.2%)
PH associated to developmental abnormalities [c]	1 (16.7%)	0	1 (6.7%)	0	1 (4.2%)
PAH associated to congenital heart disease (repaired) [d]	2 (33.3%)	2 (11.1%)	4 (26.7%)	0	4 (16.7%)
6MWD at baseline (m)					
n	6	17	14	9	23 [e]
Mean (SD)	388.50 (155.71)	461.04 (86.62)	432.76 (131.10)	456.67 (68.96)	442.12 (109.67)
Median (Min-Max)	433.50 (91.0-508.0)	446.00 (326.0-683.5)	440.50 (91.0-683.5)	442.00 (360.0-539.0)	442.00 (91.0-683.5)
WHO functional class					
n	6 (100%)	18 (100%)	15 (100%)	9 (100%)	24 (100%)
I	0	1 (5.6%)	1 (6.7%)	0	1 (4.2%)
II	4 (66.7%)	14 (77.8%)	11 (73.3%)	7 (77.8%)	18 (75.0%)
III	2 (33.3%)	3 (16.7%)	3 (20.0%)	2 (22.2%)	5 (20.8%)
IV	0	0	0	0	0
NT-proBNP at baseline (pg/mL)					
n	5	10	11	4	15
Mean (SD)	223.30 (245.75)	1362.37 (1858.44)	961.84 (1602.20)	1040.00 (1822.32)	982.68 (1595.77)
Median (Min-Max)	165.00 (42.0-646.0)	394.10 (22.0-4440.0)	313.20 (42.0-4440.0)	183.50 (22.0-3771.0)	202.00 (22.0-4440.0)
BNP at baseline (pg/mL)					
n	0	7	2	5	7
Mean (SD)	0 [f]	10.46 (9.10)	13.65 (5.16)	9.18 (10.51)	10.46 (9.10)

	Age group		Concomitant PAH medication		Total
	Riociguat ≥6 to <12 years N=6 (100%)	Riociguat ≥12 to <18 years N=18 (100%)	Riociguat ERA only N=15 (100%)	Riociguat ERA+PCA[a] N=9 (100%)	Riociguat N=24 (100%)
Median (Min-Max)	0 [f]	7.30 (2.0-27.6)	13.65 (10.0-17.3)	5.80 (2.0-27.6)	7.30 (2.0-27.6)
SF-10 physical summary score at baseline					
n	6	18	15	9	24
Mean (SD)	29.629 (15.554)	31.409 (12.984)	31.270 (15.188)	30.454 (10.349)	30.964 (13.335)
Median (Min-Max)	31.318 (5.23-47.00)	26.128 (11.58-53.81)	26.809 (5.23-53.81)	25.447 (16.13-45.63)	26.128 (5.23-53.81)
SF-10 psychosocial summary score at baseline					
n	6	18	15	9	24
Mean (SD)	44.606 (4.893)	50.151 (8.786)	48.260 (8.329)	49.607 (8.580)	48.765 (8.263)
Median (Min-Max)	43.565 (39.12-51.59)	50.699 (31.09-62.28)	45.340 (36.44-59.61)	48.913 (31.09-62.28)	48.913 (31.09-62.28)
Bone age (years) at baseline					
n	5	18	14	9	23
Mean (SD)	10.2 (2.8)	15.3 (1.9)	14.6 (3.2)	13.6 (2.7)	14.2 (3.0)
Median (Min-Max)	11.0 (6-13)	15.0 (10-19)	15.0 (6-19)	14.0 (9-16)	15.0 (6-19)
Bone age compared to chronological age at baseline					
n	5 (83.3%)	18 (100%)	14 (93.3%)	9 (100%)	23 (95.8%)
Delayed	0	1 (5.6%)	0	1 (11.1%)	1 (4.2%)
In accordance	4 (66.7%)	8 (44.4%)	6 (40.0%)	6 (66.7%)	12 (50.0%)
Advanced	1 (16.7%)	9 (50.0%)	8 (53.3%)	2 (22.2%)	10 (41.7%)
Bone morphology at baseline					
n	5 (83.3%)	18 (100%)	14 (93.3%)	9 (100%)	23 (95.8%)
Normal	5 (83.3%)	18 (100%)	14 (93.3%)	9 (100%)	23 (95.8%)
Abnormal	0	0	0	0	0
Tanner scale at baseline – Genitals (male)					
n	2 (33.3%)	11 (61.1%)	8 (53.3%)	5 (55.6%)	13 (54.2%)
Stage 1	1 (16.7%)	0	1 (6.7%)	0	1 (4.2%)
Stage 2	1 (16.7%)	1 (5.6%)	1 (6.7%)	1 (11.1%)	2 (8.3%)
Stage 3	0	1 (5.6%)	1 (6.7%)	0	1 (4.2%)
Stage 4	0	7 (38.9%)	4 (26.7%)	3 (33.3%)	7 (29.2%)
Stage 5	0	2 (11.1%)	1 (6.7%)	1 (11.1%)	2 (8.3%)
Tanner scale at baseline – Breasts (female)					
n	4 (66.7%)	7 (38.9%)	7 (46.7%)	4 (44.4%)	11 (45.8%)
Stage 1	4 (66.7%)	0	3 (20.0%)	1 (11.1%)	4 (16.7%)
Stage 2	0	2 (11.1%)	1 (6.7%)	1 (11.1%)	2 (8.3%)
Stage 3	0	3 (16.7%)	2 (13.3%)	1 (11.1%)	3 (12.5%)
Stage 4	0	0	0	0	0
Stage 5	0	2 (11.1%)	1 (6.7%)	1 (11.1%)	2 (8.3%)
Tanner scale at baseline – Pubic hair					
n	6 (100%)	18 (100%)	15 (100%)	9 (100%)	24 (100%)

	Age group		Concomitant PAH medication		Total
	Riociguat ≥6 to <12 years N=6 (100%)	Riociguat ≥12 to <18 years N=18 (100%)	Riociguat ERA only N=15 (100%)	Riociguat ERA+PCA[a] N=9 (100%)	Riociguat N=24 (100%)
Stage 1	6 (100%)	1 (5.6%)	4 (26.7%)	3 (33.3%)	7 (29.2%)
Stage 2	0	5 (27.8%)	4 (26.7%)	1 (11.1%)	5 (20.8%)
Stage 3	0	1 (5.6%)	1 (6.7%)	0	1 (4.2%)
Stage 4	0	8 (44.4%)	4 (26.7%)	4 (44.4%)	8 (33.3%)
Stage 5	0	3 (16.7%)	2 (13.3%)	1 (11.1%)	3 (12.5%)

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
In source tables the number of subjects in the concomitant PAH medication subgroup of PCA only is shown as "0". Therefore, the subgroup of PCA only is not shown in this table.
NT-proBNP and BNP analyzed irrespective of specimen type.
Baseline = last observed value prior to start of study treatment.

a. "PCA" includes prostacyclin analogues and receptor agonists
b. "PAH" was added, whereas "Hereditable" is presented in the source table.
c. One subject diagnosed with PH associated to developmental abnormalities did not meet the inclusion criterion of "Diagnosed with PAH" but entered the study, thus was recorded as important protocol deviation.
d. "PAH associated to" and "(repaired)" were added, whereas "Congenital heart disease" is presented in the source table.
e. One subject had no 6MWD value at baseline since he had the 6MWD test on 2019-01-18T10:30 while the first drug application was on 2019-01-18T09:45.
f. "0" was added, whereas the source table shows this as blank.

6MWD = 6-minutes-walking-distance; BNP = brain natriuretic peptide; ERA = endothelin receptor antagonists; NT-proBNP = N-terminal pro–brain natriuretic peptide; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue; PH = pulmonary hypertension; SD = standard deviation; SF-10 = quality of life scores (child health-related questionnaire); WHO = World Health Organization

General medical history

The most frequently reported preferred terms were pulmonary arterial hypertension (62.5%), pulmonary hypertension (33.3%), right ventricular hypertrophy (25.0%) and rhinitis allergic (20.8%).

The results were comparable across age groups and concomitant PAH medications.

Specific PAH medications

Subjects must be on standard-of-care PAH medications, allowing ERA and/or PCAs for at least 12 weeks prior to the baseline visit. Intake of PDE5 inhibitors was not allowed during the study. The most frequently used specific PAH medications as prior medications were bosentan (62.5%) and sildenafil (37.5%) (**Table 13**). Bosentan was reported as a concomitant medication for 62.5% of subjects. There were 3 subjects who reported concomitant use of PDE5 inhibitors; 1 subject received PDE5 inhibitor (sildenafil) and 2 subjects received non-specific PDE inhibitors. In one subject, riociguat treatment was stopped before starting remedial therapy with sildenafil, therefore, no protocol deviation for concomitant PDE5 inhibitor therapy was recorded. In the other 2 subjects, concomitant uses of non-specific PDE inhibitors were reported, however, adverse events reported during this period were not seen as a result of a possible drug-drug interaction.

Table 12. Specific prior and concomitant PAH medications by age group and concomitant PAH medication (safety analysis set)

	Age group		Concomitant PAH medication		Total
	Riociguat ≥6 to <12 years N=6 (100%)	Riociguat ≥12 to <18 years N=18 (100%)	Riociguat ERA only N=15 (100%)	Riociguat ERA+PCA[a] N=9 (100%)	Riociguat N=24 (100%)
ERAs					
Prior medication [b]	6(100%)	18(100%)	15(100%)	9(100%)	24(100%)
Any concomitant medication [c]	6(100%)	18(100%)	15(100%)	9(100%)	24(100%)
Any new concomitant medication [d]	0	3(16.7%)	2(13.3%)	1(11.1%)	3(12.5%)
PCAs[a]					
Prior medication [b]	2(33.3%)	7(38.9%)	0	9(100%)	9(37.5%)
Any concomitant medication [c]	2(33.3%)	8(44.4%)	1(6.7%)	9(100%)	10(41.7%)
Any new concomitant medication [d]	0	5(27.8%)	1(6.7%)	4(44.4%)	5(20.8%)
PDE5 inhibitors					
Prior medication [b]	5(83.3%)	13(72.2%)	10(66.7%)	8(88.9%)	18(75.0%)
Any concomitant medication [c]	1(16.7%)	1(5.6%)	2(13.3%)	0	2(8.3%)
Any new concomitant medication [d]	1(16.7%)	1(5.6%)	2(13.3%)	0	2(8.3%)

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
In source tables the number of subjects in the concomitant PAH medication subgroup of PCA only is shown as "0". Therefore, the subgroup of PCA only is not shown in this table.

a. "PCA" includes prostacyclin analogues and receptor agonists
b. Specific concomitant PAH medication that began before the start of study drug (regardless of when they ended)
c. Specific concomitant PAH medications that are ongoing at, began after the start of study drug, and those that were started after end of study drug
d. Specific concomitant PAH medications that began after the start of study drug, and those that were started after end of study drug

ERA = endothelin receptor antagonists; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue; PDE = Phosphodiesterase

Numbers analysed

Not applicable.

Outcomes and estimation

6MWD

An improvement in physical capacity (6MWD) with a mean change of 23.01 m was seen between baseline and Week 24 (**Table 14**). With the limitations of small sample size and potential random findings, improvement (positive mean change) of 6MWD from baseline was seen in both age subgroups and the subgroup of subjects receiving ERA+PCA as concomitant PAH medications but not in those receiving ERA only.

Table 13. Summary statistics for 6-minute walking distance (meter) by age group and concomitant PAH medication (SAF)

	Age group		Concomitant PAH medication		Total
Statistic	**Riociguat ≥6 to <12 years N=6**	**Riociguat ≥12 to <18 years N=18**	**Riociguat ERA only N=15**	**Riociguat ERA+PCA[a] N=9**	**Riociguat N=24**
Baseline	n=6	n=17 [b]	n=14	n=9	n=23
Mean (SD)	388.50 (155.71)	461.04 (86.62)	432.76 (131.10)	456.67 (68.96)	442.12 (109.67)
Median (Min-Max)	433.50 (91.0-508.0)	446.00 (326.0-683.5)	440.50 (91.0-683.5)	442.00 (360.0-539.0)	442.00 (91.0-683.5)
Change from baseline at Visit 9 (Week 24)	n=5	n=14	n=11	n=8	n=19
Mean (SD)	46.40 (89.19)	14.66 (61.82)	–5.56 (45.77)	62.31 (78.31)	23.01 (68.80)
Median (Min-Max)	30.00 (–28.0-200.0)	14.50 (–101.0-148.0)	2.00 (–101.0-58.0)	45.00 (–46.6-200.0)	16.00 (–101.0-200.0)

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
There were no subjects in the PCA only subgroup. Therefore, this subgroup is not shown.

a "PCA" includes prostacyclin analogues and receptor agonists

b One subject had no 6MWD baseline value since the 6MWD-test took place after the first drug administration.

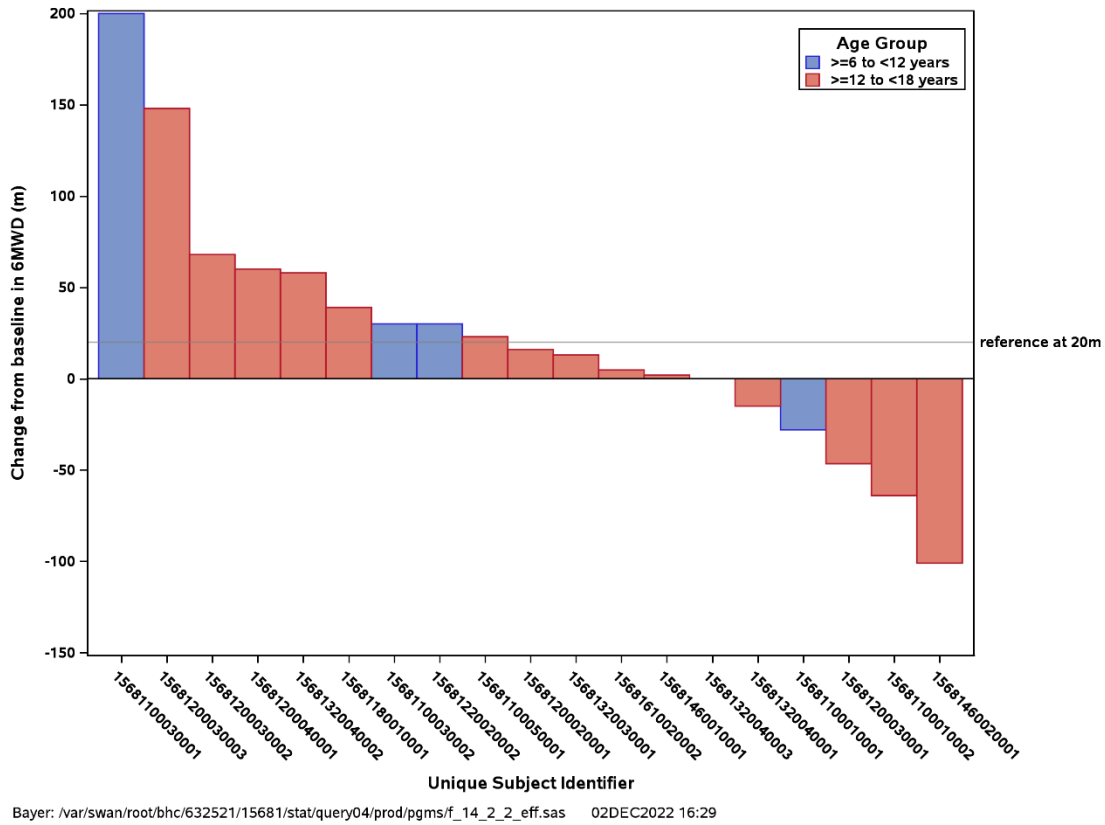
Baseline = last observed value prior to start of study treatment

ERA = endothelin receptor antagonists; Max = maximum; Min = minimum; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue; SD = standard deviation, SAF = safety analysis set

During the optional LTE phase, the mean changes from baseline in 6MWD for eligible subjects on treatment were 5.86 m (SD 44.56; n=16) at Month 6, -3.43 m (SD 74.77, n=12) at Month 12; 28.98 m (SD 66.71, n=9) at Month 18, and - 11.80 m (SD 35.40, n=4) at Month 24. Considering the low subject numbers, comparable changes were also seen in both age subgroups and in the subgroup of subjects receiving ERA+PCA as concomitant PAH medications. In the subgroup of subjects receiving ERA only, maintenance was reported for up to 2 years of treatment duration.

Responder analyses showed that 9 of 19 participants in PATENT-CHILD (47.4 %; 3 participants ≥6 to <12 years and 6 participants ≥12 to <18 years subgroups) had an improvement by at least 20 m at Week 24 compared with baseline (**Figure 17**). Regarding LTE, an improvement by at least 20 m was observed in 8/16 (50.0%), 4/12 (33.3%), 5/9 (55.6%) and 1/4 participant (25.0%) at months 6, 12, 18 and 24 in assessable patients.

Figure 17. Waterfall plot for change from baseline to Week 24 in 6-minutes-walking-distance (SAF, main phase/LTE)



NT-proBNP

For 9/24 (37.5%) of subjects, NT-proBNP data has not been collected at baseline.

For subjects with NT-proBNP values available (n=15) at baseline, the mean NT-proBNP was 982.68 pg/mL, and the median was 202.00 pg/mL (**Table 15**). Of note, the SD (1595.77) was very large, and means and medians were not comparable. The median baseline NT-proBNP was higher in the subgroup of subjects of ≥12 to <18 years compared with those of ≥6 to <12 years and was higher in the subgroup of subjects receiving ERA only as compared with those receiving ERA+PCA as concomitant PAH medications.

An improvement with a mean change of −65.77 pg/mL and a median change of −12.05 pg/mL was seen between baseline and Week 24 and were consistent with the key findings for 6MWD. The improvement (negative median change) of NT-proBNP from baseline was also seen in the subgroup of subjects receiving ERA+PCA (but not in those receiving ERA only) and the subgroup of subjects of ≥6 to <12 years but not in the older subgroup.

During the optional LTE phase, the mean changes from baseline for NT-proBNP for eligible subjects on treatment were -291.05 pg/mL (median 0.00; n=11) at Month 6, -222.78 pg/mL (median -5.50, n=12) at Month 12; -283.40 pg/mL (median -8.00, n=9) at Month 18, and -270.93 pg/mL (median -243.00, n=4) at Month 24.

When both tests were available at a site, NT-proBNP was to be chosen over BNP, and the same test was to be performed at every required visit. For subjects who had BNP values available (n=7) at baseline, the mean BNP was 10.46 pg/mL, and the median was 7.30 pg/mL. Between baseline and Week 24 (n=6), BNP values slightly increased with a mean change of 7.45 pg/mL and a median change of 1.25 pg/mL.

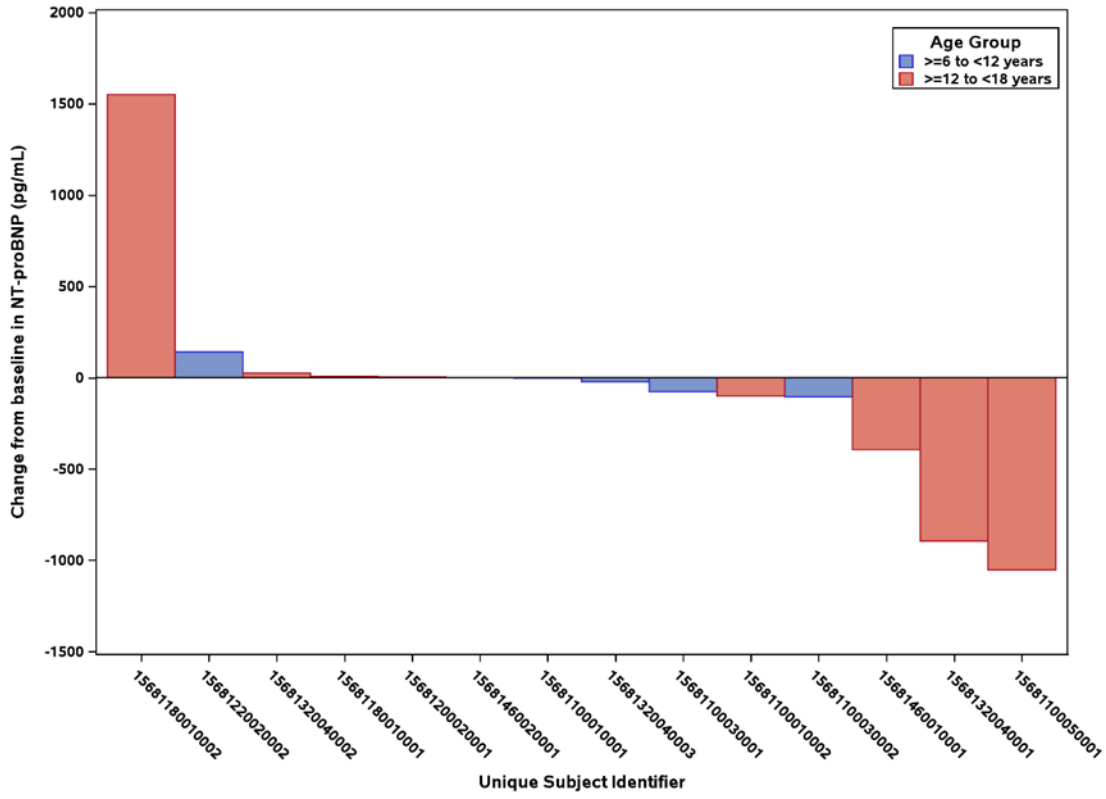
Table 14. Summary statistics for NT-proBNP (pg/mL) by age group and concomitant PAH medication (SAF)

	Age group		Concomitant PAH medication		Total
Statistic	**Riociguat ≥6 to <12 years N=6**	**Riociguat ≥12 to <18 years N=18**	**Riociguat ERA only N=15**	**Riociguat ERA+PCA[a] N=9**	**Riociguat N=24**
Baseline	n=5	n=10	n=11	n=4	n=15
Mean (SD)	223.30 (245.75)	1362.37 (1858.44)	961.84 (1602.20)	1040.00 (1822.32)	982.68 (1595.77)
Median (Min-Max)	165.00 (42.0-646.0)	394.10 (22.0-4440.0)	313.20 (42.0-4440.0)	183.50 (22.0-3771.0)	202.00 (22.0-4440.0)
Change from baseline at Visit 9 (Week 24)	n=5	n=9	n=10	n=4	n=14
Mean (SD)	–13.02 (95.49)	–95.08 (741.37)	31.02 (612.86)	–307.75 (498.98)	–65.77 (585.41)
Median (Min-Max)	–22.00 (–105.0-141.0)	0.00 (–1053.0-1550.0)	–1.05 (–895.0-1550.0)	–91.00 (–1053.0-4.0)	–12.05 (–1053.0-1550.0)

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
There were no subjects in the PCA only subgroup. Therefore, this subgroup is not shown.
a. "PCA" includes prostacyclin analogues and receptor agonists
Baseline = last observed value prior to start of study treatment
ERA = endothelin receptor antagonists; Max = maximum; Min = minimum; NT-proBNP = N-terminal prohormone of brain brain natriuretic peptide; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue; SD = standard deviation, SAF = safety analysis set

Responder analyses showed that 8 of 14 participants with reported NT-proBNP in PATENT-CHILD (57.1%) had an improvement in response at Week 24 compared with baseline (**Figure 18**). NT-proBNP improved in 5/11 (45.5%), 6/12 (50.0%), 5/9 (55.6%) and 2/4 participants (50.0%) at months 6, 12, 18 and 24 of the LTE part of the study when compared with baseline.

Figure 18. Waterfall plot for change from baseline to Week 24 in NT-proBNP (SAF, main phase/LTE)



Clinical worsening

Up to Week 24, 2 (8.3%) subjects were reported with an event of clinical worsening as hospitalization for right heart failure. Both subjects were in the subgroup of ≥12 to <18 years, and one subject each received ERA only or ERA+PCA as concomitant PAH medication. The planned Kaplan-Meier analysis for the main phase is not presented here because few subjects experienced an event of clinical worsening.

Between the LTE start and data cut-off date, 6 subjects of the older age cohort were reported with clinical worsening (**Table 16**).

Table 15. Number of subjects with clinical worsening by age group and concomitant PAH medication – up to LTE cut-off (safety analysis set, main phase/LTE)

	Age group		Concomitant PAH medication		Total
Event	Riociguat ≥6 to <12 years N=6	Riociguat ≥12 to <18 years N=18	Riociguat ERA only N=15	Riociguat ERA+PCA [a] N=9	Riociguat N=24
Number of subjects (%) with clinical worsening	0	8 (44.4%)	4 (26.7%)	4 (44.4%)	8 (33.3%)
Hospitalization for right heart failure	0	5 (27.8%)	2 (13.3%)	3 (33.3%)	5 (20.8%)
Death (all cause mortality)	0	0	0	0	0
Lung transplantation	0	2 (11.1%)	2 (13.3%)	0	2 (8.3%)
Pott's anastomosis and/or atrioseptostomy	0	0	0	0	0
Increase in WHO FC from baseline	0	2 (11.1%)	1 (6.7%)	1 (11.1%)	2 (8.3%)
Appearance/worsening symptoms of right heart failure and need for additional PAH therapy	0	0	0	0	0

Note: The technical report PH-42339 shows the data from children receiving both tablet and oral suspension formulations, comprising the main and the LTE part up to the cut-off date 07 JAN 2022.
There were no subjects in the PCA only subgroup. Therefore, this subgroup is not shown.
a "PCA" includes prostacyclin analogues and receptor agonists
ERA = endothelin receptor antagonists; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue, LTE = long-term extension, FC = functional class

WHO functional class

The majority of subjects (18 [75.0%]) had a WHO functional class of II at baseline. Five (20.8%) subjects had a WHO FC III, and 1 subject (4.2%) had WHO FC I. No subjects reported a change in WHO functional class between baseline and Week 24.

During the LTE phase, the majority of subjects who reached Month 24 (6/7 [85.7%]) remained stable regarding WHO functional class II with one subject showing improvement. Results were consistent between age and concomitant PAH medication subgroups.

QoL

For SF-10 physical and psychosocial summary scores, an improvement was seen between baseline and Week 24, respectively (**Table 17**). The same holds true for the PedsQL total scale score and the PedsQL physical health summary score, and PedsQL psychosocial health summary score between baseline and Week 24, respectively (**Table 18**). For the PedsQL subdomains physical functioning and school functioning dimensions, an improvement was seen in both age subgroups between baseline and Week 24. In contrast, for the PedsQL subdomains' emotional functioning and social functioning dimensions, an improvement was seen in the younger subgroup only.

During the LTE phase, continuous trends in further improvements in the SF-10 physical and psychosocial summary scores and the PedsQL total scale, physical health summary, and psychosocial health summary scores (including subdomains) were reported.

Table 16. Summary statistics for SF-10 questionnaire summary scores by age group and concomitant PAH medication (SAF)

	Age group		Concomitant PAH medication		Total
Statistic	**Riociguat ≥6 to <12 years N=6**	**Riociguat ≥12 to <18 years N=18**	**Riociguat ERA only N=15**	**Riociguat ERA+PCA[a] N=9**	**Riociguat N=24**
SF-10 questionnaire physical summary score					
Baseline	n=6	n=18	n=15	n=9	n=24
Mean (SD)	29.63 (15.55)	31.41 (12.98)	31.27 (15.19)	30.45 (10.35)	30.96 (13.34)
Median (Min-Max)	31.32 (5.2-47.0)	26.13 (11.6-53.8)	26.81 (5.2-53.8)	25.45 (16.1-45.6)	26.13 (5.2-53.8)
Change from baseline to Visit 9 (Week 24)	n=5	n=16	n=13	n=8	n=21
Mean (SD)	3.18 (17.93)	6.61 (10.88)	4.09 (12.66)	8.56 (12.44)	5.79 (12.46)
Median (Min-Max)	7.27 (–24.7-24.3)	4.52 (–7.1-31.8)	4.52 (–24.7-24.3)	6.46 (–7.1-31.8)	4.52 (–24.7-31.8)
SF-10 questionnaire psychosocial summary score					
Baseline	n=6	n=18	n=15	n=9	n=24
Mean (SD)	44.61 (4.89)	50.15 (8.79)	48.26 (8.33)	49.61 (8.58)	48.76 (8.26)
Median (Min-Max)	43.57 (39.1-51.6)	50.70 (31.1-62.3)	45.34 (36.4-59.6)	48.91 (31.1-62.3)	48.91 (31.1-62.3)
Change from baseline to Visit 9 (Week 24)	n=5	n=16	n=13	n=8	n=21
Mean (SD)	2.31 (9.04)	0.72 (6.34)	–0.82 (6.68)	4.23 (6.28)	1.10 (6.85)
Median (Min-Max)	3.57 (–11.6-12.5)	0.00 (–8.0-13.4)	0.00 (–11.6-12.5)	4.90 (–8.0-13.4)	0.00 (–11.6-13.4)

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
There were no subjects in the PCA only subgroup. Therefore, this subgroup is not shown.
a. "PCA" includes prostacyclin analogues and receptor agonists
Baseline = last observed value prior to start of study treatment
Score was generated by QualityMetric.
Higher values indicate more favourable physical functioning.
ERA = endothelin receptor antagonists; Max = maximum; Min = minimum; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue; SD = standard deviation, SAF = safety analysis set

Table 17. Summary statistics for PedsQL scores by age group and concomitant PAH medication (SAF)

	Age group		Concomitant PAH medication		Total
Statistic	**Riociguat ≥6 to <12 years N=6**	**Riociguat ≥12 to <18 years N=18**	**Riociguat ERA only N=15**	**Riociguat ERA+PCA[a] N=9**	**Riociguat N=24**
PedsQL total scale score					
Baseline	n=6	n=15	n=12	n=9	n=21
Mean (SD)	58.15 (18.65)	74.42 (13.18)	64.40 (15.92)	76.93 (14.63)	69.77 (16.29)
Median (Min-Max)	53.80 (37.0-84.8)	73.91 (50.0-91.3)	65.22 (37.0-88.0)	82.61 (50.0-91.3)	72.83 (37.0-91.3)
Change from baseline to Visit 9 (Week 24)	n=5	n=14	n=11	n=8	n=19
Mean (SD)	13.04 (9.75)	0.08 (9.21)	2.47 (12.10)	4.89 (9.33)	3.49 (10.81)
Median (Min-Max)	16.30 (1.1-21.7)	–0.54 (–12.0-16.3)	3.26 (–12.0-21.7)	2.72 (–6.5-21.7)	3.26 (–12.0-21.7)
PedsQL physical health summary score					
Baseline	n=6	n=15	n=12	n=9	n=21
Mean (SD)	59.90 (19.41)	66.25 (14.48)	61.46 (17.89)	68.40 (12.35)	64.43 (15.80)
Median (Min-Max)	53.13 (37.5-90.6)	65.63 (43.8-100.0)	56.25 (37.5-100.0)	65.63 (56.3-90.6)	65.63 (37.5-100.0)
Change from baseline to Visit 9 (Week 24)	n=5	n=14	n=11	n=8	n=19
Mean (SD)	10.00 (13.87)	2.23 (13.28)	2.27 (13.04)	7.03 (14.54)	4.28 (13.51)
Median (Min-Max)	9.38 (–6.3-31.3)	3.13 (–21.9-21.9)	6.25 (–21.9-18.8)	3.13 (–9.4-31.3)	6.25 (–21.9-31.3)
PedsQL psychosocial health summary score					
Baseline	n=6	n=15	n=12	n=9	n=21
Mean (SD)	57.22 (19.23)	78.78 (15.88)	65.97 (17.34)	81.48 (18.79)	72.62 (19.20)
Median (Min-Max)	54.17 (30.0-81.7)	80.00 (46.7-96.7)	69.17 (30.0-91.7)	86.67 (46.7-96.7)	76.67 (30.0-96.7)
Change from baseline to Visit 9 (Week 24)	n=5	n=14	n=11	n=8	n=19
Mean (SD)	14.67 (11.02)	–1.07 (8.15)	2.58 (13.47)	3.75 (7.96)	3.07 (11.21)
Median (Min-Max)	16.67 (1.7-26.7)	–2.50 (–11.7-15.0)	–1.67 (–11.7-26.7)	4.17 (–8.3-16.7)	1.67 (–11.7-26.7)

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
There were no subjects in the PCA only subgroup. Therefore, this subgroup is not shown.
a. "PCA" includes prostacyclin analogues and receptor agonists
Baseline = last observed value prior to start of study treatment
If 50% or more items in the scale were completed, missing items were imputed with mean of the completed items in the scale. If more than 50% of the items were missing, the score was not computed.
Higher scores indicate better quality of life.
ERA = endothelin receptor antagonists; Max = maximum; Min = minimum; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue; SD = standard deviation, SAF = safety analysis set

Echocardiographic parameters

- At baseline, the mean value of the mean estimated right atrial pressure was 9.3 (SD 3.4) mmHg. At Week 24 (Visit 9), a mean change of –0.6 (SD 3.6) mmHg was observed.
- At baseline, the mean left ventricular eccentricity index was 2.099 (SD 1.275). At Week 24 (Visit 9), a mean change of 0.002 (SD 0.907) was observed.

- At baseline, the mean pericardial effusion was 1.280 (SD 0.212) mm (n=2). At Week 24 (Visit 9), there was only one subject with the pericardial effusion value.
- At baseline, the mean pulmonary artery acceleration time was 91.568 (SD 36.853) msec. At Week 24 (Visit 9), a mean change of –7.777 (SD 35.898) msec was observed.
- At baseline, the mean right ventricular cardiac index was 4.343 (SD 1.599) L/min/m2. At Week 24 (Visit 9), a mean change of 0.188 (SD 2.094) L/min/m2 was observed.
- At baseline, the mean right ventricular cardiac output was 5.511 (SD 2.093) L/min. At Week 24 (Visit 9), a mean change of 0.457 (SD 3.066) L/min was observed.
- At baseline, the mean right atrial diastolic area was 16.944 (SD 11.071) cm2. At Week 24 (Visit 9), a mean change of 1.078 (SD 3.330) cm2 was observed.
- At baseline, the mean right atrial diastolic area index was 12.788 (SD 6.977). At Week 24 (Visit 9), a mean change of 0.643 (SD 2.314) was observed.
- At baseline, the mean right atrial systolic area was 12.017 (SD 9.391) cm2. At Week 24 (Visit 9), a mean change of 0.424 (SD 3.758) cm2 was observed.
- At baseline, the mean right atrial systolic area index was 8.996 (SD 6.021). At Week 24 (Visit 9), a mean change of 0.329 (SD 2.417) was observed.
- At baseline, the mean right ventricular fractional area change was 25.7% (SD 8.5%). At Week 24 (Visit 9), a mean change of –4.3% (SD 7.3%) was observed.
- At baseline, the mean right ventricular diastolic area was 27.155 (SD 11.993) cm2. At Week 24 (Visit 9), a mean change of 0.618 (SD 4.519) cm2 was observed.
- At baseline, the mean right ventricular diastolic area index was 20.722 (SD 6.564). At Week 24 (Visit 9), a mean change of 0.451 (SD 3.562) was observed.
- At baseline, the mean right ventricular systolic area was 20.235 (SD 9.343) cm2. At Week 24 (Visit 9), a mean change of 1.725 (SD 3.847) cm2 was observed.
- At baseline, the mean right ventricular systolic area index was 15.613 (SD 5.745). At Week 24 (Visit 9), a mean change of 1.244 (SD 3.277) was observed.
- At baseline, the mean systolic pulmonary artery pressure was 117.2 (SD 51.6) mmHg. At Week 24 (Visit 9), a mean change of 5.7 (49.0) mmHg was observed.
- At baseline, the mean TAPSE was 18.82 (SD 4.21) mm. At Week 24 (Visit 9), a mean change of –1.27 (SD 3.87) mm was observed.
- At baseline, the mean tricuspid regurgitation peak velocity was 4.915 (SD 1.100) m/s. At Week 24 (Visit 9), a mean change of –0.085 (SD 0.726) m/s was observed.

Overall, the number of subjects enrolled and with echocardiographic evaluation was small, and for certain parameters, only a few subjects (pericardial effusion [1 subject], systolic PAP [3]) had assessments at both baseline and Week 24 to allow for analysis of the change. Evaluation of the mean changes in this small population did not allow to identify trends across all parameters.

The same holds true for the echocardiographic data reported during the LTE phase.

Ancillary analyses

Not applicable.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18. Summary of efficacy for the pivotal trial

Title: Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with pulmonary arterial hypertension (PAH)		
Study identifier	PATENT-CHILD (Protocol no.15681) EudraCT number 2014-003952-29	
Design	Open-label, non-randomized, multi-center, single arm, individual dose titration	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks (8 weeks of titration and 16 weeks of maintenance) Not applicable Until market approval of riociguat for the pediatric population or until the participants become 18 years of age (whatever comes first)
Hypothesis	Exploratory	
Treatments groups	riociguat (BAY 63-2521)	An individual dose titration (IDT) scheme according to a body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for pulmonary arterial hypertension (PAH). Children ≥50 kg at screening: 1.0 - 2.5 mg TID Children <50 kg at screening: Bodyweight-adjusted dose equivalent to the exposure of (0.5 mg) 1.0 - 2.5 mg TID 26 subjects were enrolled (signed informed consent form), including 2 screening failures. 24 subjects were treated
Endpoints and definitions	**Primary endpoint:** No primary efficacy endpoint for this study	

	Primary safety endpoint: Change from baseline to the end of treatment (Week 24) of safety and tolerability assessed by incidence of adverse events (AEs) and serious AEs (SAEs), recording of vital signs and left-hand x-ray and laboratory panel.	• Number of subjects with any treatment-emergent adverse events (TEAEs) • Change in heart rate from baseline • Change in blood pressure from baseline • Change in respiratory rate from baseline • Number of subjects with transitions from baseline in bone age compared to chronological age • Change in hematology/clinical chemistry parameters from baseline
	Primary PK endpoint: Pre- and post-dose blood samples for PK characterization of riociguat and its active metabolite BAY 60-4552	• Plasma concentrations of riociguat/BAY 60-4552 at Weeks 0, 4 and 8
	Secondary efficacy endpoints:	
	Number of subjects with clinical worsening and Time to clinical worsening (TTCW), N (%)	• Hospitalization for right heart failure • Death • Lung transplantation • Pott's anastomosis and atrioseptostomy • Worsening of PAH symptoms, which must include either: an increase in WHO FC *OR* appearance/worsening symptoms of right heart failure *AND* need for additional PAH therapy
	Change from baseline in 6 minute walking distance (6MWD) test at Week 24 (meter)	Exercise capacity
	Change form baseline in World Health Organization Functional class (WHO FC) at Week 24	Functional capacity
	Change from baseline in N-terminal pro–brain natriuretic peptide (NT-proBNP) in blood (pg/ml) at Week 24	Laboratory biomarker
	Change from baseline in Brain natriuretic peptide (BNP) in serum at Week 24 (pg/ml)	Laboratory biomarker, when both tests were available, NT-proBNP was chosen over BNP and the same test was performed at every required visit
	Change from baseline in SF-10 questionnaire, Physical summary score (PHS-10) at Week 24	Quality of Life, Physical summary score

	Change from baseline in SF-10 questionnaire, Psychosocial summary score (PSS-10) at Week 24	Quality of Life, Psychosocial summary score
	Change from baseline in PedsQL, Total scale score at Week 24	Quality of Life, PedsQL Generic Core Scales self-report, PedsQL Total scale score
	Change from baseline in PedsQL, Physical health Summary Score at Week 24	Quality of Life, PedsQL Generic Core Scales self-report, PedsQL Physical health Summary Score
	Change from baseline in PedsQL Psychosocial health summary score at Week 24	Quality of Life, PedsQL Generic Core Scales self-report, PedsQL Psychosocial health summary score
Database lock	Main phase: 30 JUL 2020 (data cut-off: 07 MAR 2020) Last data lock for LTE phase: 6 MAY 2022 (data cut-off: 07 JAN 2022)	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	Safety analysis set (SAF). A subject is included in SAF if he/she was assigned to receive study medication and had received at least one dose of the study medication. 24 weeks	

Main study results Descriptive statistics and estimate variability	**Treatment group**	**riociguat (BAY 63-2521)**
	Number of subjects with clinical worsening	
	Number of subjects assessed	24
	N (%)	2 (8.3%)
	Change from baseline in 6MWD at Week 24, (m)	
	Number of subjects	19
	Mean	23.01
	Standard deviation	68.80
	Median	16.00
	Min, Max	–101.0, 200.0
	Change from baseline in WHO FC at Week 24	
	Number of subjects	21
	N (%) by FC	-2 WHO FC (0 [0.0%]) -1 WHO FC (0 [0.0%]) 0 WHO FC (21 [(100.0%]) 1 WHO FC (0 [0.0%])
	Change from baseline in NT-proBNP at Week 24, (pg/ml)	
	Number of subjects	14
	Mean	-65.77
	SD	585.41
	Median	-12.05
	Min, Max	-1053.0, 1550.0
	Change from baseline in BNP at Week 24, (pg/ml)	
	Number of subjects	6
	Mean	7.45
	SD	10.65
	Median	1.25
	Min, Max	0.0, 22.5

	Change form baseline in PHS-10 at Week 24	
	Number of subjects	21
	Mean	5.79
	Standard deviation	12.46
	Median	4.52
	Min, Max	−24.7, 31.8
	Change from baseline in PSS-10 at Week 24	
	Number of subjects	21
	Mean	1.10
	Standard deviation	6.85
	Median	0.00
	Min, Max	−11.6, 13.4
	Change from baseline in PedsQL Total scale score at Week 24	
	Number of subjects	19
	Mean	3.49
	Standard deviation	10.81
	Median	3.26
	Min, Max	−12.0, 21.7
	Change from baseline in PedsQL Physical health summary score at Week 24	
	Number of subjects	19
	Mean	4.28
	Standard deviation	13.51
	Median	6.25
	Min, Max	−21.9, 31.3
	Change from baseline in PedsQL Psychosocial health summary score at Week 24	
	Number of subjects	19
	Mean	3.07
	Standard deviation	11.21
	Median	1.67
	Min, Max	−11.7, 26.7
Effect estimate per comparison	Not applicable. Explorative and descriptive study	
Notes		
Analysis description	No statistical testing was done, all analysis are descriptive	

Clinical studies in special populations

Not applicable.

In vitro biomarker test for patient selection for efficacy

Not applicable.

Analysis performed across trials (pooled analyses and meta-analysis)

Comparison and integrated analyses of paediatric and adult data

Paediatric exploratory efficacy data from the main study part (first 24 weeks of treatment) in PATENT-CHILD are displayed side-by-side with pooled data from the Phase 3 studies in adults (PATENT-1 and

PATENT-2), within the first 24 weeks of treatment, to allow clinical comparisons. To note: the use of the PATENT-1 and PATENT-2 populations for comparison is considered acceptable as the aetiology of IPAH, FPAH, and some associated forms (e.g. APAH associated with CHD) is comparable in paediatric and adult PAH, although there are some differences in the proportions of the individual underlying causes of APAH (e.g., CTD vs CHD).

Statistical methods for the integrated analysis

As the study duration of PATENT-1 (12 weeks) was shorter than the duration of the main study part of PATENT-CHILD, data from subsequent treatment weeks from the open-label LTE study PATENT-2 were also taken into account up to a total of 24 weeks of observation in order to have a similar observation period of 24 weeks for adults and children. Only subjects randomized to the riociguat IDT group (individual up-titration up to 2.5 mg) of PATENT-1 were taken into account for the integrated analysis of efficacy (N=254). In addition, for a direct comparison of responses between adults and paediatric patients, a 'matched exposure' group from the adult population was selected (N=33). This 'matched exposure' consists of adult subjects showing individual PK exposure (AUC(0 8h)ss) similar to the observed individuals' PK exposure (AUC(0-8h)ss) in paediatric subjects regardless of their background therapy or smoking status. No statistical comparisons were performed.

The following treatment labels were used in the side-by-side presentation of the adult data with the paediatric data:

- PATENT-CHILD IDT
- PATENT-1/2 IDT (referred to as "Pool 1" hereafter)
- PATENT-1/2 IDT (matched exposure group) (referred to as "Pool 1 [matched exposure group]" hereafter)

Study participants comparison

A comparison of the main inclusion criteria of the PATENT-CHILD, PATENT-1 and PATENT-2 studies is provided in **Table 20**.

Table 19. Main inclusion criteria of PATENT-CHILD, and PATENT-1 and -2

	PATENT-CHILD (Study 15681)	PATENT-1 (Study 12934)	PATENT-2 (Study 12935)
Diagnosis and main criteria for inclusion	• Children with PAH from 6 years to <18 years • Subjects currently on standard of care PAH medications (including ERA/PCA) who need additional treatment • Subjects on stable PAH treatment (incl. ERA/PCA), in WHO FC I-III • PCWP or LVEDP ≤15 mmHg • PVR >240 dyn*sec*cm^{-5} • mPAP ≥25 mmHg	• Symptomatic PAH (Group 1, Venice Clinical Classification of PH; PH subtypes as specified in inclusion criteria) • Eligibility and baseline 6MWD test between 150 and 450 m • PVR >300 dyn*sec*cm^{-5} • mPAP >25 mmHg • Treatment-naïve subjects and subjects pre-treated with an ERA or a PCA • Unspecific treatments for the treatment of PH such as oral anticoagulants, diuretics, digitalis, calcium channel blockers or oxygen supplementation were permitted	• Subjects (with symptomatic PAH) who have completed 12 weeks of treatment in PATENT-1 • Subjects must have given written informed consent

Abbreviations: ERA = endothelin receptor antagonist, PAH = pulmonary arterial hypertension, mPAP = mean pulmonary arterial pressure, PCA = prostacyclin analogue, PH = pulmonary hypertension, PVR = Pulmonary vascular resistance, WHO FC = Word Health Organization functional class, 6MWD = 6-minute walking distance, PCWP = pulmonary capillary wedge pressure, LVEDP = left ventricular end-diastolic pressure

Baseline data comparison

Baseline characteristics were comparable in both pooled groups of adult subjects apart from median NT-proBNP levels at baseline (pg/mL) (Pool 1: 389.5; Pool 1 [matched exposure group]: 241.2) and the proportion of treatment-naïve subjects (Pool 1: 48.4%; Pool 1 [matched exposure group]: 39.4%)(**Table 21**).

Furthermore, the majority of paediatric subjects were diagnosed with idiopathic PAH (75.0%), followed by CHD-associated PAH (16.7%). In adults, the respective proportions were lower for idiopathic PAH (Pool 1: 58.7%; Pool 1 [matched exposure group]: 60.6%) and CHD-associated PAH (5.9% and 9.1%, respectively). PAH due to connective tissue disease was reported in 28.0% and 21.2% of adult subjects, respectively, but not in the paediatric population, which is consistent with major registries such as TOPP and REVEAL-CHILDREN (Barst et al. 2012, Berger et al. 2012).

In the paediatric population, a WHO functional class of I or II was reported for the majority of subjects (WHO FC II: 75%) compared to the pooled adult subjects, where most subjects (~55%) had a less favourable WHO functional class of III or IV.

In PATENT-CHILD, all 24 subjects were pre-treated: 62.5% with ERAs and 37.5% with ERAs + PCAs. In contrast, approximately half of the adult subjects in Pool 1 were treatment-naïve (48.4%), and 43.7% of subjects were pre-treated with ERAs. In Pool 1 (matched exposure group), approximately half of the subjects were pre-treated with ERAs (48.5%), and 39.4% were treatment-naïve.

Table 20. Demographics and baseline characteristics (SAF)

	PATENT-CHILD Riociguat IDT N=24 (100%)	Pool 1 Riociguat IDT N=254 (100%)	Pool 1 (matched exposure group) N=33 (100%)
Sex			
M	13 (54.2%)	51 (20.1%)	9 (27.3%)
F	11 (45.8%)	203 (79.9%)	24 (72.7%)
Age (years)			
n	24	254	33
Mean (SD)	12.8 (2.8)	51.1 (16.6)	48.0 (16.4)
Median	13.0	52.5	50.0
Min, Max	6, 17	18, 80	20, 75
Age group (years)			
≥6 - <12	6 (25.0%)	0	0
≥12 - <18	18 (75.0%)	0	0
≥18 - <65	0	188 (74.0%)	26 (78.8%)
≥65 - <75	0	48 (18.9%)	6 (18.2%)
≥75	0	18 (7.1%)	1 (3.0%)
Weight (kg)			
n	24	254	33
Mean (SD)	46.4 (15.9)	68.6 (18.4)	68.4 (18.3)
Median	45.5	65.0	65.0
Min, Max	12, 81	38, 140	38, 126
Weight Group			
<50 kg	16 (66.7%)	30 (11.8%)	3 (9.1%)
≥50 kg	8 (33.3%)	224 (88.2%)	30 (90.9%)
Height (cm)			
n	24	254	33
Mean (SD)	155.1 (17.8)	162.0 (9.1)	164.7 (9.7)
Median	158.6	160.5	165.0
Min, Max	107, 179	142, 195	142, 184
Body mass index (kg/m^2)			
n	24	254	33
Mean (SD)	18.7 (4.0)	25.9 (5.5)	25.1 (6.0)
Median	18.6	25.2	23.7
Min, Max	11, 30	16, 50	17, 49
Type of PAH/other type of PH			
Anorexigen or amphetamine assoc. PAH	0	1 (0.4%)	0
Congenital heart disease (operated) assoc. PAH [a]	4 (16.7%)	15 (5.9%)	3 (9.1%)
Connective tissue disease assoc. PAH	0	71 (28.0%)	7 (21.2%)
PH associated to developmental abnormalities [b]	1 (4.2%)	0	0
Familial PAH [c]	1 (4.2%)	7 (2.8%)	2 (6.1%)
Idiopathic PAH	18 (75.0%)	149 (58.7%)	20 (60.6%)
Portal pulmonary hypertension	0	11 (4.3%)	1 (3.0%)
WHO Functional Class at Baseline			
Class I	1 (4.2%)	5 (2.0%)	0
Class II	18 (75.0%)	108 (42.5%)	15 (45.5%)
Class III	5 (20.8%)	140 (55.1%)	18 (54.5%)
Class IV	0	1 (0.4%)	0
WHO Functional Class at Baseline group			
Class I/II	19 (79.2%)	113 (44.5%)	15 (45.5%)
Class III/IV	5 (20.8%)	141 (55.5%)	18 (54.5%)
6MWD at Baseline (m)			
n	23	254	33
Mean (SD)	442.1 (109.7)	361.4 (67.7)	368.2 (72.8)
Median	442.0	374.5	381.0
Min, Max	91, 684	160, 468	217, 450
NT-proBNP at Baseline (pg/mL)			
n	15	230	28
Mean (SD)	982.7 (1595.8)	1020.5 (1792.7)	387.3 (391.1)
Median	202.0	389.5	241.2

	PATENT-CHILD Riociguat IDT N=24 (100%)	Pool 1 Riociguat IDT N=254 (100%)	Pool 1 (matched exposure group) N=33 (100%)
Min, Max	22, 4440	5, 17648	32, 1747
Type of pretreatment for PAH			
Therapy-Naive	0	123 (48.4%)	13 (39.4%)
Pre-Treated with ERA	15 (62.5%)	111 (43.7%)	16 (48.5%)
Pre-Treated with PCA	0	18 (7.1%)	4 (12.1%)
Pre-Treated with PDE5 inhibitor	0	0	0
Pre-Treated with ERA and PCA	9 (37.5%)	2 (0.8%)	0

Pool 1 = This pooled arm includes subjects initially randomized to riociguat IDT from PATENT-1 and PATENT-2.
Pool 1 (matched exposure group) = This pooled arm includes subjects initially randomized to riociguat IDT from PATENT-1 and PATENT-2 who had similar exposure to subjects in PATENT-CHILD.
a In PATENT-CHILD, the classification was “PAH due to congenital heart disease (repaired)”.
b One subject in PATENT-CHILD diagnosed with PH associated to developmental abnormalities did not meet the inclusion criterion of “diagnosed with PAH” but entered the study, thus was recorded as important protocol deviation.
c In PATENT-CHILD, the classification was “heritable PAH”.
6MWD = 6-minutes-walking-distance; assoc. = associated; BNP = brain natriuretic peptide; ERA = endothelin receptor antagonists; F = female; IDT = individual dose titration; M = male; Min = minimum; Max = maximum; NT-proBNP = N-terminal pro–brain natriuretic peptide; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue; PDE5 = phosphodiesterase 5; PH = pulmonary hypertension; SD = standard deviation; WHO = World Health Organization, SAF = safety analysis set

Outcomes/endpoints comparison

The endpoints used in PATENT-CHILD are consistent with those used in the adult PATENT-1 and PATENT-2 studies (**Table 22**).

Table 21. Comparison of efficacy variables between PATENT-CHILD, and PATENT-1 and -2 studies

	PATENT-CHILD (Study 15681)	PATENT-1 (Study 12934)	PATENT-2 (Study 12935)
Variables	Primary variable(s): Change from baseline to end of main phase (week 24) of safety and tolerability assessed by incidence of AEs, vital signs, left hand bone monitoring, pharmacokinetic analyses Exploratory efficacy variables: Change from baseline to week 24 (end of main phase) in: 6MWD, WHO FC, NT-proBNP, QoL scores, echocardiographic parameters, TTCW, RHC	Primary efficacy variable after 12 weeks: Change from baseline in 6MWD Secondary efficacy variables: Change from baseline in: PVR, NT-proBNP, WHO FC, TTCW, QoL scores Additional efficacy variables: Hemodynamic parameters, HRU Safety variables: AEs, laboratory parameters, vital signs, ECG parameters, blood gas analysis Other variables: Exploratory biomarkers, PK measurements, pharmacogenetic assessment	Efficacy variables: Change from baseline (PATENT-1) after 24 weeks in 6MWD, NT-proBNP, WHO FC, TTCW, QoL scores, HRU Safety variables: AEs, laboratory parameters, vital signs, ECG parameters, blood gas analysis Other variables: PK measurements

Abbreviations: AE = Adverse event, ECG = electrocardiogram, NT-proBNP = N-terminal pro-brain natriuretic peptide, PAH = pulmonary arterial hypertension, PVR = Pulmonary vascular resistance, QoL = quality of life, TTCW = time to clinical worsening, WHO FC = Word Health Organization functional class, 6MWD = 6-minute walking distance, RHC = right heart cathetereization, HRU = healthcare resource use, PK = pharmacokinetic

Numbers analysed comparison

The number of subjects valid for safety analysis was 24 in the PATENT-CHILD riociguat IDT group, 254 in Pool 1 and 33 in Pool 1 (matched exposure group).

Outcomes and estimation comparison

Administration of riociguat in a dosage of 1.0-2.5 mg TID in the adult PATENT-1 study resulted in a statistically significant and clinically meaningful improvement in 6MWD as compared to placebo in subjects with symptomatic PAH. In addition, riociguat had statistically significant and clinically relevant superior effects over placebo on the predefined secondary efficacy variables PVR, NT-proBNP, WHO FC, TTCW, and Borg CR 10 Scale. The long-term 6MWD data from PATENT-2 indicated maintenance of the riociguat treatment effect, with clinically relevant improvement in 6MWD, observed for at least 18 months. Improvements in NT-proBNP, WHO FC, Borg CR 10 Scale, and EQ-5D, as well as PVR, were consistent with favourable key findings seen in PATENT-1.

A side-by-side comparison of the adult data to the PATENT-CHILD main phase results shows that the outcomes are generally consistent between adult and paediatric populations (**Table 23** and **Figure 19**).

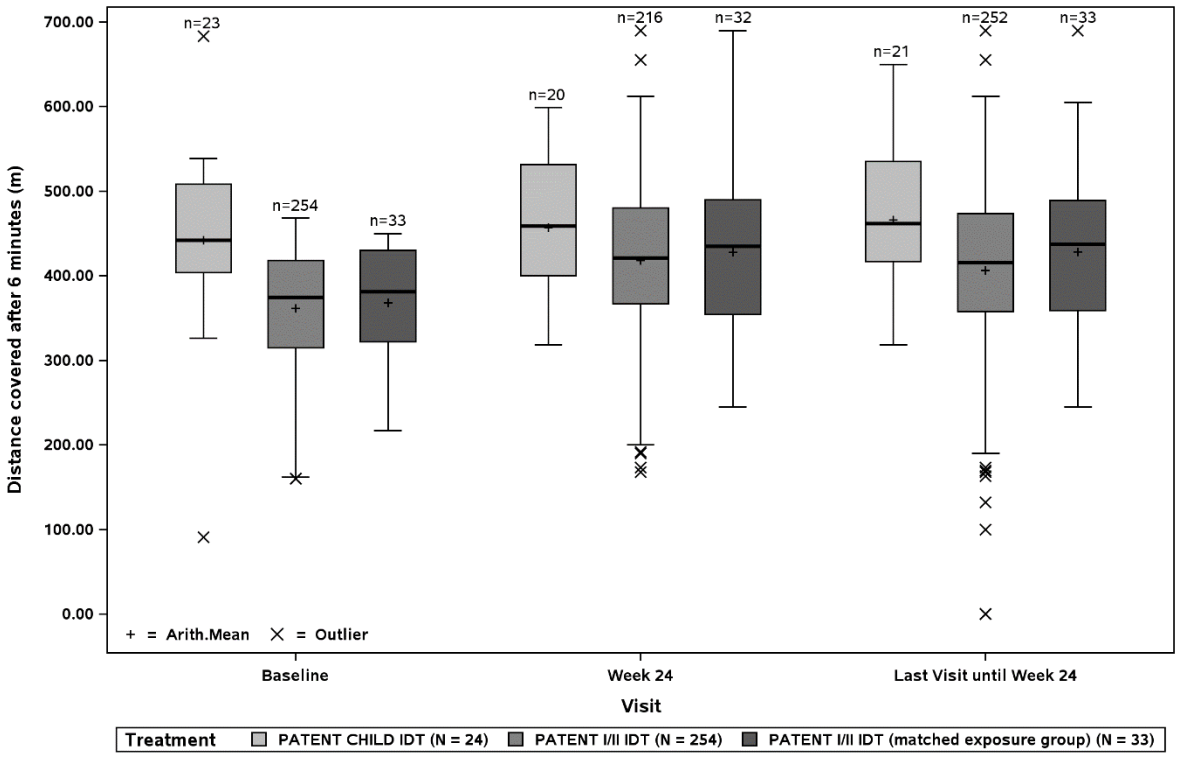
Table 22. Summary statistics of efficacy outcomes and change from baseline PATENT-CHILD and PATENT-1/-2 studies

	PATENT-CHILD Riociguat IDT N=24	Pool 1 Riociguat IDT N=254	Pool 1 (matched exposure group) N=33
6MWD (m)			
Baseline			
N	23	254	33
Mean (SD)	442.1 (109.7)	361.4 (67.7)	368.2 (72.8)
Median (Min to Max)	442.0 (91, 684)	374.5 (160, 468)	381.0 (217, 450)
Change from baseline at Week 24			
N	19	216	32
Mean (SD)	23.0 (68.8)	53.1 (60.0)	59.5 (74.5)
Median (Min to Max)	16.0 (–101, 200)	47.5 (–103, 309)	44.0 (–80, 309)
WHO FC			
Baseline			
N	24 (100.0%)	254 (100.0%)	33 (100.0%)
1	1 (4.2%)	5 (2.0%)	0
2	18 (75.0%)	108 (42.5%)	15 (45.5%)
3	5 (20.8%)	140 (55.1%)	18 (54.5%)
4	0	1 (0.4%)	0
Change from baseline at Week 24			
N	21 (100.0%)	221 (100.0%)	32 (100.0%)
-2	0	2 (0.9%)	1 (3.1%)
-1	0	72 (32.6%)	8 (25.0%)
0	21 (100.0%)	143 (64.7%)	22 (68.8%)
1	0	4 (1.8%)	1 (3.1%)
NT-proBNP (pg/mL)			
Baseline			
N	15	230	28
Mean (SD)	982.7 (1595.8)	1020.5 (1792.7)	387.3 (391.1)
Median (Min to Max)	202.0 (22, 4440)	389.5 (5, 17648)	241.2 (32, 1747)
Change from baseline at Week 24			
N	14	199	28
Mean (SD)	–65.8 (585.4)	–337.1 (1197.7)	–17.3 (433.9)
Median (Min to Max)	–12.1 (–1053, 1550)	–51.7 (–12024, 2772)	–35.6 (–703, 1844)

	PATENT-CHILD Riociguat IDT N=24	Pool 1 Riociguat IDT N=254	Pool 1 (matched exposure group) N=33
Clinical Worsening (CW)			
Number of subjects (%) with clinical worsening	2 (8.3%)	10 (3.9%)	0
PATENT-CHILD and PATENT-1/2			
Death (all cause mortality)	0	2 (0.8%)	0
PATENT-CHILD			
Hospitalization for right heart failure	2 (8.3%)	NA	NA
Lung transplantation	0	NA	NA
Pott's anastomosis and/or atrioseptostomy	0	NA	NA
Increase in WHO FC from baseline	0	NA	NA
Appearance/worsening symptoms of right heart failure and need for additional PAH therapy	0	NA	NA
PATENT-1/2			
Hospitalization due to pulmonary hypertension	NA	4 (1.6%)	0
Heart/Lung transplantation	NA	0	0
Atrial septostomy	NA	0	0
Persistent worsening of FC due to pulmonary hypertension	NA	1 (0.4%)	0
Start of new pulmonary hypertension treatment	NA	3 (1.2%)	0
Decrease in 6MWT due to pulmonary hypertension	NA	4 (1.6%)	0

Pool 1 = This pooled arm includes subjects initially randomized to riociguat IDT from PATENT-1 and PATENT-2.
Pool 1 (matched exposure group) = This pooled arm includes subjects initially randomized to riociguat IDT from PATENT-1 and PATENT-2 who had similar exposure to subjects in PATENT-CHILD.
Baseline = last observed value prior to start of study medication
Abbreviations: CI = confidence interval, NT-proBNP = N-terminal pro-brain natriuretic peptide, PVR = Pulmonary vascular resistance, QoL = quality of life, SD = standard deviation, WHO FC = Word Health Organization functional class, 6MWD = 6-minute walking distance, CW = clinical worsening, NA = not applicable

Figure 19. Box plot by visit - Distance covered after 6 minutes (m) (SAF)



6MWD

In Pool 1 and Pool 1 (matched exposure group), the mean 6MWD at baseline was 361.4 m and 368.2 m, respectively, and between baseline and Week 24, an improvement in 6MWD was seen with a mean change of 53.1 m (mean relative change: 15.3%) and 59.5 m (17.3%), respectively. Considering pre-treated adult subjects in Pool 1 and Pool 1 (matched exposure group) only, the mean 6MWD at baseline was slightly lower, with 353.0 m and 352.5 m, respectively. Between baseline and Week 24, an improvement in 6MWD was seen with a mean change of 53.5 m (mean relative change: 15.8%) and 57.8 m (18.3%), respectively. In the PATENT-CHILD study, the improvement in 6MWD at week 24 was 23.0 m.

Potential reasons for the observed lower magnitude of effect on 6MWD in the paediatric population may be related to i) higher mean 6MWD at baseline (442.1 m in PATENT-CHILD compared to 361.4 m and 368.2 m in PATENT-1 [Pool 1 and Pool 1-matched exposure group, respectively]), ii) a higher proportion of patients with WHO functional class II at baseline (75% in PATENT-CHILD compared to 42.5% and 45.5% in PATENT-1, respectively), and iii) a greater proportion of patients on background PAH medications at baseline (100% in PATENT-CHILD compared to 51.6% and 60.6% in PATENT-1, respectively). All these factors suggest the paediatric study population had a lower baseline risk for disease progression, which may have contributed to a lower potential for improvement and lower observed magnitude of effect on 6MWD with riociguat treatment.

Results of the post-hoc subgroup analyses by a low and high risk for progression based on 6MWD at baseline in pre-treated subjects are presented below:

- in the subgroup of subjects with a low-risk level (based on baseline 6MWD), similar mean 6MWD values at baseline and similar improvements of 6MWD at Week 24 were shown in the 3 groups (mean change of 23.2 m in the PATENT-CHILD riociguat IDT

group [n=20], 19.8 m in the Pool 1 [n=13] and 20.8 m Pool 1 (matched exposure group) [n=4]),

- in the subgroup of subjects with a high-risk level (based on baseline 6MWD), both the mean 6MWD at baseline and improvement of 6MWD at Week 24 were lower in the PATENT-CHILD riociguat IDT group (n=3) compared with the adult subjects in Pool 1 (n=118) and Pool 1 (matched exposure group) (n=16) (mean change of 21.5 m vs 57.4 m and 67.7 m, respectively).

NT-proBNP

In Pool 1 and Pool 1 (matched exposure group), the mean NT-proBNP at baseline was 1020.5 pg/mL (median 389.5 pg/mL) and 387.3 pg/mL (241.2 pg/mL), respectively, and between baseline and Week 24, an improvement in NT-proBNP was seen with a mean change of –337.1 pg/mL (median change –51.7 pg/mL) and –17.3 pg/mL (–35.6 pg/mL), respectively. In Pool 1, the median ratio to baseline at Week 24 was 0.71, and in Pool 1 (matched exposure group), it was 0.85. Similar mean change results were seen between baseline and last visit until Week 24 in Pool 1 and Pool 1 (matched exposure group) compared to those between baseline and Week 24. Considering pre-treated adult subjects in Pool 1 and Pool 1 (matched exposure group) only, the mean NT-proBNP at baseline was slightly lower, with 920.3 pg/mL and 367.2 pg/mL, respectively. Between baseline and Week 24, an improvement in NT-proBNP was seen with a mean change of –107.5 pg/mL and –37.9 pg/mL, translating in median ratios to baseline at Week 24 of 0.87 and 0.89, respectively. In the PATENT-CHILD riociguat IDT group, the mean NT-proBNP was 982.7 pg/mL, and the median was 202.0 pg/mL. Between baseline and Week 24, NT-proBNP improved with a mean change of –65.8 pg/mL and a median change of –12.1 pg/mL. As a result, the median ratio to baseline at Week 24 was 0.88.

Results of the post-hoc subgroup analyses by a low and high risk for progression based on 6MWD at baseline in pre-treated subjects are presented below:

- in the subgroup of subjects with a low-risk level (based on baseline 6MWD), the median NT-proBNP at baseline was higher in the PATENT-CHILD riociguat IDT group (n=20) compared with the adult subjects in Pool 1 (n=13) and Pool 1 (matched exposure group) (n=4). The improvement in NT-proBNP (negative median change) from baseline at Week 24 in the PATENT-CHILD riociguat IDT group was lower compared with the adult subjects in Pool 1 and higher compared with the adult subjects in Pool 1 (matched exposure group) (-12.1 pg/ml vs -32.9 pg/ml and 38.2 pg/ml, respectively),
- in the subgroup of subjects with a high-risk level (based on baseline 6MWD), the median NT-proBNP at baseline and improvement in NT-proBNP (negative median change) from baseline at Week 24 were both higher in the PATENT-CHILD riociguat IDT group (n=3) compared with the adult subjects in Pool 1 (n=118) and Pool 1 (matched exposure group) (n=16) (-435.0 pg/ml vs -8.5 pg/ml and -71.6 pg/ml, respectively).

Supportive study(ies)

Not applicable.

2.4.1. Discussion on clinical efficacy

Riociguat tablets were approved in the EU in 2014 for the treatment of adult patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). This application for Adempas (riociguat) is a Type II variation for adding an indication in paediatric patients aged 6 to less than 18 years with PAH.

The application is based on the results of the completed paediatric development program in line with the approved EU PIP, EMEA-000718-PIP01-09-M06 (PIP decision number P/0289/2016) and with the completed full compliance check (EMA/PDCO/533423/2020).

The totality of evidence included in this submission supporting the efficacy of riociguat for paediatric is based on the assumption that similar exposures and pharmacodynamic effects in children compared to adults will result in similar efficacy in children. In this context, a physiologically based pharmacokinetic (PBPK) modelling study (study 15463) has been conducted to predict the pharmacokinetic properties of riociguat in the paediatric population. The primary efficacy data obtained in the proposed target population, i.e. paediatric patients aged 6 -18 years old with PAH, is derived from the phase 3 open-label, individual dose titration study 15681 (PATENT-CHILD). The dosing regimens in the PATENT-CHILD were aimed at achieving systemic exposures in the range of that seen in adult PAH patients. Additionally, the MAH has conducted clinical comparisons in which paediatric data are displayed side-by-side with pooled data from the phase 3 studies in adults (PATENT-1/2).

Extrapolation plan

The extrapolation concept provided by the MAH is very sparse. According to the MAH several considerations justify the overall approach to extrapolate efficacy from adults, including the demonstration of the similarity of disease, the pharmacology of the drug and the response to therapy, as well as the safety of use in all the relevant populations. Although these considerations are generally in line with the reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018) and the draft ICH E11A guideline, the interpretation differs, particularly concerning similar responses to therapy.

Disease similarity

Regarding disease similarity, it is acknowledged that the pathophysiology of PAH is similar among children enrolled in PATENT-CHILD (6 to <18 years) and adults. Historically, the definition of PH in children has been the same as in adults, i.e. mPAP ≥25 mmHg and PVR ≥ 240 dys s cm^{-5} (3 Wood units. However, the distribution of PAH aetiologies in children is slightly different from that in adults, with a larger proportion of PAH associated with CHD in children, whereas in both populations, the majority of patients have IPAH.

Similar drug pharmacology.

The MAH argued that the hemodynamic mechanism of action of riociguat as an sGC stimulator is responsible for PAH efficacy and is expected to be similar in adults and children. Although this can be acknowledged, this does not automatically mean that there is similar drug pharmacology, which also refers to absorption, distribution, metabolism, and excretion (ADME) properties besides the mechanism of

action. For example, the mean exposure obtained in the paediatric population in the PATENT-CHILD Study was clearly lower than in adult PAH patients, i.e. towards the 25th percentile for all comparison groups. Furthermore, it was shown that for a major part of the paediatric subjects (9/24) dosed in the PATENT-CHILD Study 15681, clearance was higher than predicted from the PBPK model. This lower exposure in paediatric patients is only partially explained by the lower dose-equivalents for children in the maintenance phase of PATENT-CHILD than for the adult population and the presence of increased riociguat clearance in a part of the paediatric population. Nevertheless, the observed, and as yet unexplained, reduced exposure in the paediatric population as compared to adults does not appear to result in reduced efficacy when comparing the efficacy (6-minute walking distance) of the paediatric patients with that in adults and with the other paediatric patients. These findings are consistent with the corresponding PK/PD profiles in adult subjects with PAH, i.e. no clear relationship between changes in 6MWD and riociguat trough concentrations.

Similar exposure response

Similar exposure-response between the adult and paediatric population has not been demonstrated. In adult PH patients, there is a close and direct relationship between riociguat plasma concentrations and haemodynamic effects such as decrease in systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR), decrease in systolic blood pressure (SB) and increase in cardiac output (CO) after administration of a wide range of single doses (0.5 – 5 mg) or at steady state (1.0 – 2.5 mg TID). However, such a relationship between plasma concentrations and haemodynamic effects has not been demonstrated for the paediatric population since right heart catheterization (RHC) to assess such haemodynamic parameters was not performed in the paediatric subjects in the PATENT-CHILD study. Therefore, PK/PD relationships were investigated for 6MWD and NT-proBNP, a diagnostic biomarker for the presence of heart failure. However, no PK/PD relationship between riociguat exposure and 6MWD or NT-proBNP were observed in the adult and the paediatric population. The MAH argued that overall the PK/PD profiles for 6MWD and NT-proBNP in paediatric subjects are consistent with the corresponding PK/PD profiles observed in adult subjects and that the PK/PD relationships are considered similar. Nevertheless, in the PATENT-CHILD trial, there was a positive trend in improvement in exercise capacity (mean change of 23.01 m at week 24; see also below). Responder analyses showed that 9 of 19 subjects in PATIENT-CHILD (47.4%; 3 subjects ≥ 6 to 12 years and 6 subjects ≥12 to < 18 years) had an improvement by at least 20 m at week 24. To note, an improvement of 20 m is considered clinically relevant in adults. Therefore, the favourable trend can be considered of clinical relevance. Furthermore, differences in PK/PD responses between adults and paediatric subjects are not anticipated. Overall, the extrapolation of data is acceptable given the favourable trend in 6MWD in the direction of the adult population and the similar safety profiles between adults and the paediatric population.

Design and conduct of clinical study (PATENT-CHILD; study 15681)

The inclusion and exclusion criteria are appropriate to reflect paediatric patients with PAH. Key inclusion included paediatric subjects aged 6-18 years diagnosed with PAH (idiopathic PAH (IPAH), hereditable PAH (HPAH), PAH associated with connective tissue disease, or PAH associated with congenital heart disease), evidenced by a mPAP ≥ 25 mmHg, PAWP ≤15 mm Hg, and a PVR ≥ 240 dyn s cm^{-5} (3 Wood units) via RHC, and WHO FC I-III. Furthermore, eligible paediatric subjects had to be on the guideline-recommended standard of care PAH medication, i.e. endothelin receptor antagonist (ERA) and/or prostacyclin analogues (PCA), for at least 12 weeks prior to baseline visit. The key exclusion criterion of concomitant use of PDE5 inhibitors and non-specific PDE5 inhibitors (theophylline, dipyridamole), nitrates or NO donors is in line with the current contra-indications for riociguat based on adult data and, therefore appropriate. Furthermore, subjects were ineligible if they had an active state of hemoptysis or pulmonary

haemorrhage within 3 months prior to screening or systolic blood pressure (SBP) more than 5 mmHg lower than the age-, sex- and height-adapted level of the 50th SBP percentile.

The study design of PATENT-CHILD is appropriate to achieve the primary and secondary objectives of the study. The study consisted of two parts: 1) the main study part, which consisted of two phases, i.e. titration phase of up to 8 weeks and a maintenance phase of up to 16 weeks, and 2) a long-term extension (LTE) part until market approval or riociguat for the paediatric population or until a subject turns 18 years of age. All subjects received a body-weight-adjusted dose of riociguat to achieve a similar exposure as that observed in adults treated for PAH using the approved IR tablets (0.5, 1, 1.5, 2, 2.5 mg) for children with bodyweight ≥ 50kg or the new granules-for-oral-suspension (0.15 mg/mL) for children with bodyweight < 50 kg. The starting dose was the body weight-adjusted equivalent of the 1.0 mg dose in adults, and the dose could be up-titrated with 2 weeks intervals to a maximum of 2.5 mg equivalent TID based on systolic blood pressure and whether the participant showed signs of hypotension. Down-titration was permitted at all times for safety reasons. A follow-up period of 60 days (±8) after the last treatment dose can be considered appropriate for information on the safety of riociguat off-treatment.

The efficacy assessment was not the primary goal of this clinical study, but safety, tolerability and pharmacokinetics. The efficacy variables were evaluated as secondary endpoints of the main study part in an exploratory manner. Therefore, the study has only limited informative value regarding efficacy. Efficacy variables included change from baseline to end of treatment (Week 24) in 6MWD, WHO FC, NT-proBNP, quality of life (QoL) scores and time to clinical worsening (TTCW), which are in line with the paediatric addendum to the CHMP guideline (EMA 2012) and therefore acceptable. It is acknowledged that it is not feasible to perform statistically powered clinical studies for efficacy in children with PAH, as is done for adults since PAH is a rare disease in adults and has an even lower incidence in children. According to the guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (EMA/CHMP/213972/2010), for medicinal products where the benefit-risk profile is known in adult PAH, "*an extensive paediatric development is not foreseen as their efficacy and safety are already established in adult PAH. The main remaining issues in paediatric clinical development is defining the therapeutic dose, and short and long-term safety. Considering their mechanism of action, the primary endpoint for the dose-finding study should be haemodynamic parameters measured at 12 weeks*". According to the same guideline, invasive measurements are the only acceptable haemodynamic endpoints. In the PATENT-CHILD study, right heart catheterization (RCH) to assess and follow-up hemodynamic parameters were not indicated in the clinical study protocol as RHC is not recommended in paediatric studies due to the high rate of serious complications (Olliver et al. 2019). The role of non-invasive techniques such as echocardiography is less clear at present; nevertheless, such measurements are encouraged to complement understanding of the disease course and any treatment activity according to the guideline. In the paediatric study, echocardiographic parameters is included as the efficacy variable, which is considered appropriate. Nevertheless, the echocardiographic evaluations were sparse (see below).

The sample size was determined based on an accurate PK evaluation and the feasibility of the study in a reasonable time frame. Efficacy outcomes were evaluated in an exploratory manner. No statistical analyses were performed.

Efficacy data and additional analyses

The dosing regimens for both tablet and granules for oral suspension formulations were aimed at achieving systemic exposures in the range of that seen in adult PAH patients. Although, however, no indication is sought for patients < 50 kg treated with the granules for oral suspension formulation, data on experience with the granules-for-oral-suspension is considered supportive for review of experience with tablets and therefore included in the overall results, which is considered acceptable.

Twenty-four subjects (6 subjects in the ≥6 to <12 years old cohort and 18 subjects in the ≥12 to <18 years cohort) entered the study, of which 21 subjects (87.5%) completed the 24-week main treatment period and entered the LTE period. Three patients discontinued the main treatment period due to adverse events. At the cut-off date of 7 Jan 2022, 8 of the 21 subjects (33.3%) were still in the LTE part of the study. Of the total of 13 subjects who terminated the LTE part of the study, 5 subjects stopped as they reached the age of 18 years, and 8 subjects did not complete the LTE period with adverse events (n=3) and physician decision (n=3) as the most common reason.

Regarding formulations, 16 paediatric subjects started the study on suspension and 8 paediatric subjects started on riociguat tablets. Of the 16 on suspension, 6 switched to tablets at 24 weeks or later. Furthermore, at the end of the titration phase, the majority (16/22; 72.7%) were on the highest riociguat dose of 2.5 mg or the body-weight equivalent.

The proportion of subjects with important protocol deviations was relatively high (37.5% (n=9), however, these deviations were not considered to have an important effect on the outcome of the study since most of the deviations concerned written informed consent was signed after the study specific procedure (in/ex criteria not met) or omission of pregnancy testing (procedure deviations).

This study was a multicentre study (n=19) conducted worldwide, and half of the subjects were from Europe.

Regarding baseline data, the majority of the patients (n=18/24) were in the older ≥ 12 to < 18 years cohort, with the remainder (6/24) in the younger ≥6 to <12 years cohort (mean age: 12.8 years). In the younger cohort, all subjects had a body weight (BW) < 50 kg, whereas in the older cohort, 10 subjects had a BW ≥ 50 kg and 8 subjects a BW <50 kg. The aetiologies of PAH were idiopathic (n=18, 75.0%), PAH associated to congenital heart disease (repaired) (n=4, 16.7%), heritable (n=1, 4.2%), and pulmonary hypertension associated with developmental abnormalities (n=1, 4.2%). Only patients receiving stable doses of ERA (n=15, 62.5%) or ERA + PCA (n=9, 37.5%) were enrolled and continued their PAH treatment during the study. Furthermore, at baseline, the majority of patients were WHO functional class (FC) II (n=18, 75%); one patient (4.2%) was WHO FC I, and five patients (20.8%) were WHO FC III.

The PATENT-CHILD study showed favourable trends in the exploratory endpoints. Treatment with riociguat improved 6MWD with a mean change of 23.01 m at Week 24. An improvement in 6MWD was observed in both age cohorts, although the increase was larger in the younger age cohort compared with the older age cohort (46.40 m vs 14.66 m). Furthermore, an improvement in 6MWD was observed in the subgroup of subjects receiving ERA+PCA as concomitant PAH medications (62.31 m) but not in those receiving ERA only (-5.56 m). During the LTE part of the study, inconsistent results in 6MWD were observed with a change of 5.86 m (SD 44.56; n=16) at Month 6, -3.43 m (SD 74.77, n=12) at Month 12; 28.98 m (SD 66.71, n=9) at Month 18, and – 11.80 m (SD 35.40, n=4) at Month 24. However, the results should be interpreted cautiously due to the limited number of subjects and the high standard deviations. Responder analyses showed that 9 of 19 subjects in PATIENT-CHILD (47.4%; 3 subjects ≥ 6 to 12 years and 6 subjects ≥12 to < 18 years) had an improvement by at least 20 m at week 24 despite that all subjects were already on concomitant PAH medication. Even after one year of treatment still about half of the paediatric subjects had an improvement by ≥20 m. To note, an improvement of 20 m is considered clinically relevant in adults. Therefore, the favourable trend can be considered of clinical relevance.

Regarding NT-proBNP, an improvement with a mean change of –65.77 pg/mL and a median change of –12.05 pg/mL was observed between baseline and Week 24. An improvement in a median change in NT-proBNP was observed in the younger age cohort and the subgroup of subjects receiving ERA+ PCA but not in the older age group nor in the subgroup of ERA only. During the LTE part of the study, the mean changes from baseline for NT-proBNP -291.05 pg/mL (median 0.00; n=11) at Month 6, -222.78 pg/mL

(median -5.50, n=12) at Month 12; -283.40 pg/mL (median -8.00, n=9) at Month 18, and -270.93 pg/mL (median -243.00, n=4) at Month 24. Similar to 6MWD, the results should be interpreted with caution due to the limited number of subjects and the high standard deviations, which resulted in different trends in terms of means and medians. Nevertheless, responder analyses showed that 57.1% of the paediatric subjects had an improvement in NT-proBNP at week 24, which is considered clinically relevant although there was a high variety in effect size. These improvements were maintained up to 24 months.

Paediatric patients treated with riociguat showed no improvement in WHO FC, i.e. no subjects reported a change in WHO functional class between baseline and Week 24. Furthermore, there were 2 subjects with a TTCW event of hospitalization for right heart failure (both in the ≥12 to <18 years cohort). Between LTE start and data cut-off date, an additional 6 subjects of the older age cohort were reported with clinical worsening, including 3 events of hospitalization for right heart failure, 2 events of lung transplantation and 2 events of increase in WHO FC from baseline. Regarding quality of life (QoL), for SF-10 physical and psychosocial summary scores, an improvement with a mean change of 5.79 and 1.10 was observed at Week 24, respectively. For PedsQL total scale score, an improvement with a mean change of 3.49 was observed at Week 24. An improvement was also seen in the PedsQL physical health summary score (mean change of 4.28) and PedsQL psychosocial health summary score (mean change of 3.07) at Week 24.

Although trends of improvement were seen in single echocardiographic parameters such as right ventricular cardiac output (RV-CO; 16 participants), the PK/PD analysis revealed no significant correlation between change in echocardiographic parameters and riociguat exposure due to the limited number of subjects with echocardiographic measurements and the high standard deviation.

Comparison and integrated analyses of paediatric and adult data

The MAH has performed a side-by-side clinical comparison of the paediatric exploratory efficacy data from the main study part (first 24 weeks of treatment) in PATENT-CHILD with pooled data from the Phase 3 studies in adults (PATENT-1 and PATENT-2), within the first 24 weeks of treatment in order further to support the favourable efficacy results of the PATENT-CHILD study. Furthermore, as the study duration of PATENT-1 (12 weeks) was shorter than the duration of the main study part of PATENT-CHILD (24 weeks), data from subsequent treatment weeks from the open-label LTE study PATENT-2 were also taken into account up to a total of 24 weeks (referred to as "Pool 1" hereafter). Additionally, a "matched exposure" group from the PATENT-1/2 was selected, which showed individual PK exposure (AUC(0 8h)ss) similar to the observed individuals' PK exposure (AUC(0-8h)ss) in paediatric subjects regardless of their background therapy ((referred to as "Pool 1 [matched exposure group]" hereafter).

Regarding study participants, the adult and paediatric populations are generally comparable, with some differences. For example, PATENT-1 (and PATENT-2) included patients with symptomatic PAH and WHO FC II-III, either treatment-naïve or pre-treated with an ERA or a PCA, whereas the PATENT-CHILD study included patients with WHO FC I-III on the standard of care (including ERA+PCA or ERA only). The types of PAH in the children studied in PATENT-CHILD were consistent with those included in PATENT-1, namely IPAH, HPAH, and PAH associated to CHD repaired types. However, the majority of paediatric subjects were diagnosed with idiopathic PAH (75.0%), followed by CHD-associated PAH (16.7%), whereas in adults, the respective proportions were lower for idiopathic PAH (Pool 1: 58.7%; Pool 1 [matched exposure group]: 60.6%) and CHD-associated PAH (5.9% and 9.1%, respectively). PAH due to connective tissue disease was reported in 28.0% and 21.2% of adult subjects, respectively, but not in the paediatric population.

In Pool 1 and Pool 1 (matched exposure group), the improvement in mean 6MWD was 53.1 m and 59.5 m, respectively, while the improvement in mean 6MWD in the paediatric population was 23.0 m. The MAH argued that the lower effect size could be explained by the lower baseline risk in the paediatric patients because the paediatric patients had 1) a higher mean 6MWD at baseline (442.1 m in PATENT-CHILD compared to 361.4 m and 368.2 m in PATENT-1 [Pool 1 and Pool 1-matched exposure group, respectively]), 2) a higher proportion of patients with WHO functional class II at baseline (75% vs 42.5% and 45.5%, respectively), and 3) a greater proportion of patients on background PAH medications at baseline (100% vs to 51.6% and 60.6%, respectively). The latter argument does not hold since subgroup analyses of pre-treated adult subjects in Pool 1 and Pool 1 (matched exposure group) showed an approximately similar improvement in mean 6MWD of 53.5 m and 57.8 m, respectively. To further confirm that differences in baseline risk can explain the difference, the MAH conducted post-hoc subgroup analyses by low and high risk for progression based on 6MWD at baseline in pre-treated subjects. In the subgroup with a low risk level similar improvements of 6MWD at week 24 were observed (mean change of 23.2 m in the PATENT-CHILD riociguat IDT group (n=20) compared with 19.8 m in the Pool 1 (n=13) and 20.8 m Pool 1 (matched exposure group) (n=4), whereas in the subgroup of subjects with a high risk level the improvement of 6MWD in the paediatric population was lower compared with the adult population (mean change of 21.5 m (n=3) vs 57.4 m (n=118) and 67.7 m (n=16), respectively). Although the explanation can be followed, firm conclusions can not be made due to the limited sample size and the high variability (SD).

Regarding NT-proBNP, similar as observed with 6MWD, the median NT-proBNP at baseline was lower and the improvement in NT-proBNP at week 24 was lower in the paediatric group compared with Pool 1 and Pool 1 (matched exposure group) (median change of -12.1 pg/ml vs -51.7 pg/ml and -35.6 pg/ml, respectively). In addition, post-hoc subgroup analyses by a low and high risk for progression based on 6MWD showed inconsistent results in terms of NT-proBNP. Nevertheless, it must be pointed out that the standard deviations are very large and that the trends in mean and median are not comparable. Also, the comparisons in terms of WHO FC and TTCW are difficult to interpret due to the limited sample size.

Overall, the efficacy variables of PATENT-CHILD show a favourable trend in the direction of PATENT-1/-2. However, firm conclusions on a similar effect size in terms of 6MWD and NT-proBNP improvement achieved with a comparable riociguat exposure between the paediatric PAH population and the adult PAH population are difficult to made due to the limited sample size in the paediatric population, the fact that the paediatric patients appears at lower risk for progression at baseline and the high variability (SD) in efficacy outcomes.

2.4.2. Conclusions on the clinical efficacy

Although the efficacy outcomes of PATENT-CHILD show favourable trends which are consistent with the effects observed in the adult PATENT-1/-2 studies, these efficacy variables were only evaluated in an exploratory manner. As such, the MAH has included an extrapolation concept based on the principles of the EMA reflection paper on extrapolation (EMA 2018) and in the current draft ICH E11A guideline on paediatric extrapolation (EMA 2022). Although similar PK/PD relationships between the adult and paediatric population could not be demonstrated, given the favourable trend in 6MWD in the direction of the adult population and the similar safety profiles between adults and the paediatric population, extrapolation of data is considered valid.

2.5. Clinical safety

For the evaluation of safety, paediatric safety data from the main treatment phase (24 weeks of treatment) in the pivotal PATENT-CHILD study provides the most relevant data source for the use of

riociguat in children with PAH. The safety analysis set (SAF) included all randomized children who received at least one dose of study medication.

In Study 15681, all 24 children were included in the SAF. In addition, descriptive analyses of the PATENT-CHILD LTE phase based on the interim release date of the clinical database (cut-off date 07 JAN 2022) are provided. No integrated analysis of long-term safety data was performed.

The primary safety outcome of this pivotal study was the incidence of TEAEs and TESAEs as well as discontinuations from the study. Furthermore, the change from baseline to Week 24 in heart rate, blood pressure, x-ray of the left hand, and laboratory parameters were also assessed.

Patient exposure

In total, the mean (SD) treatment duration was 22.01 (6.44) weeks and the median duration was 24 weeks, ranging from 0.9 to 25.1 weeks (**Table 24**). The mean duration of treatment was higher in the ⩾ 12 to <18 subgroups (22.63 weeks), as compared with the ⩾6 to <12 group (20.14 weeks). Similarly, higher mean duration of treatment was observed in the ERA+PCA concomitant PAH medication subgroup (23.30 weeks) compared to the ERA only (21.24 weeks) subgroup.

Regarding cumulative treatment exposure, more than 90% of subjects received treatment for at least 16 weeks, corresponding to Visit 7. Treatment duration of at least 20 weeks was reported for about 87.5% of subjects. No notable differences were observed regarding treatment across age and concomitant PAH medication subgroups

Table 23. Treatment duration by age group and concomitant PAH medication (safety analysis set)

	Age group		Concomitant PAH medication		Total
	Riociguat ≥6 to <12 years N=6 (100%)	Riociguat ≥12 to <18 years N=18 (100%)	Riociguat ERA only N=15 (100%)	Riociguat ERA+PCA[a] N=9 (100%)	Riociguat N=24 (100%)
Titration phase (V1-V4): Duration of treatment (weeks)					
≤7	1 (16.7%)	1 (5.6%)	2 (13.3%)	0	2 (8.3%)
>7 - <9	5 (83.3%)	17 (94.4%)	13 (86.7%)	9 (100%)	22 (91.7%)
Maintenance phase (V5-V9): Duration of treatment (weeks)					
≤15	0	2 (11.1%)	0	2 (22.2%)	2 (8.3%)
>15 - <17	5 (83.3%)	13 (72.2%)	12 (80.0%)	6 (66.7%)	18 (75.0%)
≥17	0	2 (11.1%)	1 (6.7%)	1 (11.1%)	2 (8.3%)
Total (V1-V9): Duration of treatment (weeks)					
≤23	1 (16.7%)	2 (11.1%)	2 (13.3%)	1 (11.1%)	3 (12.5%)
>23 - <25	5 (83.3%)	15 (83.3%)	12 (80.0%)	8 (88.9%)	20 (83.3%)
≥25	0	1 (5.6%)	1 (6.7%)	0	1 (4.2%)
Total (V1-V9): Duration of treatment (weeks)					
n	6	18	15	9	24
n_{miss}	0	0	0	0	0
Mean	20.14	22.63	21.24	23.30	22.01
SD	9.45	5.30	8.00	2.04	6.44
Min	0.9	2.3	0.9	18.0	0.9
Q1	23.86	23.71	24.00	23.57	23.71
Median	23.93	24.07	24.14	23.86	24.00
Q3	24.14	24.43	24.43	24.00	24.36
Max	24.1	25.1	25.1	24.9	25.1

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings of the report.
Treatment duration = (date of last treatment – date of first treatment+1)/7 of each treatment phase
No subject received concomitatnt PAH medication PCA only.
"PCA" includes prostacyclin analogues and receptor agonists
ERA = endothelin receptor antagonists; Max = maximum; Min = minimum; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue; SD = standard deviation; V = visit

LTE phase

At the cut-off date of the LTE phase of PATENT-CHILD, the mean (SD) treatment duration was 109.79 (80.38) weeks, and the median duration was 114.64 weeks, ranging from 0.9 to 311.9 weeks. The median treatment duration was comparable between age groups, whereas it was considerably shorter in the subgroups of subjects pretreated with ERA and PCA compared with those pretreated with ERA only (54.29 vs 127.71 weeks).

Exposure to study drug

At the end of the 8-week titration phase (Visit 5), 16 (72.7%) subjects were on the highest riociguat dose of 2.5 mg or the body-weight equivalent, 1 (4.5%) subject each was on 2.0 mg, on 1.5 mg, and on 1.0 mg, and 3 (13.6%) subjects were on 0.5 mg or the respective body-weight equivalent.

General frequency of adverse events

During the main phase of Study 15681, treatment-emergent adverse events (TEAEs) were reported in 20/24 (83.3%) subjects, mostly of mild or moderate intensity (**Table 25**). The overall frequency of TEAEs ranged from 42.1% to 70.6% across the different equivalent doses. Overall, most of the TEAEs had outcomes reported as recovered/resolved (54.2%). TEAEs were reported as recovering/resolving, recovering/resolving with sequelae in 8.3% of subjects each, and not recovered/resolved in 12.5% of subjects.

TEAEs related to the study drug occurred in 7/24 (29.2%) subjects. The majority of them were mild and moderate intensity, with 1(4.2%) subject, in the riociguat group 1.0 mg dose group experiencing severe drug-related TEAE. The percentage of a subject with serious adverse events (SAEs) and TEAE leading to discontinuation of study treatment was 16.7% and 12.5%, respectively. TEAEs of special interest were reported for 4 (16.7%) of subjects. No deaths occurred in the study.

Table 24. Summary of number (%) of subjects with TEAEs by equivalent dose (safety analysis set)

Primary SOC PT	Riociguat 0.5 mg N=5 (100%)	Riociguat 1.0 mg N=24 (100%)	Riociguat 1.5 mg N=19 (100%)	Riociguat 2.0 mg N=17 (100%)	Riociguat 2.5 mg N=17 (100%)	Riociguat Total N=24 (100%)
Number (%) of subjects with at least one such AE						
Any TEAE	**3 (60.0%)**	**12 (50.0%)**	**8 (42.1%)**	**8 (47.1%)**	**12 (70.6%)**	**20 (83.3%)**
Any drug-related TEAE	1 (20.0%)	5 (20.8%)	0	1 (5.9%)	3 (17.6%)	7 (29.2%)
Any severe TEAE	0	1 (4.2%)	0	1 (5.9%)	0	2 (8.3%)
Any drug-related severe TEAE	0	1 (4.2%)	0	0	0	1 (4.2%)
Any serious TEAE	1 (20.0%)	2 (8.3%)	1 (5.3%)	1 (5.9%)	0	4 (16.7%)
Any drug-related serious TEAE	0	2 (8.3%)	0	0	0	2 (8.3%)
Any TEAE of special interest	1 (20.0%)	3 (12.5%)	0	1 (5.9%)	1 (5.9%)	4 (16.7%)
Any TEAE leading to discontinuation of study medication	1 (20.0%)	2 (8.3%)	0	0	0	3 (12.5%)
Any drug-related TEAE leading to discontinuation of study medication	1 (20.0%)	2 (8.3%)	0	0	0	3 (12.5%)
Any serious TEAE leading to discontinuation of study medication	0	2 (8.3%)	0	0	0	2 (8.3%)
Any TEAE leading to death	0	0	0	0	0	0

Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
AE = adverse event, N = number of subjects, PT = preferred term; SOC = system organ class;
TEAE = treatment-emergent adverse event

Common TEAEs

The most frequently reported TEAEs during the main treatment period by primary SOCs were infections and infestations (58.3%), nervous system disorders (33.3%), and general disorders and administration

site conditions (25%) (**Table 26**). The most frequently reported primary PTs were headache (29.2%), abdominal pain, nasopharyngitis and upper respiratory tract infection (16.7% each).

The most common TEAEs in total by preferred term were headache (29.2% of subjects), abdominal pain, nasopharyngitis and upper respiratory tract infection (16.7% each). The preferred term frequencies and the ranking of the most frequently preferred terms were generally comparable across equivalent treatment doses.

Table 25. Number (%) of subjects with TEAEs by equivalent dose, by SOC and PT

Primary SOC Preferred term	Riociguat 0.5 mg N=5 (100%)	Riociguat 1.0 mg N=24 (100%)	Riociguat 1.5 mg N=19 (100%)	Riociguat 2.0 mg N=17(100%)	Riociguat 2.5 mg N=17(100%)	Riociguat Total N=24 (100%)
Number (%) of subjects with at least one such AE	**3 (60.0%)**	**12 (50.0%)**	**8 (42.1%)**	**8 (47.1%)**	**12 (70.6%)**	**20 (83.3%)**
Cardiac disorders	**0**	**1 (4.2%)**	**0**	**1 (5.9%)**	**0**	**2 (8.3%)**
Right ventricular failure	0	1 (4.2%)	0	1 (5.9%)	0	2 (8.3%)
Gastrointestinal disorders	**0**	**1 (4.2%)**	**4 (21.1%)**	**2 (11.8%)**	**2 (11.8%)**	**4 (16.7%)**
Abdominal pain	0	1 (4.2%)	2 (10.5%)	1 (5.9%)	1 (5.9%)	4 (16.7%)
Diarrhoea	0	0	1 (5.3%)	0	1 (5.9%)	1 (4.2%)
Dyspepsia	0	0	1 (5.3%)	0	0	1 (4.2%)
Food poisoning	0	0	0	0	1 (5.9%)	1 (4.2%)

Nausea	0	0	0	1 (5.9%)	0	1 (4.2%)
Retching	0	0	0	1 (5.9%)	0	1 (4.2%)
General disorders and administration site conditions	**1 (20.0%)**	**3 (12.5%)**	**1 (5.3%)**	**0**	**2 (11.8%)**	**6 (25.0%)**
Asthenia	0	0	1 (5.3%)	0	0	1 (4.2%)
Chest pain	0	1 (4.2%)	0	0	0	1 (4.2%)
Fatigue	0	0	0	0	1 (5.9%)	1 (4.2%)
Injection site pain	0	0	0	0	1 (5.9%)	1 (4.2%)
Pyrexia	1 (20.0%)	2 (8.3%)	0	0	0	3 (12.5%)
Infections and infestations	**2 (40.0%)**	**3 (12.5%)**	**1 (5.3%)**	**4 (23.5%)**	**8 (47.1%)**	**14 (58.3%)**
Device related infection	0	1 (4.2%)	0	0	0	1 (4.2%)
Furuncle	0	0	0	0	1 (5.9%)	1 (4.2%)
Gastroenteritis	0	0	0	0	2 (11.8%)	2 (8.3%)
Infection	0	0	0	0	1 (5.9%)	1 (4.2%)
Nasopharyngitis	0	2 (8.3%)	0	1 (5.9%)	4 (23.5%)	4 (16.7%)
Pharyngitis	0	0	1 (5.3%)	0	0	1 (4.2%)
Pharyngotonsillitis	0	0	0	0	1 (5.9%)	1 (4.2%)
Pneumonia	0	0	0	1 (5.9%)	0	1 (4.2%)
Rhinitis	0	0	0	1 (5.9%)	0	1 (4.2%)
Upper respiratory tract infection	2 (40.0%)	0	0	1 (5.9%)	1 (5.9%)	4 (16.7%)
Vascular device infection	0	1 (4.2%)	0	0	0	1 (4.2%)
Investigations	**1 (20.0%)**	**2 (8.3%)**	**0**	**0**	**1 (5.9%)**	**2 (8.3%)**
Blood pressure systolic decreased	0	1 (4.2%)	0	0	1 (5.9%)	1 (4.2%)
Electrocardiogram QT prolonged	1 (20.0%)	1 (4.2%)	0	0	0	1 (4.2%)
Oxygen saturation decreased	0	0	0	0	1 (5.9%)	1 (4.2%)
Musculoskeletal and connective tissue disorders	**0**	**0**	**1 (5.3%)**	**0**	**0**	**1 (4.2%)**
Pain in extremity	0	0	1 (5.3%)	0	0	1 (4.2%)
Nervous system disorders	**0**	**7 (29.2%)**	**2 (10.5%)**	**1 (5.9%)**	**1 (5.9%)**	**8 (33.3%)**
Dizziness	0	2 (8.3%)	0	0	0	2 (8.3%)
Headache	0	6 (25.0%)	2 (10.5%)	1 (5.9%)	1 (5.9%)	7 (29.2%)
Presyncope	0	1 (4.2%)	0	0	0	1 (4.2%)
Psychiatric disorders	0	0	0	0	1 (5.9%)	1 (4.2%)
Insomnia	0	0	0	0	1 (5.9%)	1 (4.2%)
Respiratory, thoracic and mediastinal disorders	**1 (20.0%)**	**1 (4.2%)**	**2 (10.5%)**	**0**	**0**	**3 (12.5%)**
Asthma	1 (20.0%)	0	0	0	0	1 (4.2%)
Dyspnoea	0	0	1 (5.3%)	0	0	1 (4.2%)
Epistaxis	0	0	1 (5.3%)	0	0	1 (4.2%)

Haemoptysis	0	1 (4.2%)	0	0	0	1 (4.2%)
Skin and subcutaneous tissue disorders	**0**	**1 (4.2%)**	**1 (5.3%)**	**0**	**2 (11.8%)**	**3 (12.5%)**
Acne	0	0	0	0	1 (5.9%)	1 (4.2%)
Eczema	0	0	0	0	1 (5.9%)	1 (4.2%)
Pain of skin	0	1 (4.2%)	1 (5.3%)	0	0	1 (4.2%)
Skin swelling	0	0	1 (5.3%)	0	0	1 (4.2%)
Surgical and medical procedures	**0**	**0**	**1 (5.3%)**	**0**	**0**	**1 (4.2%)**
Tooth extraction	0	0	1 (5.3%)	0	0	1 (4.2%)
Vascular disorders	**1 (20.0%)**	**2 (8.3%)**	**0**	**1 (5.9%)**	**1 (5.9%)**	**3 (12.5%)**
Diastolic hypotension	1 (20.0%)	0	0	0	0	1 (4.2%)
Hypotension	1 (20.0%)	2 (8.3%)	0	1 (5.9%)	1 (5.9%)	3 (12.5%)

AE = adverse event, N = number of subjects, PT = preferred term; SOC = system organ class;
TEAE = treatment-emergent adverse event
Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
A subject is counted only once within each preferred term or any primary SOC.AEs are attributed to the most recently received dose at the date/time of AE onset. N represents all subject at risk for an adverse event in the respective equivalent dose group. A subject may be included in multiple equivalent dose groups, thus the N may not necessary sum up to Total

Treatment related TEAEs

At least one study drug-related TEAEs during the main treatment period occurred in 7/24 (29.2%) of subjects. The most common drug-related TEAEs in total by the preferred term was hypotension, reported for 3 subjects (12.5%). All other preferred terms (ie, "blood pressure systolic decreased", "diastolic hypotension", "headache", "presyncope", and "right ventricular failure") were reported for 1 subject (4.2%), each.

Adverse drug reactions

The most common adverse reaction related to riociguat reported in PATENT-CHILD during the first 24 weeks was hypotension (3/24 subjects [12.5%]). All other events (i.e., "blood pressure systolic decreased", "diastolic hypotension" , "headache", "insomnia", "presyncope", and "right ventricular failure") were reported by 1 subject (4.2%), each.

During the LTE phase, the events "vomiting", "pulmonary arterial hypertension" and "headache" were reported in one subject each.

Adverse drug reactions and events assessed as related to riociguat and reported in more than one subject were considered for inclusion in the ADR section of the label using the same Medical Term Groupings as for the initial submission. With the cut-off date 07 JAN 2022, there were 4/24 subjects reported with hypotension and 2/24 subjects reported with a headache were applied as done in the initial submission. With the cut-off date 07 JAN 2022, there were 4/24 subjects reported with hypotension and 2/24 subjects reported with a headache.

These safety data did not show an increase in ADR incidence and did not identify any new ADR.

LTE phase

As expected for a longer reporting period (median treatment duration 114.64 weeks [0.9 – 311.9]), higher frequencies of AEs were reported when including the optional LTE phase (95.8%) compared to the main phase (83.3%) of PATENT-CHILD. The most frequently reported TEAEs until the LTE cut-off by primary SOC were consistent with the main phase and there was no dose-related pattern of AEs. Of note,

the majority of drug-related TEAEs were already reported during the main phase. No deaths were reported in the LTE phase up to the cut-off date of 07 JAN 2022.

Serious adverse events, deaths, and other significant events

Serious adverse events

Serious TEAEs were reported for 4 (16.7%) subjects in total (**Table 27**). The most common serious TEAEs in total by preferred term were a right ventricular failure (reported for 2 [8.3%] subjects), asthma, the pain of skin, skin swelling, and hypotension (reported for 1 [4.2%] subject, each).

Drug-related serious TEAEs were reported for 2 (8.3%) subjects. The only two drug-related serious TEAEs reported were right ventricular failure and hypotension, reported for 1 (4.2%) subject each.

Table 26. Number (%) of subjects with TESAEs by equivalent dose (mg) by SOC and PT (safety analysis set)

Primary SOC PT	Riociguat 0.5 mg N=5 (100%)	Riociguat 1.0 mg N=24 (100%)	Riociguat 1.5 mg N=19 (100%)	Riociguat 2.0 mg N=17(100%)	Riociguat 2.5 mg N=17(100%)	Riociguat Total N=24 (100%)
Number (%) of subjects with at least one such AE	**1 (20.0%)**	**2 (8.3%)**	**1 (5.3%)**	**1 (5.9%)**	**0**	**4 (16.7%)**
Cardiac disorders	0	1 (4.2%)	0	1 (5.9%)	0	2 (8.3%)
Right ventricular failure	0	1 (4.2%)	0	1 (5.9%)	0	2 (8.3%)
Infections and infestations	0	1 (4.2%)	0	0	0	1 (4.2%)
Vascular device infection	0	1 (4.2%)	0	0	0	1 (4.2%)
Respiratory, thoracic and mediastinal disorders	1 (20.0%)	0	0	0	0	1 (4.2%)
Asthma	1 (20.0%)	0	0	0	0	1 (4.2%)
Skin and subcutaneous tissue disorders	0	1 (4.2%)	1 (5.3%)	0	0	1 (4.2%)
Pain of skin	0	1 (4.2%)	0	0	0	1 (4.2%)
Skin swelling	0	0	1 (5.3%)	0	0	1 (4.2%)
Vascular disorders	0	1 (4.2%)	0	0	0	1 (4.2%)
Hypotension	0	1 (4.2%)	0	0	0	1 (4.2%)

AE = adverse event, N = number of subjects, PT = preferred term; SOC = system organ class;
TESAE = treatment-emergent serious adverse event
Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
A subject is counted only once within each preferred term or any primary SOC.AEs are attributed to the most recently received dose at the date/time of AE onset. N represents all subject at risk for an adverse event in the respective equivalent dose group. A subject may be included in multiple equivalent dose groups, thus the N may not necessary sum up to Total.

Deaths

No deaths occurred in the study.

AEs of special interest

Overall, 4 (16.7%) subjects reported treatment-emergent AESI (**Table 28**). All treatment-emergent AESI were of moderate intensity and were all reported with an outcome as "recovered/resolved". Treatment-emergent AESI of "hypotension" was reported for 3 (12.5%) subjects. "Hemoptosis" was reported for 1

(4.2%) subject. No bone and/or growth anomalies were reported during the main treatment period of the study.

Discontinuation of study medication due to treatment-emergent AESIs was reported for 2 cases (1 case each of "symptomatic hypotension" and "hypotension"). A decrease in study medication dose was reported for one subject due to a treatment-emergent AESI of hypotension. No change of dose and/or discontinuation of study medication due to treatment-emergent AESIs was recorded for the other 2 subjects reporting hypotension and hemoptosis.

Table 27. Number (%) of subjects with TEAEs of special interest by equivalent dose (mg) by SOC an PT (safety analysis set)

SOC PT	Riociguat 0.5 mg N=5 (100%)	Riociguat 1.0 mg N=24 (100%)	Riociguat 1.5 mg N=19 (100%)	Riociguat 2.0 mg N=17 (100%)	Riociguat 2.5 mg N=17 (100%)	Riociguat Total N=24 (100%)
Number (%) of subjects with at least one such AE	**1 (20.0%)**	**3 (12.5%)**	**0**	**1 (5.9%)**	**1 (5.9%)**	**4 (16.7%)**
Respiratory, thoracic and mediastinal disorders	0	1 (4.2%)	0	0	0	1 (4.2%)
Haemoptysis	0	1 (4.2%)	0	0	0	1 (4.2%)
Vascular disorders	1 (20.0%)	2 (8.3%)	0	1 (5.9%)	1 (5.9%)	3 (12.5%)
Hypotension	1 (20.0%)	2 (8.3%)	0	1 (5.9%)	1 (5.9%)	3 (12.5%)

AE = adverse event, N = number of subjects, PT = preferred term; SOC = system organ class;
TEAEs = treatment-emergent adverse events.
Note: "Riociguat" corresponds to "BAY 63-2521" in the data tables and listings in Sections 14 and 16.2.
A subject is counted only once within each preferred term or any primary SOC.AEs are attributed to the most recently received dose at the date/time of AE onset. N represents all subject at risk for an adverse event in the respective equivalent dose group. A subject may be included in multiple equivalent dose groups, thus the N may not necessary sum up to Total

Bone age and bone morphology

At baseline, bone age considered by the specialist as "in accordance" with chronological age was reported for the majority (11 [52.4%]) of the subjects, followed by "advanced", reported for 9 (42.9%) subjects. Only in 1 (4.8%) subject was the bone age considered "delayed" compared to the chronological age.

At Week 24, bone age considered by the specialist "advanced", as compared to the chronological age, was reported for the majority (11 [52.4%]) of the subjects, followed by "in accordance", reported for 6 (28.6%) subjects, "delayed" reported for 3 (14.3%]) subjects, and "missing" reported for 1 (4.8%) subject. For this last subject, the reviewer specialist assessed the x-ray of the left hand as "not evaluable".

At baseline, bone morphology considered by the specialist as "normal", as compared to the chronological age, was reported for almost all (20 [95.2%]) subjects. Only for 1 (4.8%) subject, the bone morphology was reported as "missing" . For this last subject, the x-ray of left hand was assessed as "not evaluable" by the reviewer specialist. For none of the subjects, "abnormal" bone morphology was reported.

At Week 24, no changes in the analysis of bone morphology, as compared to baseline, were observed.

Until the LTE cut-off up to Month 54, bone age was reported for individual subjects only and assessed as either "in accordance" or "advanced" regarding chronological age. Bone morphology was reported for individual subjects only and always assessed as "normal".

In addition to the evaluation of x-rays, an overall assessment including height, weight and pubertal development using the Tanner scale was performed. These were reviewed on an ongoing basis by the DMC

No bone and/or growth anomalies were reported during the main treatment phase of the study.

Laboratory findings/vital signs

The mean and median changes in laboratory safety parameters between baseline and subsequent study visits were small and comparable across age and concomitant PAH medication subgroups. No clinically significant abnormalities of laboratory parameters were reported as adverse events. No clinically meaningful changes in SBP, DBP, heart rate, weight, or ECG parameters were identified.

Hematology

Treatment-emergent high values occurring in ≥15% of subjects were observed for hematocrit (17.4%), erythrocytes and monocytes (16.7%, each), and eosinophils (15.8%). Treatment-emergent low values occurring in ≥15% of subjects were observed for lymphocytes (16.7%).

Clinical chemistry

Treatment-emergent low and high values for any clinical chemistry parameters were reported for very few subjects (less than 15%).

Blood pressure

At baseline, the mean SBP was 112.9 mmHg (SD 10.9) and was higher in the subgroup of subjects of ≥12 to <18 years (115.3 mmHg, SD 10.9) compared with those of ≥6 to <12 years (105.5 mmHg, SD 6.9).

The mean change from baseline in SBP at Week 24 was –3.1 mmHg. While this decrease was pronounced in the ≥12 to <18 years subgroup (mean change: –6.2 mmHg at Week 24), an SBP increase was observed in the ≥6 to <12 years subgroup (mean change: 6.6 mmHg at Week 24). Decreases ranged from -9.3 to -2.1 in the ≥12 to <18 years subgroup. For this subgroup, the decrease in mean change from baseline for SBP was most pronounced at the 2-hour post-dose time point (-9.3 mmHg). Mean changes from baseline ranged from -1.0 to +6.6 in the ≥6 to <12 years subgroup. The mean change from a baseline of -1.0 occurred at the 2-hour post-dose time point.

Although a decrease was observed in the mean change from baseline in SBP in the ≥12 to <18 years subgroup, the mean SBP in this age group did not fall below 95 mmHg at any time point during the titration or maintenance phase. This is also the case for the ≥6 to <12 years subgroup, where mean SBP values were above 90 mmHg during the titration and maintenance phase. However, due to the small number of subjects in the 2 age subgroups, the results should be interpreted with caution.

Heart rate

In the total group, the overall mean baseline values for heart rate was 84.5 beats/minute (BPM). Higher baseline values were observed in the age ≥6 to <12 years subgroup (mean value: 91.7 BPM), compared to the ≥12 to <18 years subgroup (mean value: 82.2 BPM), which was consistent with the fact that heart rate decreases with age.

For heart rate, the overall mean increase from baseline to Week 24 was +4.1 BPM. Mean change from baseline ranged from -4.0 (at 4 hour post-dose) to +6.5 (Week 20). No notable differences were found between the age subgroups.

In vitro biomarker test for patient selection for safety

Safety in special populations

A summary of subjects with TEAEs stratified by age (≥6 to <12 years and ≥12 to <18 years) is shown for the paediatric population in PATENT-CHILD (**Table 29**). The small sample size of the 2 paediatric subgroups limits meaningful conclusions; therefore, the following results need to be interpreted with caution.

Overall, the safety profile of riociguat was generally comparable across the 2 age subgroups, with similar incidences of TEAEs, serious TEAEs and TEAEs of special interest, and TEAEs leading to discontinuation of study medication.

Table 28. Summary of number (%) of subjects with TEAEs stratified by age subgroups – PATENT-CHILD Study, (SAF)

	Age groups	
	Riociguat ≥6 to <12 years N=6 (100%)	**Riociguat ≥12 to <18 years N=18 (100%)**
Number (%) of subjects with at least one such AE		
Any TEAE	**5 (83.3%)**	**15 (83.3%)**
Any drug-related TEAE	2 (33.3%)	5 (27.8%)
Any severe TEAE	0	2 (11.1%)
Any drug-related severe TEAE	0	1 (5.6%)
Any TESAE	1 (16.7%)	3 (16.7%)
Any drug-related serious TEAE	1 (16.7%)	1 (5.6%)
Any TEAE of special interest	1 (16.7%)	3 (16.7%)
Any TEAE leading to discontinuation of study medication	1 (16.7%)	2 (11.1%)
Any TESAE leading to discontinuation of study medication	1 (16.7%)	1 (5.6%)
Any TEAE leading to death	0	0

AE= adverse events; TEAE= treatment emergent adverse events; TESAE= treatment emergent serious adverse events, SAF = safety analysis set

Discontinuation due to adverse events

TEAEs leading to discontinuation of study medication were reported for 3 (12.5%) subjects. The only two TEAEs reported were a right ventricular failure (1 [4.2%] subject) and hypotension (2 [8.3%] subjects).

Comparison and integrated analyses of paediatric and adult data

Paediatric data are displayed side-by-side with data from the pooled groups (Pool 1 and Pool 2, as described below) from the adult Phase 3 studies for the indications of PAH (PATENT-1) and CTEPH (CHEST-1), together with the LTE PATENT-2 and CHEST-2 studies, within the first 24 weeks of treatment, to allow clinical comparison. Adult data are considered supportive for the evaluation of paediatric safety data.

Statistical methods for the integrated analysis

As the study duration of the main study part of PATENT-CHILD (24 weeks) was longer than the duration of the PATENT-1 (12 weeks) and CHEST-1 (16 weeks), data from subsequent initial treatment weeks from the LTE study PATENT-2 and CHEST-2 were also taken into account up to a total of 24 weeks of observation in order to have a similar observation period of 24 weeks for the paediatric and adult population. Therefore, no statistical comparisons or conclusions were performed.

The following treatment labels were used in the side-by-side presentation of the adult data with the paediatric data:

- PATENT-CHILD IDT
- PATENT-1/2 IDT (referred to as "Pool 1" hereafter)
- PATENT/CHEST-1/2 (IDT, CD) (referred to as "Pool 2" hereafter)

General frequency of adverse events comparisons

In PATENT-CHILD, there was no dose-related pattern of AEs and any numerical differences seen between the different equivalent doses were not regarded as clinically relevant.

In the total paediatric population, the percentage of subjects experiencing TEAEs (83.3%) was numerically lower than those in the adult pooled groups (ranging 94.7% to 94.9%)(**Table 30**). Similarly, the percentage of subjects experiencing drug-related TEAEs (29.2%) was lower than those in the adult pooled groups (ranging 68.4% to 72%). The percentage of subjects experiencing TESAEs (16.7%) was rather comparable to the incidences of TESAEs in the adult pooled groups (ranging 19.3% to 22%).

Table 29. Summary of number (%) of subjects with TEAEs up to week 24 (+2 days), PATENT-CHILD Study, PATENT1/2 (Pool 1), and PATENT1/2 and CHEST ½ (Pool 2) (SAF)

	PATENT-CHILD Riociguat IDT N=24 (100%)	**Pool 1 Riociguat IDT N=254 (100%)**	**Pool 2 Riociguat IDT, CD N=490 (100%)**
	Paediatric population	*Adult population*	
Number (%) of subjects with at least one such AE			
Any TEAE	**20 (83.3%)**	**241 (94.9%)**	**464 (94.7%)**
Any drug-related TEAE	7 (29.2%)	183 (72.0%)	335 (68.4%)
Any severe TEAE	2 (8.3%)	48 (18.9%)	81 (16.5%)
Any drug-related severe TEAE	1 (4.2%)	19 (7.5%)	27 (5.5%)
Any serious TEAE	4 (16.7%)	49 (19.3%)	108 (22.0%)
Any drug-related serious TEAE	2 (8.3%)	12 (4.7%)	24 (4.9%)
Any TEAE of special interest	5 (20.8%)	44 (17.3%)	77 (15.7%)
Any TEAE leading to discontinuation of study medication	3 (12.5%)	19 (7.5%)	26 (5.3%)
Any serious TEAE leading to discontinuation of study medication	2 (8.3%)	9 (3.5%)	15 (3.1%)
Any TEAE leading to death	0	2 (0.8%)	6 (1.2%)

Pool 1 = This pool includes subjects valid for safety from PATENT-1 and PATENT-2 studies.

Pool 2 = This pool includes subjects receiving Riociguat IDT and CD, from PATENT-1; PATENT-2, CHEST-1 and CHEST-2 studies

AE= adverse events; CD = capped dose; IDT= individual dose titration;TEAE= treatment emergent adverse events

Common TEAEs comparisons

In PATENT-CHILD, 83.3% of subjects had TEAEs during the main treatment phase. Most frequently reported primary SOCs were infections and infestations (58.3%), nervous system disorders (33.3%), and general disorders and administration site conditions (25%)(**Table 31**). These incidences were generally lower or comparable with those observed in the adult pooled groups, with the exception of the SOC "infections and infestations", that was reported by a higher percentage of subjects in the paediatric population (58.3%) as compared to the adult pooled groups (ranging 47.6% to 48.4%).

In PATENT-CHILD, the most frequently reported primary PTs were headache (29.2%), abdominal pain, nasopharyngitis and upper respiratory tract infection (16.7% each). Most incidences on the PT level were lower or comparable with those observed in the adult pooled groups, with the exception of the PT "abdominal pain" and "upper respiratory tract infection", which was reported by a higher percentage of subjects in the paediatric population (16.7%) as compared to the adult pooled groups (upper respiratory tract infection: ranging 6.7% to 7.1%; abdominal pain: 3.5% to 4.3%).

Table 30. Summary of number (%) of subjects with TEAEs up to Week 24 (+2 days) by SOCs (>2% in any group). PATENT-CHILD Study, PATENT-1/2 (Pool 1), and PATENT-1/2 and CHEST-1/2 (Pool 2) (SAF)

Primary SOC	PATENT-CHILD Riociguat IDT N=24 (100%)	Pool 1 Riociguat IDT N=254 (100%)	Pool 2 Riociguat IDT, CD N=490 (100%)
	Paediatric population	Adult population	
Number (%) of subjects with at least one such AE	***20 (83.3%)***	***241 (94.9%)***	***464 (94.7%)***
Blood and lymphatic system disorders	0	35 (13.8)	50 (10.2%)
Cardiac disorders	2 (8.3%)	57 (22.4%)	101 (20.6)%
Eye disorders	0	24 (9.4%)	45 (9.2%)
Gastrointestinal disorders	4 (16.7%)	158 (62.2%)	291 (59.4%)
General disorders and administration site conditions	6 (25.0%)	121 (47.6%)	213 (43.5%)
Hepatobiliary disorders	0	7 (2.8%)	10 (2.0%)
Infections and infestations	14 (58.3%)	123 (48.4%)	233 (47.6%)
Injury, poisoning and procedural complication	0	22 (8.7%)	48 (9.8%)
Investigations	2 (8.3%)	53 (20.9%)	106 (21.6%)
Metabolism and nutrition disorders	0	33 (13%)	65 (13.3%)
Musculoskeletal and connective tissue disorders	1 (4.2%)	61 (24.0%)	120 (24.5%)
Nervous system disorders	8 (33.3%)	126 (49.6%)	261 (53.3%)
Psychiatric disorders	1 (4.2%)	21 (8.3%)	37 (7.6%)
Renal and urinary disorders	0	11 (4.3%)	23 (4.7%)
Reproductive system and breast disorders	0	7 (2.8%)	20 (4.1%)
Respiratory, thoracic and mediastinal disorders	3 (12.5%)	94 (37.0%)	177 (36.1%)
Surgical and medical procedures	1 (4.2%)	5 (2.0%)	7 (1.4%)
Skin and subcutaneous tissue disorders	3 (12.5%)	39 (15.4%)	76 (15.5%)
Vascular disorders	3 (12.5%)	54 (21.3%)	98 (20.0%)

Primary SOC	PATENT-CHILD Riociguat IDT N=24 (100%)	Pool 1 Riociguat IDT N=254 (100%)	Pool 2 Riociguat IDT, CD N=490 (100%)
	Paediatric population	Adult population	

Pool 1 = This pool includes subjects receiving riociguat IDT valid for safety from PATENT-1 and PATENT-2 studies.

Pool 2 = This pool includes subjects receiving riociguat IDT and CD, from PATENT-1; PATENT-2, CHEST-1 and CHEST-2 studies

AE= adverse events; CD = capped dose; IDT= individual dose titration;TEAE= treatment emergent adverse events, SOC = system organ class, SAF = safety analysis set

Serious adverse events and deaths, other significant events

Serious adverse events

In PATENT-CHILD, at least one TESAE was reported in 4/24 (16.7%) subjects after 24 weeks of treatment with riociguat. This rate was generally comparable with those observed across the adult pooled groups (ranging 19.3 to 22%).

The most frequently reported primary SOC for TESAEs in the paediatric population was cardiac disorders (in 2/24 [8.3%] subjects; (preferred term: right ventricular failure) except for the SOC "cardiac disorders", which was reported by a slightly higher percentage of subjects in the paediatric population (8.3%) as compared to the adult pooled groups (ranging 3.1% to 4.9%), incidences were generally comparable with those observed in the adult pooled groups.

In PATENT-CHILD, after 24 weeks of treatment with riociguat, 2 (8.3%) subjects reported one study of drug-related TESAE. One subject reported cardiac disorder (MedDRA SOC, PT: right ventricular failure), and 1 subject reported vascular disorders (MedDRA SOC, PT: hypotension).

Deaths

In PATENT-CHILD, no deaths were reported in the main and the LTE phase up to the cut-off date of 07 JAN 2022.

Across the pooled adult groups, after 24 weeks of treatment with riociguat, a low incidence of TEAEs with a fatal outcome (ranging 0.8% to 1.2%) was reported. Of the total number of deaths (N=6) reported, none were considered by the investigator to be study drug-related.

AEs of special interest

A total of 5 (20.8%) subjects reported treatment-emergent AESI in PATENT-CHILD (**Table 32**). Treatment-emergent AESI of "hypotension" was reported for 4 (16.7%) subjects. Of the 5 subjects in total who reported an event of hypotension, 2 experienced hypotension during the first dose titration step and were discontinued from the study. Of note, one of the 2 subjects reported echocardiography results which were indicative of progression of underlying disease and which confound the case. Of the remaining 3 subjects, one experienced hypotension during the titration phase. In conclusion, there are 2 unconfounded cases where hypotension occurred during titration, one during the first dose step (1.0 mg) and the second during the last dose step (2.5 mg). The totality of these cases (and cases overall) do not demonstrate that a higher dose leads to higher exposure which results in a clinically significant decrease of blood pressure.

"Hemoptysis" was reported for 1 (4.2%) subject. All treatment-emergent AESI were of moderate intensity and were all reported with an outcome as "recovered/resolved".

Across the pooled adult groups, a similar incidence of treatment-emergent AESIs (ranging 15.7% to 17.3%) was observed. Overall, "hypotension" was reported for 15 % subjects in the Pool 1 and 13.5% of subjects in Pool 2. "Hemoptysis" was reported for 2.8% subject in Pool 1 and 2.4 % of subjects in Pool 2

Table 31. Summary of number (%) of subjects with treatment emergent AESIs up to Week 24 (+2 days) by SOCs and Ptsin PATENT-CHILD Study, PATENT-1/2 (Pool 1), and PATENT-1/2 and CHEST-1/2 (Pool 2) (SAF)

	PATENT-CHILD Riociguat IDT N=24 (100%)	**Pool 1 Riociguat IDT N=254 (100%)**	**Pool 2 Riociguat IDT, CD N=490 (100%)**
	Paediatric population	Adult population	
Number (%) of subjects with ANY AESI	***5 (20.8%)***	***44 (17.3%)***	***77 (15.7%)***
Hypotension			
Number (%) of subjects with at least one such AE	**4 (16.7%)**	**38 (15.0%)**	**66 (13.5%)**
Investigations	**1 (4.2%)**	**3 (1.2%)**	**7 (1.4%)**
Blood pressure decrease	0	1 (0.4%)	5 (1.0%)
Blood pressure systolic decrease	1 (4.2%)	2 (0.8%)	2 (0.4%)
Vascular disorders	**3 (12.5%)**	**35 (13.8%)**	**59 (12.0%)**
Diastolic hypotention	1 (4.2%)	0	0
Hypotension	3 (12.5%)	34 (13.4%)	57 (11.6%)
Orthostatic hypotension	0	1 (0.4%)	2 (0.4%)
Respiratory tract bleeding events			
Number (%) of subjects with at least one such AE	**1 (4.2%)**	**7 (2.8%)**	**12 (2.4%)**
Respiratory, thoracic and mediastinal disorders	**1 (4.2%)**	**7 (2.8%)**	**12 (2.4%)**
Haemoptysis	1 (4.2%)	7 (2.8%)	12 (2.4%)

Pool 1 = This pool includes subjects receiving riociguat IDT valid for safety from PATENT-1 and PATENT-2 studies.

Pool 2 = This pool includes subjects receiving riociguat IDT and CD, from PATENT-1; PATENT-2, CHEST-1 and CHEST-2 studies

AE= adverse events; AESI = adverse events of special interest; CD = capped dose; IDT= individual dose titration; SOC= system organ class, SAF = safety analysis set

Discontinuation due to adverse events

Riociguat was well-tolerated in the paediatric population, with few (3 [12.5%]) subjects experiencing AEs that led to study drug discontinuation during the main phase of PATENT-CHILD. The reported SOCs were "vascular disorder" (preferred term: hypotension), reported for 2 (8.3%) subjects, and "cardiac disorders" (preferred term: right ventricular failure), reported for 1 (4.2%) subject. The most frequently reported TEAE resulting in discontinuation of the study drug (including the LTE phase) by primary SOC was vascular disorders (8.3%). The most frequently reported primary PT was hypotension (8.3%).

All TEAEs leading to study drug discontinuation were considered study drug-related by the investigator.

Across the pooled adult groups, a lower incidence of TEAEs (per SOC) leading to study drug discontinuation (ranging 5.3% to 7.5%) was observed, as compared to the paediatric population

2.5.1. Discussion on clinical safety

The evaluation of safety relies primarily on the extrapolation of the adult safety profile. Paediatric safety data from the main treatment phase (24 weeks of treatment, n=24) in the pivotal PATENT-CHILD study provide another data source for the use of riociguat in children with PAH. Finally, post marketing data are available from off-label use in the paediatric population. The approach to safety is acceptable.

Documented exposure for safety analysis is extremely limited (10.12 person-years), but acceptable in the context of the agreed PIP and the rarity of the condition.

Based on the limited data for all adverse events, the paediatric safety profile is considered consistent with the adult data.

Among the TESAE and AESI, **hypotension** stands out as possibly preventable. Hypotension is also often cited as a cause for treatment discontinuation. The SmPC recommends dose titration based on blood pressure.

Laboratory findings were not remarkable. Safety related to drug-drug interactions and other interactions is expected to be similar to safety in adults. The MAH's conclusion, that no new findings were identified in the post marketing data, is agreed.

2.5.2. Conclusions on clinical safety

Riociguat was well-tolerated in the paediatric population. All in all, tolerability can be considered similar to the adult population.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The PRAC considered that the risk management plan version 8.4 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.4 with the following content:

Safety concerns

Table 33: Summary of the Safety Concerns

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

Pharmacovigilance plan

III.1 Routine Pharmacovigilance activities

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: Bone safety in patients < 18 years old'

III.1.2 Other forms of routine pharmacovigilance activities

For each Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (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

The MAH has included information on PATENT CHILD Phase III Study – Long term Extension (SN 15681).

Table 34: On-going and planned additional pharmacovigilance activities

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Category 3: 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	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'	Ongoing	Six6 months after LPLV (EOS as per protocol)

Risk minimisation measures

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 35: Description of routine risk minimization measures by safety concern

Safety Concern	Routine Risk Minimisation 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

2.7. Update of the Product information

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

4.1 Therapeutic indications

Chronic thromboembolic pulmonary hypertension (CTEPH)

Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with
- inoperable CTEPH,
- persistent or recurrent CTEPH after surgical treatment,

to improve exercise capacity (see section 5.1).

Pulmonary arterial hypertension (PAH)

Adults
Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity.
Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease (see section 5.1).

Paediatrics
Adempas is indicated for the treatment of PAH in paediatric 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 (see section 5.1).

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Kerendia. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Paediatric PAH is a rare and complex condition associated with diverse cardiac, pulmonary, and systemic diseases, significant morbidity and mortality. It shares similarities with adult PAH, but there are important known differences in vascular function, fetal origins of disease, growth and development, genetics, natural history, underlying disease, responses of the right ventricle, responsiveness to PAH-specific therapies, and gaps in knowledge, particularly in the youngest age groups. Because of the limitations in conducting paediatric studies, therapeutic strategies used for adult PAH have not been studied sufficiently in children to allow the definition of potential toxicities or optimal dosing.

There is a high medical need for additional treatment options for PAH in light of the poor life expectancy and impact on the daily life of children and their relatives despite of available treatment options, and to provide treating physicians with suitable instructions and appropriate formulations for paediatric use.

3.1.2. Available therapies and unmet medical need

The most important PAH-specific therapies in adults include phosphodiesterase-5 (PDE5)-inhibitors, endothelin receptor antagonists (ERAs) and prostanoids. Two of these products have also been authorised for the paediatric population, PDE5i Revatio (sildenafil) and ERA Volibris (ambrisentan). Bosentan has dosing instructions for paediatrics but no indication. Use of other ERAs and prostanoids in the treatment of paediatric PAH is common but off-label.

The most current approach in the management of paediatric PAH promotes the identification of appropriate targets for goal-oriented therapy, also considering a risk stratification to determine the need for additional therapy.

To address this unmet medical need, the sponsor initiated a paediatric development program to make riociguat, an oral PAH and CTEPH treatment in adults, available for children with PAH.

3.1.3. Main clinical studies

The completed paediatric development program is in line with the approved EU PIP, EMEA-000718-PIP01-09-M06 (PIP decision number P/0289/2016) as also indicated by the completed full compliance check by the EMA (EMA/PDCO/533423/2020).

This submission is primarily based on an extrapolation exercise.

The MAH submitted one clinical study performed in children (Study 15681, PATENT-CHILD). PATENT-CHILD was a 24-participant trial in patients 6-<18 years, designed to evaluate PK, safety and tolerability with exploratory efficacy endpoints over a time period of 24 weeks. The riociguat dosing regimens used in the study were targeted to achieve systemic exposures similar to that observed in adults treated for PAH. This study included two dosing regimens: Children with body-weight ≥50 kg received riociguat tablets, while children with body weight <50 kg received a granules-for-oral-suspension to achieve bodyweight-adjusted dosing. Both dosing regimens were chosen to achieve exposure levels in the range seen in adults. Long-term data in children are also presented. The primary focus of this submission is the safety and efficacy of riociguat for the treatment of PAH to support the use of Adempas tablets in children aged 6 to <18 years with bodyweight ≥50 kg.

Because of the small study population and the similarities in exposure for children dosed with tablets and granules for oral suspension and the potential switch between formulations due to body weight changes, the data for this study are submitted, including children receiving both tablet and oral suspension formulations to support the evaluation.

3.2. Extrapolation of adult data

According to the Applicant, several considerations justify the overall approach to extrapolate efficacy from adults, including the demonstration of the similarity of disease, the pharmacology of the drug and the response to therapy, as well as the safety of use in all the relevant populations. Although these considerations are generally in line with the reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018) and the draft ICH E11A guideline, the interpretation differs in terms of similar responses to therapy.

Disease similarity

Regarding disease similarity, it is considered that the pathophysiology of PAH is similar among children enrolled in PATENT-CHILD (6 to <18 years) and adults. Historically, the definition of PH in children has been the same as in adults, i.e. mPAP ≥25 mmHg and PVR ≥ 240 dyn s cm-5 (3 Wood units). However, the distribution of PAH aetiologies in children is different from that in adults, with a larger proportion of PAH associated with CHD in children, whereas in both populations, the majority of patients have IPAH.

Similar drug pharmacology

The hemodynamic mechanism of action of riociguat as an sGC stimulator is responsible for PAH efficacy and is expected to be similar in adults and children. This does, however, not automatically mean that there is similar drug pharmacology, which also refers to absorption, distribution, metabolism, and excretion (ADME) properties besides mechanism of action. For example, the mean exposure obtained in the paediatric population in the PATENT-CHILD Study was clearly lower than in adult PAH patients, i.e. towards the 25th percentile for all comparison groups. Furthermore, it was shown that for a major part of the paediatric subjects (9/24) dosed in the PATENT-CHILD Study 15681, clearance was higher than predicted from the PBPK model. This lower exposure in paediatric patients is only partially explained by the lower dose-equivalents for children in the maintenance phase of PATENT-CHILD than for the adult population and the presence of increased riociguat clearance in a part of the paediatric population. However, lower exposure in the paediatric population does not lead to reduced efficacy in this population. These findings are consistent with the corresponding PK/PD profiles in adult subjects with PAH, i.e. no clear relationship between changes in 6MWD and riociguat trough concentrations.

Similar exposure response

Similar exposure-response between the adult and paediatric populations could not be demonstrated. In adult PH patients, there is a close and direct relationship between riociguat plasma concentrations and

haemodynamic effects such as decrease in systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR), decrease in systolic blood pressure (SB) and increase in cardiac output (CO) after administration of a wide range of single doses (0.5 – 5 mg) or at steady state (1.0 – 2.5 mg TID). However, such a relationship between plasma concentrations and haemodynamic effects has not been demonstrated for the paediatric population since right heart catheterization (RHC) to assess such haemodynamic parameters was not performed in the paediatric subjects in the PATENT-CHILD study and exposure-effect for blood pressure and echographic measurements were not reported. Therefore, PK/PD relationships were investigated for 6MWD and NT-proBNP. However, no PK/PD relationship between riociguat exposure and 6MWD or NT-proBNP were observed in the adult and the paediatric population.

Discussion and conclusion

According to the reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018) the primary focus will usually be to establish a line of reasoning about the relationship between dose, exposure, pharmacodynamic (PD) effects and clinical responses.

However, there is no proof that similar exposures result in similar pharmacodynamic effects. Moreover, in both adult and the paediatric population no PK/PD relationship was observed between riociguat exposure and 6MWD nor NT-proBNP. Furthermore, side-by-side clinical comparison of the paediatric exploratory efficacy data from the PATENT-CHILD study with pooled data from the Phase 3 studies in adults (PATENT-1 and PATENT-2), demonstrated that the efficacy outcomes of PATENT-CHILD show a favourable trend in the direction of PATENT-1/-2. However, firm conclusions on a similar effect size in terms of 6MWD and NT-proBNP improvement achieved with a comparable riociguat exposure between the paediatric PAH population and the adult PAH population are difficult to made due to the limited sample size in the paediatric population, the fact that the paediatric patients appear at lower risk for progression at baseline and the high variability (SD) in the key efficacy outcomes. Nevertheless, in the PATENT-CHILD trial there was a positive trend in improvement in exercise capacity (mean change of 23.01 m at week 24; see also below). Responder analyses showed that 9 of 19 subjects in PATIENT-CHILD (47.4%; 3 subjects ≥ 6 to 12 years and 6 subjects ≥12 to < 18 years) had an improvement by at least 20 m at week 24. To note, an improvement of 20 m is considered clinically relevant in adults. Therefore, the favourable trend can be considered of clinical relevance. Furthermore, differences in PK/PD responses between adults and paediatric subjects are not anticipated.

Overall, given the favourable trend in 6MWD in the direction of the adult population and the similar safety profiles between adults and the paediatric population, extrapolation of data is acceptable.

3.3. Favourable effects

No confirmatory evidence for efficacy has been submitted.

3.4. Uncertainties and limitations about favourable effects

The evaluation of efficacy is based on data obtained from the clinical program in the paediatric population, comprising data from the 24-week main phase of the pivotal Phase 3 study PATENT-CHILD (Study 15681), conducted in subjects ≥6 years to <18 years in the PAH indication. In this study, children with bodyweight ≥50 kg received riociguat tablets according to the dosing regimen approved for adults, while children with bodyweight <50 kg received a body weight-adjusted dose using granules for oral suspension. In both cases, these dosing regimens were aimed at achieving riociguat systemic exposures in the range of that seen in adults. Because of this and the small size of PATENT-CHILD, the data for PATENT-CHILD are presented in its totality to support the evaluation. The granules formulation has not yet been proposed for authorisation by the MAH.

Exploratory results for benefits

In PATENT-CHILD, exploratory efficacy evaluation was based on 6MWD, WHO FC, NT-proBNP, QoL and echocardiographic parameters at Week 24 compared to baseline and TTCW. In addition, subjects who required treatment with riociguat for more than 24 weeks were offered participation in the optional long-term extension part.

At baseline, as expected, the mean 6MWD was 442.12 m and was higher with increased age. The mean 6MWD at baseline was higher in the subgroup of subjects receiving ERA + PCA as concomitant PAH medications than those receiving ERA only as concomitant PAH medications.

In the overall population, between baseline and Week 24 (Visit 9), an improvement in 6MWD was seen with a mean change of 23.01 m. The positive mean change of 6MWD from baseline was also seen in the two age subgroups (<12/≥12 years) and the subgroup of subjects receiving ERA + PCA as concomitant PAH medications but not in those receiving ERA only as concomitant PAH medication. Responder analyses showed that 9 of 19 subjects in PATIENT-CHILD (47.4%; 3 subjects ≥ 6 to 12 years and 6 subjects ≥12 to < 18 years) had an improvement by at least 20 m at week 24.

The findings for NT-proBNP were consistent with 6MWD, namely that beneficial trends were observed. Such improvement trends were also seen in the SF 10 and Paediatric Quality of Life Inventory (PedsQL) scores.

Clinical worsening was observed in 2 (8.3%) subjects in total who were reported with hospitalization for right heart failure. Both subjects were in the subgroup of ≥ 12 to < 18 years, one subject was in the subgroup of receiving ERA only as concomitant PAH medication and one subject was in the subgroup of receiving ERA + PCA. Both patients had idiopathic PAH.

The majority of subjects (18 [75.0%]) had a WHO functional class of II at baseline. No changes in WHO functional class were seen between baseline and Week 24.

Right heart catheterization (RHC) was not indicated in the Clinical Study Protocol. Therefore, a PK/PD analysis for hemodynamic parameters, e.g. pulmonary vascular resistance (PVR), cardiac index, etc, was not applicable.

Although trends of improvement were seen in single echocardiographic parameters such as right ventricular cardiac output (RV-CO; 16 participants), the PK/PD analysis revealed no significant correlation between change in echocardiographic parameters and riociguat exposure due to the limited number of subjects with echocardiographic measurements and the high standard deviation

Overall, the improvements or maintenance of the riociguat treatment effect observed for paediatric subjects on-treatment with riociguat for up to 2 years were generally consistent with long-term effects in the adult population.

During the optional LTE phase, improvements or stabilization in 6MWD were maintained for eligible subjects on treatment with observed mean changes from baseline of +5.86 m (SD 44.56; n=16) at months 6, -3.43 m (SD 74.77, n=12) at Month 12; +28.98 m (SD 66.71, n=9) at Month 18 and -11.80 m (SD 35.40, n=4) at Month 24. Later visits only included data from 4 or fewer subjects.

A majority of subjects remained stable on treatment regarding WHO functional class II between baseline and Month 24. Another six subjects in the subgroup of ≥12 to <18 years experienced a clinical worsening: 2 subjects each following lung transplantation or due to deterioration of WHO FC and one subject each for hospitalization due to right heart failure or deterioration of PAH (worsening of cardiac catheterization parameters). No deaths occurred during the observation period.

Sample size

The sample size of PATENT-CHILD did not provide sufficient power for confirmatory analyses. This holds especially true when evaluating the results in the small subgroups of different disease etiologies (4 subjects diagnosed with congenital heart disease associated PAH after shunt closure (CHD-PAH) and 18 subjects with idiopathic PAH). Low subject numbers, are a known restriction for most paediatric development programs in PAH. The design of PATENT-CHILD was agreed to by the PDCO.

Efficacy in a pre-treated paediatric population

Potential reasons for the observed lower magnitude of effect on 6MWD in the paediatric population may be related to (1) higher mean 6MWD at baseline (442.1 m in PATENT-CHILD compared to 361.4 m and 368.2 m in adult trial PATENT-1 [Pool 1 and Pool 1-matched exposure group, respectively]), (2) a higher proportion of patients with WHO functional class II at baseline (75% in PATENT-CHILD compared to 42.5% and 45.5% in PATENT-1, respectively), and (3) a greater proportion of patients on background PAH medications at baseline (100% in PATENT-CHILD compared to 51.6% and 60.6% in PATENT-1, respectively).

3.5. Unfavourable effects

Hypotension is the most relevant associated risk due to riociguat's pharmacological properties and mode of action via vasodilation. This risk has been thoroughly characterized since the beginning of the riociguat development in adults.

The MoA of riociguat is the same in the adult and paediatric populations. Therefore, the observed AEs are mostly based on the MoA and are not age/ population specific.

The observed safety profile in the paediatric population (PATENT-CHILD) is consistent with what has been observed in adults and as described in the label.

In the PATENT-CHILD study, hypotension or diastolic hypotension was reported in 4/24 subjects (16.7%) during the main phase of the study. The applied systolic blood pressure monitoring during the titration phase allowed early identification of subjects susceptible to hypotension, and dose adjustments were made.

In an integrated analysis comparing PATENT-CHILD data to adult data, the incidence rate of hypotension in the paediatric population was comparable to that observed in the adult population: 16.7% (N = 24) and 13.5% (N = 490), respectively.

As expected for a longer reporting period, higher frequencies of drug-related TEAEs were reported when including the LTE phase (37.5%) compared to the main phase (29.2%) of PATENT-CHILD. The most common adverse reactions, including the long-term extension phase, were hypotension and headaches.

Based on the data of the paediatric subjects enrolled in PATENT-CHILD, the paediatric safety profile of riociguat was similar to adults, and riociguat administered as a tablet or oral suspension was well-tolerated.

No new safety findings were observed in the paediatric population.

3.6. Uncertainties and limitations about unfavourable effects

This open-label study introduced a treatment, riociguat, previously unknown to most investigators for children.

Open-label design

PATENT-CHILD was conducted with a single-treatment arm in an open-label fashion. An open-label design was agreed to with PDCO during the original PIP review. All participants used concomitant medication.

No data is available in children below 6 years of age

Due to the bone findings in juvenile rat studies, the study of riociguat use was waived in children below 6 years of age.

Bone effects

PATENT-CHILD was too short of concluding the potential bone effects of riociguat in patients 6-<18 years of age.

3.7. Effects Table

Table 32. Effects Table for Adempas in the paediatric population.

Effect	Short Description	Unit	Riociguat treatment N=24	Uncertainties/ Strength of evidence	References
Favourable Effects					
Physical capacity (6MWD)	Change from baseline to Week 24 (mean (SD))	m	23.01 (68.80)	**SoE:** favourable trend consistent with PATENT-1/2 study data in adults. **Unc**: - single arm open-label, only exploratory, descriptive statistics, limited sample size, high standard deviations for 6MWD and NT-proBNP, no clear treatment effect in patients treated with ERA only	PATENT-CHILD
WHO FC	Change from baseline to Week 24		All subjects remained stable in WHO FC compared to baseline		
NT-proBNP	Change from baseline to Week 24 (mean (SD))	pg/ml	-65.77 (585.41)		
TTCW	Number of subjects with CW	N (%)	2 (8.3%) (Hospitalization for right heart failure, both)		
Unfavourable Effects					
ADR	Hypotension	N (%)	3 (12.5%)	**SoE**: - no new safety signal identified - safety results consistent with the adult population **Unc**: - single arm open label - limited sample size	PATENT-CHILD
	Headache	N (%)	1 (4.2%)		
	Diastolic hypotension	N (%)	1 (4.2%)		

Abbreviations: TTCW: time to clinical worsening

3.8. Benefit-risk assessment and discussion

3.8.1. Importance of favourable and unfavourable effects

The extrapolation concept is considered sufficient despite the uncertainty regarding the principle of demonstration of similarity of exposure-response between the paediatric and adult populations. In the PATENT-CHILD trial there was a positive trend in improvement in exercise capacity (mean change of 23.01 m at week 24), which can be considered of clinical relevance, and favourable trends in the exploratory endpoints of, WHO FC, NT-proBNP, QoL and echocardiographic parameters; although, the sample size of this study did not provide sufficient power for confirmatory analyses. Overall, given the favourable trend in 6MWD in the direction of the adult population and the similar safety profiles between adults and the paediatric population, extrapolation of data is considered valid.

3.8.2. Balance of benefits and risks

The efficacy and safety profile of riociguat is well-established for adults, having been evaluated in placebo-controlled Phase 3 studies (PATENT 1 and CHEST 1) of more than 650 subjects. The proposed extension of indication is primarily based on extrapolation of the adult data. Riociguat's mechanism of action as sGC stimulator applies to the disease in adults and children. Also, disease aetiology differs between paediatrics and adults, although the types of PAH (IPAH and HPAH) in the paediatric population enrolled in PATENT-CHILD were consistent with those included in PATENT-1; in the paediatric population, a higher proportion of subjects with CHD-PAH was reported. The pathophysiological features of the types of PAH included may be similar in the adult and the paediatric population.

According to the guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (EMA/CHMP/213972/2010), for medicinal products where the benefit-risk profile is known in adult PAH, "*an extensive paediatric development is not foreseen as their efficacy and safety are already established in adult PAH. The main remaining issues in paediatric clinical development is defining the therapeutic dose, and short and long-term safety. Considering their mechanism of action, the primary endpoint for the dose-finding study should be haemodynamic parameters measured at 12 weeks*". According to the same guideline, invasive measurements are the only acceptable haemodynamic endpoints. However, right heart catheterization (RHC) was not indicated in the Clinical Study Protocol. This was consistent with RHC not being recommended in paediatric studies due to the high rate of serious complications (Ollivier et al. 2019), which is acknowledged. It has to be noted that the completed paediatric development program is in line with the approved EU PIP, EMEA-000718-PIP01-09-M06 (PIP decision number P/0289/2016) as also indicated by the completed full compliance check by the EMA (EMA/PDCO/533423/2020). Since hemodynamic parameters measured via RHC were not obtained in PATENT-CHILD, a PK/PD analysis for hemodynamic parameters, e.g. pulmonary vascular resistance (PVR), cardiac index, etc, was not applicable. Therefore, PK/PD relationships were investigated for the exercise capacity test 6-minute walking distance test (6MWD) and the biomarker NT-proBNP. However, in both adult and the paediatric population no PK/PD relationship was observed between riociguat exposure and 6MWD nor NT-proBNP.

Based on the efficacy results from PATENT-CHILD, such as 6MWD, WHO functional class, and NT-proBNP, only favourable trends were reported in paediatric subjects aged 6 to less than 18 years. Furthermore, due to the low sample size and the high variability, some effects are difficult to interpret. For example, in the overall population, between baseline and Week 24 (Visit 9), an improvement in 6MWD was seen with a mean change of 23.01 m. The positive mean change of 6MWD from baseline was also seen in the two

age subgroups (<12/≥12 years) and the subgroup of subjects receiving ERA + PCA as concomitant PAH medications but not in those receiving ERA only as concomitant PAH medication.

Available safety data show a similar profile as observed in the adult population, mostly attributed to the mode of action of riociguat or the underlying disease. Hypotension is the most common reaction, whereas blood pressure is also monitored for dose titration. No new safety concern was identified in the completed main part, and ongoing LTE part of PATENT-CHILD, and the currently available data do not indicate important differences in the safety profile with what has been observed in adults and as described in the approved Product Information.

3.9. Conclusions

The overall benefit /risk balance of Adempas in the paediatric population is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to add the treatment of PAH in paediatric 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 for ADEMPAS, based on results from pivotal study PATENT-CHILD (Study 15681); this is a Phase III, Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with PAH; As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.4 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric

Investigation Plan P/0289/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Adempas is not similar to Opsumit within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

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