25 April 2025
EMA/167451/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on Extension of marketing authorisation

Adempas

International non-proprietary name: Riociguat

Procedure No. EMEA/H/C/002737/X/0041

Note

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

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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. Submission of the dossier

Bayer AG submitted on 29 May 2024 extensions of the marketing authorisation concerning:

Extension application to introduce a new pharmaceutical form associated with a new strength (0.15 mg/ml granules for oral suspension) for the Pulmonary arterial hypertension (PAH) paediatric indication. As a consequence, update of the indication to include dosing in children with PAH aged 6 to less than 18 years with bodyweight < 50 kg. Furthermore, the film coated tablets presentations are updated to accommodate the new pharmaceutical form. In addition, contact details for local representatives of Belgium, Luxembourg, Greece and Ireland, have also been updated.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c), (d) Extensions of marketing authorisations.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision 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.

The PDCO issued an opinion on compliance for the PIP P/0289/2016.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

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 1. 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*
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	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).

1.6. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt Co-Rapporteur: N/A

The application was received by the EMA on	29 May 2024
The procedure started on	20 June 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 September 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	17 October 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	18 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	27 January 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 September 2024
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	27 February 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	26 March 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 April 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Adempas on	25 April 2025
The CHMP adopted a report on similarity of Adempas with Winrevair on (see Appendix on similarity)	25 April 2025

2. Scientific discussion

2.1. Problem statement

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

This application for Adempas (riociguat) is a line extension to add a new pharmaceutical form/strength, i.e. Adempas 0.15 mg/ml granules for oral suspension. Adempas tablets were previously approved to support dosing in children with PAH aged 6 to less than 18 years with bodyweight ⩾ 50 kg. Now with the introduction of the paediatric granules for oral suspension formulation, a change of the existing indication, ie dosing in children with PAH aged 6 to less than 18 years with bodyweight < 50 kg is proposed.

2.1.1. Disease or condition

PAH is a rare disease where pulmonary arterial pressure is elevated and can affect both adults and children.

2.1.2. 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).

2.1.3. 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.

2.1.4. Clinical presentation, diagnosis

Historically, the definition of PH in children has been the same as in adults, i.e. mPAP $\geqslant$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 <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).

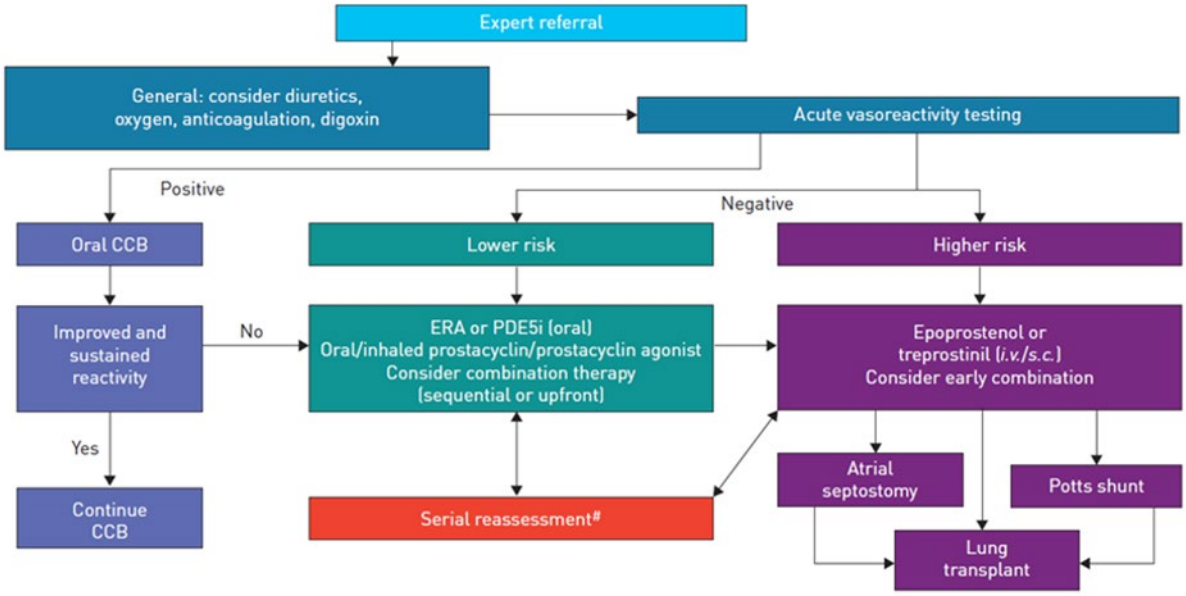
2.1.5. Management

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 product under review riociguat (Adempas), 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. 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.

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
Source: (Rosenzweig et al. 2019)

2.2. 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 is approved in the EU in 2014 for the treatment of adult patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). On 31 May 2023, the CHMP adopted a positive opinion on an extension of the indication to include treatment of PAH in paediatric patients aged 6 to less than 18 years with PAH with WHO FC II to II based on an extrapolation exercise and the results of the phase III study PATENT-CHILD (EMEA/H/C/002737/II/0037).

The **proposed** 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)

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 and body weight ≥ 50kg~~ with WHO Functional Class (FC) I to III in combination with endothelin receptor antagonists (see section 5.1).

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

Starting dose

The recommended starting dose is 1 mg 3 times daily for 2 weeks. Tablets should be taken 3 times daily approximately 6 to 8 hours apart (see section 5.2).

Titration

*Paediatric PAH patients ~~of~~ **aged** 6 to < 18 years ~~of age or older~~ **with body weight ≥ 50 kg***

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

Titration of riociguat dose is to be performed based on the patient's systolic blood pressure and general tolerability at the discretion of the treating physician/healthcare provider. **If the patient has no signs or symptoms of hypotension and systolic blood pressure is ⩾ 90 mmHg for the 6 to < 12 year age group or ⩾ 95 mmHg for the 12 to < 18 year age group, the dose should be increased in 2-week intervals by 0.5 mg 3 times daily to a maximum daily dose of 3 times 2.5 mg**. ~~If systolic blood pressure is ⩾ 90 mmHg for the 6 to < 12 years age group or ⩾ 95 mmHg for the 12 to < 18 years 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 3 times daily~~.

If systolic blood pressure falls below these specified levels the dosage should be maintained ~~provided~~ **as long as** the patient does not show any signs or symptoms of hypotension. If at any time during the up-titration phase systolic blood pressure decreases below the specified levels, ~~or~~**and** the patient shows signs ~~and~~**or** symptoms of hypotension the current dose should be decreased by 0.5 mg 3 times daily. ~~(See below for further information on other indications and other age groups)~~

Maintenance dose

The established individual dose should be maintained unless signs and symptoms of hypotension occur.

The maximum total daily dose is 7.5 mg (i.e., 2.5 mg 3 times daily) for adults and paediatric patients with body weight of at least 50 kg.

If a dose is missed, treatment should be continued with the next dose as planned. If not tolerated, dose reduction should be considered at any time.

The **proposed** indication for Adempas 0.15 mg/ml **granules** for oral suspension is as follows:

Adempas is indicated for the treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 6 to less than 18 years with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists (see section 5.1).

The **proposed** posology for the paediatric indication for Adempas 0.15 mg/ml granules for oral suspension is as follows:

Starting Dose

Paediatric PAH patients (aged 6 to less than 18 years, weighing less than 50 kg.)
Patients will start with a body weight-adjusted riociguat dose given as oral suspension to achieve systemic exposures equivalent to the starting dose in adults (1.0 mg 3 times daily in adults; see Table 1). The oral suspension should be taken 3 times daily approximately 6 to 8 hours apart with or without food. During therapy, the dosage is adjusted for body weight changes and according to the titration and maintenance scheme below.

Titration

Table 1: Body weight-adjusted Adempas dose for patients aged 6 to less than 18 years with a body weight less than 50 kg. Single dose (mL) to be given 3 times daily.

Body weight (kg)	Dose in special circumstances*	Starting dose	Dose after first increase	Dose after second increase	Dose after third increase (= Maximum dose)
	0.5 mg equivalent (mL)	1.0 mg equivalent (mL)	1.5 mg equivalent (mL)	2.0 mg equivalent (mL)	2.5 mg equivalent (mL)
12 kg to < 14 kg	1.0	1.8	2.6	3.4	4.2
14 kg to <16 kg	1.0	1.8	2.8	3.8	4.6
16 kg to <18 kg	1.0	2.0	3.2	4.2	5.0
18 kg to <20 kg	1.0	2.2	3.4	4.4	5.5
20 kg to <25 kg	1.2	2.6	3.8	5.0	6.5
25 kg to <30 kg	1.4	3.0	4.4	6.0	7.5
30 kg to <35 kg	1.8	3.4	5.0	6.5	8.5
35 kg to <40 kg	1.8	3.8	5.5	7.5	9.5
40 kg to <50 kg	2.2	4.4	6.5	9.0	11.0

- single dose (mL) to be given three times a day.

Titration scheme

Titration of riociguat dose is to be performed based on the patient's systolic blood pressure and general tolerability, at the discretion of the treating healthcare professional.

The dose should be increased by a body-weight adjusted equivalent to 0.5 mg 3 times daily for oral suspension every 2 weeks to a maximum dose, a body-weight adjusted equivalent to 2.5 mg 3 times daily, if the patient has no signs or symptoms of hypotension or if systolic blood pressure is

- ≥ 90 mmHg for the 6 to < 12 year age group

- ≥ 95 mmHg for the 12 to < 18 year age group.

If systolic blood pressure falls below these specified levels, the dosage should be maintained as long as the patient does not show any signs or symptoms of hypotension. If at any time during the up-titration phase systolic blood pressure decreases below the specified levels, or the patient shows signs or symptoms of hypotension, the current dose should be decreased stepwise by a body-weight adjusted equivalent to 0.5 mg 3 times daily.

Maintenance dose
The established individual dose should be maintained unless signs and symptoms of hypotension occur. The maximum dose depends on the body weight and is shown in Table 1.
If not tolerated, dose reduction should be considered at any time.

2.3. Type of Application and aspects on development

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. Due to delays in the technical transfer of the manufacturing of the granules formulation to a commercial manufacturing facility, the Applicant has decided to separate the submission of type II variation to add a paediatric indication to tablets (for children ≥50 kg) (previous type II application; EMEA/H/C/002737/II/0037) from that of the granules for oral suspension (for children < 50 kg) submission (current line extension application).

The extension of indication was 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).

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	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*
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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).

2.4. Quality aspects

2.4.1. Introduction

The finished product, subject of this line extension, is presented as granules for oral suspension containing 0.15 mg per ml of riociguat as active substance.

Other ingredients are: anhydrous citric acid (E330), strawberry flavour (consists of maltodextrin, propylene glycol (E1520), triethyl citrate (E1505), flavouring substances and flavouring preparation), hypromellose, mannitol (E421), microcrystalline cellulose and carmellose sodium, sodium benzoate (E211), sucralose (E955) and xanthan gum (E415).

The product is available in a brown glass bottle. The following medical devices are packed with the bottle of granules:
- one 100 mL water syringe (polypropylene), used to measure and add 200 mL of non-carbonated drinking water to the bottle containing riociguat 10.5 g granules (for single use only).
- one bottle adapter (polypropylene/polyethylene/silicone)
- two 5 mL graduated blue syringes (polypropylene) for oral dosing to extract and orally administer Adempas (1 is a spare syringe)
- two 10 mL blue syringes (polypropylene) for oral dosing

2.4.2. Active Substance

The active substance is riociguat. This is a line-extension of the already authorised product Adempas film-coated tablets, using the same active substance. The active substance part of the dossier remained unchanged.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

The finished product, subject of this line extension is Adempas 0.15 mg/mL granules for oral suspension. Before administration, the granules are reconstituted with 200 mL of non-carbonated drinking water into a homogenous suspension. containing 0.15 mg/mL of the active substance.

The finished product is supplied in a brown glass bottle of 250 ml, filled with 10.5 g ± 0.2 g white to off-white immediate release granules for oral suspension containing 0.3% of the active substance, equivalent to 31.5 mg of riociguat. The bottle is closed with a PP (Polypropylene) white opaque child resistant screw cap. The finished product is provided with a syringe (100 ml) for reconstitution and two different size syringes (5 and 10 ml; liquid dosing device) and a suitable adapter. Before administration, the granules are reconstituted with 200 mL of non-carbonated drinking water into a homogenous suspension containing. 0.15 mg/mL of the active substance.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. Standards. There are no novel excipients used in the finished product formulation. The list of excipients is also included in section 6.1 of the SmPC.

The aim of the development was to provide an easy to swallow oral liquid formulation for the paediatric patient population from 6 to 18 years, weighting less than 50 kg, allowing dosing calculated on the body weight.

A suspension was chosen based on the physico-chemical characteristics of the active substance. Riociguat is practically insoluble in water and neutral aqueous buffers, hence a suspension in acetate buffer (pH 4.5) was chosen, due to the decrease in solubility with increasing pH. Particle size and polymorphic form (thermodynamically stable modification I) are also controlled at the level of the active substance.

Pharmaceutical development of the finished product contains QbD (Quality by Design) elements.

The formulation development was mainly based on the established QTPP (Quality Target Product Profile)defined as: oral, immediate release form, suspendable, with patient acceptance (taste and texture) amongst other critical QTPPs.

The critical quality attributes (CQAs) identified were suspendability, blend uniformity of dosage units, pH, identity, microbial purity, stability, container closure system and dissolution, amongst others.

The selection of the excipients was made considering the pharmaceutical dosage form, the paediatric patients' acceptance and the preferred manufacturing method by fluid bed granulation.

The manufacturing development has been evaluated through the use of risk assessment and design of experiments to identify the critical process parameters. No design spaces were claimed for the manufacturing process of the finished product.

The applicant has developed the following dissolution method for QC testing: paddle apparatus (Ph. Eur., USP and JP), 50 rpm, 900 ml phosphate buffer (6.8). The method exhibits discriminatory power with respect to relevant critical quality attributes, e.g. particle size distribution (PSD) of the active substance. For the comparative dissolution, testing is performed using dissolution media with three different pH (1.2, 4.5 and 6.8) according to ICH M9. During the procedure, to address a MO raised by the CHMP, the dissolution limit was tightened, in line with batch data, from the initially proposed Q = 80% after 15 min to Q = 85%.

The batches used in the clinical studies were manufactured according to the proposed manufacturing process and composition; hence, they are representative for the commercial product. Dissolution results confirm that the dissolution of the clinical batches is comparable to the dissolution commercial batches ($f_2 \geq 50$).

During the procedure a MO was raised related to the suspendability of the granules as the Rapporteur had observed the formation of a cake and/or sediment upon reconstitution of placebo formulation samples following the instructions given in the PI. The cake/sediments would not dissolved after vigorous shacking. In response to the MO a thorough root cause analysis for the formation of the cake was provided, linking the cake/sediment formation to the fact that the samples were not transported in the dedicated carton box, which offers adequate protection against an increased compaction of the granules due to vibrational stress during transport. Additionally the applicant provided data demonstrating that pre-densified granules (subjected to additional vibrations) would suspend within a reasonable timeframe. As an additional measure, the instructions for use was updated to indicate how to handle the occurrence of potential sediment (cake) and clumps adequately. The preparation of the suspension has been clearly described in the instructions for use. Sufficient data has been provided showing that the suspension can be resuspended by shaking for 10 seconds before each administration. The shaking times indicated are longer than the required actual time to mitigate the risk of over- or underdosing due to the formation of cakes/sediments.

A human factor validation test was conducted to demonstrate that the liquid dosing devices can be used safely and effectively by healthcare professionals as well as patients/caregivers.

The primary packaging is brown glass bottle. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The child resistant closure is compliant with ISO 8317.

The following devices are supplied with the finished product:

- 100 ml syringe to be used to measure and add the required volume of 200 ml non-carbonated drinking water to the bottle containing the granules to prepare the suspension in the required concentration.
- Liquid Dosing Devices (LDD), i.e. 5 ml and 10 ml syringes. These syringes have a blue plunger and a red push-button that enables dose fixation. Once the volume is locked, it cannot be changed thus ensuring that always the same volume is withdrawn and administered. The LDD is only compatible with the provided bottle adapter. Dose accuracy studies have been performed with all syringes, meeting the requirement of Ph.Eur. 2.9.27.
- Bottle adapter with air venting and liquid stop fits in the glass bottle neck. The adapter is inserted after the addition of water to the granules. The adapter in combination with the LDD allows to withdraw the prescribed dose without spilling.

During the procedure, the CHMP raised a MO requesting the submission of valid CE certificate for the following co-packed medical devices: Adapter, 5 ml and 10 ml syringes. The MO was resolved with the provision of the valid CE certificates.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured by Patheon France, France. The main steps of the manufacturing process are: manufacturing of the granulation liquid, manufacturing of the premix, fluid bed granulation, drying, sieving and blending with citric acid anhydrous and xanthan gum. The bottles are closed with screw caps.
manufacturing process is adequate.

The manufacturing process have been validated by manufacturing four commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Fluid bed granulation, drying and filling and closure were identified as critical process steps. The in-process controls are adequate for this pharmaceutical form. No design space is claimed for the manufacturing process.

2.4.3.3. Product specification, analytical procedures, batch analysis

The finished product specification, presented in Table 4, includes tests for formulation (visual), colour (visual), suspendability (visual), appearance of solution (visual), colour of suspension (visual), pH-value of suspension (potentiometric, Ph. Eur.), identification riociguat (HPLC), identification sodium benzoate (HPLC), dissolution (HPLC), assay riociguat (HPLC), assay sodium benzoate (HPLC), degradation products (HPLC) and

microbiological quality (Ph. Eur.). The release and shelf-life requirements are identical. The specifications are considered acceptable.

During the procedure, to address a MO the dissolution limit was tightened from Q=80 to Q=85%, in line with batch data provided.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches by ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

Initially, the applicant performed confirmatory testing as a possible risk on the formation of two nitrosamines (compound 1 and 2)but did not provide an acceptable intake limits and this was raised as MO.

With the LoQ responses the applicant provided acceptable intakes for both nitrosamines were derived using the Carcinogenic Potency Categorisation Approach (CPCA) in line with the EMA guidance. The CPCA derived AI (Acceptable Intake) of 1500 ng/day (Potency Category 4) for compound 1 and AI of 100 ng/day (Potency Category 2) for compound 2 compound. The CPCA derived AIs are deemed acceptable. Omission of routine testing can be accepted as the levels of these nitrosamine impurities are found consistently below 10% of their acceptable intakes in the finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The reference standards are the same as used for the film-coated tablets. Information on the reference standard for sodium benzoate is adequate.

Batch analysis results are provided for three commercial batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

The claimed shelf-life for the product is 24 months when packed in brown glass bottle with white PP screw cap.

Stability data have been provided on three commercial scale batches (20 kg) stored at 25°C/60% RH (12 months), 30°C/75% RH (12 months) and 40°C/75% RH (6 months), with additional data from pilot and clinical batches stored at 25°C/60% RH (24 & 60 months), 30°C/75% RH (24 & 60 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were packed in the in the primary packaging proposed for marketing. The following parameters were investigated: appearance, suspendability, pH-value, dissolution, assay, degradation products and microbial purity.

The stability data show a slight increase in one of the impurities at all three storage conditions. No clear trends or changes are observed in the other tested parameters at all three storage conditions. All results were within the specification limits.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Based on the stability data, the claimed shelf-life is justified. Data have been provided to justify the in-use shelf life of 14 days at room temperature for the reconstituted suspension and this has been accepted.

Stress studies were performed exposing samples to of temperature, humidity, acidic and alkaline and oxidative stress. The test methods are stability indicating.

Based on available stability data, the proposed shelf-life of 24 months and "do not store above 30°C" and "do not freeze" as stated in the SmPC (section 6.3 and 6.4) are acceptable. Also the SmPC recommends to "store the reconstituted suspension upright".

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. During the procedure four major objections were raised related to the Risk Assessment on Nitrosamines, the dissolution method specification, the expired CE certificate for the medical devices and on the formation of a cake/sediment on placebo samples. All the issues have been adequately addressed.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

No new data on pharmacology.

2.5.3. Pharmacokinetics

No new data on pharmacokinetics.

2.5.4. Toxicology

2.5.4.1. Other toxicity studies

The Applicant submitted five new non-clinical toxicity studies, all covering impurities found in the newly formulated drug product and. There are two leachables identified related to the liquid dosing device and two impurities related to the new formulation of the drug product.

All leachables and impurities were first tested in silico by a rule-based (Derek Nexus) and statistical-based (Leadscope) QSAR model for alerts on potential genotoxicity. The QSARs were negative for both leachables , but was alerting for one of the impurities.

No further toxicological information is provided on the leachables. The maximum amount of drug product for the heaviest patients is 33 mL per day and the mean concentrations of the leachables are 360.3 ng/mL for one of the leachables and 41.03 ng/mL for the other, measured in the prepared product that was in the liquid dosing device for 10 minutes. The total intake of the leachables per day is therefore 12 ug for one of the leachables and 1.4 ug for the other, which is below the qualification threshold for non-genotoxic impurities.

For one impurity the QSAR overall call was positive for genotoxicity. An Ames test cannot be performed for this compound. Riociguat itself is not genotoxic. The positive alert for mutagenicity of the impurity is caused by the N-methylol structure present in the molecule. This structure alerts as a formaldehyde donor in Derek Nexus. The Applicant argues that this formaldehyde formation is the reason for the genotoxicity alert. Formaldehyde has a oral permitted daily exposure of 0.2 mg/kg/day based on non-carcinogenic endpoints according to the Applicant. In ICH M7 it is described that formaldehyde is an example of an impurity where the exposure from other sources such as food will be much higher and therefore the acceptable intake is higher than for other carcinogenic impurities. In Appendix 3 formaldehyde is listed with an acceptable intake of 10000 ug/day for all routes except inhalation. This impurity will be controlled at TTC-based acceptable intake levels (see Quality dossier).

According to the Applicant the QSARs for this compound were negative and based on the structure this is plausible. The molecule is almost similar to another molecule , except for the N-methylol group, that is missing from this structure. According to ICH guideline (Q3B) the qualification threshold for degradation products in new drug products is 1.0% or 50 µg total daily intake (TDI) for a maximum daily dose of the drug substance of < 10 mg. The maximum daily dose of riociguat suspension is 33 mL (three times 11.0 mL). This

corresponds to 4.95 mg riociguat drug substance. Therefore, the qualification threshold of a specified degradation product has been calculated with 50 µg/4.95 mg to 1.0%. However, the Applicant wants a threshold of 1.8% since a level of 1.2% was found in stability studies performed at the final commercial manufacturing site (see Quality dossier for details).

In order to justify this higher limit an in vitro bacterial mutagenicity, an in vitro micronucleus test and a 4-week repeat-dose toxicity study in rats were performed. All studies were performed under GLP.

In the Salmonella/microsome preincubation test (Ames test) concentrations up to 5000 ug per plate were used (precipitation above 1600 ug) on five Salmonella typhimurium LT2 mutants, comprising the histidineauxotrophic strains TA1535, TA100, TA1537, TA98 and TA102, both in the absence and the presence of metabolic activation. A positive control was included. Based on the results from this assay, it is concluded that the impurity iis non-mutagenic.

The potential of the impurity to induce structural chromosomal aberrations was tested in the in vitro mammalian cell micronucleus test with Chinese hamster V79 cells. Chinese hamster V79 cells were exposed in the absence and in the presence of metabolic activation (rat liver S9 mix) for 4 hours to concentrations of up to 40 µg/mL without and with S9 mix and for 24 hours without metabolic activation to concentrations of up to 40 µg/mL 4-amino-6-hydroxy-riociguat. Based on the results in this assay, 4-amino-6-hydroxy-riociguat is considered to be nonclastogenic for mammalian cells in vitro in the absence or presence of metabolic activation.

In the in vivo 4-week rat study, male and female rats were orally administered vehicle control article or 0.014 or 0.2 mg/kg/day of 4-amino-6-hydroxy riocibuat for four weeks once daily. The rats were randomly assigned to a control (vehicle) and two treatment groups consisting of 12 males and 12 females each. There were no adverse findings related to 4-amino-6-hydroxy riocibuat in any of the groups and the NOAEL was established at 0.2 mg/kg/day.

The Applicant applies a safety factor 10 for the conversion to humans, which would lead to an acceptable intake of 0.02 mg/kg/day. This additional safety factor of 10 was applied in the conversion from the NOAEL to account for inter- and intraspecies variability, although not strictly required. The maximum daily dose for paediatric patients is 0.16 mg/kg/day. If the drug product contains 1.8% impurity levels would lead to an intake of 0.003 mg/kg/day of 4-amino-6-hydroxy riocibuat per day.

2.5.5. Ecotoxicity/environmental risk assessment

The Applicant submits a calculation for a refined Fpen and a PECsw for the paediatric subpopulation, based on the number of children within the EU and the paediatric incidence of PAH. This results in a PECsw of 0.00934 ng/L, which is subsequently compared to the PECsw of 0.038 ug/L from the original Adempas dossier. This PECsw was determined for the treatment of PAH indicated for adults only.

PECsw calculation

The potential increase in environmental exposure was calculated considering the actual prevalence calculated from literature data and the EU population concerned. According to EUROSTAT (3) in 2023 the EU-27 countries total population was 448,753,823 inhabitants. In the relevant age group (6-18 years) for this extension application there are 69,807,398 inhabitants.

The estimated pediatric incidence of PAH is 0.5-2.2 cases per million children-years and the prevalence is 2-16 cases per million children, respectively (4)(5)(6). Considering 69,807,398 inhabitants in the group of 6-18 years and the prevalence for PAH of 2-16 cases per million this calculates as 140 to 1,117 children affected by the disease.

Based on this data the refined FPEN taking account of prevalence was calculated as 3.11x10-7 to 2.49x10-6.

$$F_{PEN} = \frac{Prevalence\ EU}{inhabitants\ EU}$$

The refined PECSW for this line extension was calculated considering the higher value of the range for the refined FPEN as 0.00000934 = 0.00934 ng/L.

$$PEC_{SW} = \frac{DOSE_{ai} \times F_{PEN}}{WASTEW_{inhab} \times D \times 100}$$

where

DOSEai = Maximum daily dose of active ingredient (7.5 mg)

FPEN = Percentage of market penetration (refined FPEN range reported above)

WASTEWinhab = Volume of wastewater per capita and day (200 L x inh-1 x d-1)

D =Factor for dilution of wastewater by surface water flow (default factor: 10)

This original PECsw (0.038) was calculated with using a non-refined (default) Fpen of 0.01, and triggered a phase II ERA. The conclusions of all the Phase I and Phase II studies are displayed in the ERA summary table as presented in the Adempas EPAR. Since the Applicant used the default Fpen for PAH in adults at MAA, the current paediatric PAH indication can considered to be included in the previous ERA assessment and therefore not requiring a new ERA assessment. In this previous phase II assessment one study in fish (OECD 210) was not accepted by the regulators and a new study was warranted. This study, however, could not be identified in the dossier. After a refined Fpen for the ERA was used based on the adult prevalence data used for the application for orphan designation, the PECsw was calculated to be 0.075 ng/L, which is below the action limit for phase II.

The Applicant did not provide a phase II fish study in this procedure and opted to recalculate the PECsw based on refined Fpen values for both the adult and paediatric indication. The Applicant used a PAH prevalence in children of $3.11*10^{-6}$. For adults a prevalence of $3.80*10^{-5}$ was applied, resulting in a combined Fpen of $4.11*10^{-5}$. The resulting PECsw was calculated to be 0.000154 µg/L. Phase II ERA studies are therefore no longer required and the Applicant submitted an updated ERA table without the phase II data.

Table 3 ERA table (summary of main studies)

Substance (INN/Invented Name): riociguat			
CAS-number (if available): 625115-55-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	EU test method A.8 (Shake-flask method)	log K_{ow} 1.77 at pH 4 log K_{ow} 2.37 at pH 7 log K_{ow} 2.30 at pH 9	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000154	µg/L	> 0.01 threshold (N)

2.5.6. Discussion on non-clinical aspects

The Applicant submitted five new non-clinical toxicity studies, all covering impurities found in the newly formulated drug product and. There are two leachables identified (methyl benzoate and oleamide) related to the liquid dosing device and two impurities (riociguat hemiaminal and 4-amino-6-hydroxy-riociguat) related to the new formulation of the drug product.

No further toxicological information is provided on the leachables, other than the QSARs that predict they are non-genotoxic. The total intake of the leachables per day is therefore 12 ug for methyl benzoate and 1.4 ug for oleamide, which is below the qualification threshold for non-genotoxic impurities.

For impurity riocibuat-hemiaminal the QSAR overall call was positive for genotoxicity. This impurity will be controlled at TTC-based acceptable intake levels (see Quality dossier).

For the impurity 4-amino-6-hydroxy riocibuat the QSAR data indicate the impurity is non-genotoxic. The molecule is almost similar to riocibuat-hemiminal, except for the genotoxic N-methylol group, that is missing from this structure. According to ICH guideline (Q3B) the qualification threshold for degradation products in new drug products is 1.0% or 50 µg total daily intake (TDI) for a maximum daily dose of the drug substance of < 10 mg. The Applicant wants a threshold of 1.8% since a level of 1.2% was found in stability studies performed at the final commercial manufacturing site (see Quality dossier for details).

In order to justify this higher limit an *in vitro* bacterial mutagenicity, an in vitro micronucleus test and a 4-week repeat-dose toxicity study in rats were performed. All studies were performed under GLP. Based on the results from the bacterial mutagenicity assay, it is concluded 4-amino-6-hydroxy riocibuat is non-mutagenic. The results from the *in vitro* micronucleus test reveal that 4-amino-6-hydroxy-riociguat is considered to be non-clastogenic for mammalian cells in the absence or presence of metabolic activation.There were no adverse findings related to 4-amino-6-hydroxy riocibuat in any of the groups in the 4-week rat study and the NOAEL was established at 0.2 mg/kg/day.

The Applicant applies a safety factor 10 for the conversion to humans, which would lead to an acceptable intake of 0.02 mg/kg/day. The maximum daily dose for paediatric patients is 0.16 mg/kg/day. If the drug product contains 1.8% impurity levels would lead to an intake of 0.003 mg/kg/day of 4-amino-6-hydroxy riocibuat per day. Overall, however, the limit of 1.8% appears to be acceptable from a toxicological point of view.

For the ERA assessment, the Applicant submitted a calculation for a refined Fpen and a PECsw for the paediatric subpopulation, based on the number of children within the EU and the paediatric incidence of PAH. This results in a PECsw of 0.00934 ng/L, which is subsequently compared to the PECsw of 0.038 ug/L from the original Adempas dossier. This PECsw was determined for the treatment of PAH indicated for adults only.

This original PECsw (0.038) was calculated with using a non-refined (default) Fpen of 0.01, and triggered a phase II ERA. The conclusions of all the Phase I and Phase II studies are displayed in the ERA summary table as presented in the Adempas EPAR. Since the Applicant used the default Fpen for PAH in adults at MAA, the current paediatric PAH indication can considered to be included in the previous ERA assessment and therefore not requiring a new ERA assessment. In this previous phase II assessment one study in fish (OECD 210) was not accepted by the regulators and a new study was warranted. This study, however, could not be identified in the dossier. After a refined Fpen for the ERA was used based on the adult prevalence data used for the application for orphan designation, the PECsw was calculated to be 0.075 ng/L, which is below the action limit for phase II.

The Applicant did not provide a new phase II fish study in this procedure and opted to recalculate the PECsw based on refined Fpen values for both the adult and paediatric indication. The Applicant used a PAH prevalence in children of $3.11*10^{-6}$. For adults a prevalence of $3.80*10^{-5}$ was applied, resulting in a combined Fpen of $4.11*10^{-5}$. The resulting PECsw was calculated to be 0.000154 µg/L. Phase II ERA studies are therefore no longer required and the Applicant submitted an updated ERA table, without the phase II data.

2.5.7. Conclusion on the non-clinical aspects

Considering the above data, Riociguat is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Clinical pharmacology

No new clinical data have been provided for this application. The application introduces a new formulation i.e. granules for oral suspension and with this new formulation, the indication can be extended to paediatric patients of 6 years and older without a bodyweight restriction. The paediatric indication has been approved in 2023 in procedure EMEA/H/C/002737/II/0037. An oral suspension had been used in the pivotal paediatric PATENT-CHILD study in paediatric patients weighing < 50 kg in that procedure. However, the granules for suspension were not available for commercial purposes at that time.

The use of oral suspension in procedure EMEA/H/C/002737/II/0037 was further supported by study 14986 comparing bioavailability of the suspension with the immediate release tablets and with a food effect study 15463. Comparable bioavailability of riociguat and M-1 in terms of AUC and Cmax was demonstrated

between the oral suspension suspensions and the immediate-release tablet. Therefore, using the oral suspension or the tablet at the same dose is expected to yield comparable exposure. In addition, the food effect observed for the 0.15 mg/mL paediatric suspension was comparable to results reported for the currently registered immediate release tablet. Both the tablet as the suspension can be given regardless of food.

The newly developed commercial presentation of riociguat granules-0.3%-for-oral-suspension is a non-integral drug-device combination kit. There are slight differences in the devices proposed for the commercial kit compared to that used in the PATENT-CHILD study. However, these changes do not result in clinically relevant differences in dosing (see quality assessment for the assessment of the proposed commercial LDD/syringe).

2.6.2. Conclusions on clinical pharmacology

In conclusion, with application of this new formulation granules for oral suspension, the modification of the indication

"Paediatrics

Adempas is indicated for the treatment of PAH in paediatric patients aged 6 to 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)."

is acceptable. Also the modifications in section 4.2 and 5.2 regarding dosing in paediatric patients weighing < 50 kg and statements on exchangeability of the oral suspension and the immediate release tablets are acceptable.

2.6.3. Clinical efficacy

Adempas is approved in the EU in 2014 for the treatment of adult patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). On 31 May 2023, the CHMP adopted a positive opinion on an extension of the indication to include treatment of PAH in paediatric patients aged 6 to less than 18 years with PAH with WHO FC II to II based on an extrapolation exercise and the results of the phase III study PATENT-CHILD (EMEA/H/C/002737/II/0037).

This application for Adempas (riociguat) is a line extension to add a new pharmaceutical form/strength, i.e. Adempas 0.15 mg/ml granules for oral suspension and with this new formulation, the indication can be extended to paediatric patients of 6 years and older without a bodyweight restriction: Adempas tablets were previously approved to support dosing in children with PAH aged less than 18 years with bodyweight ⩾ 50 kg. Now with the introduction of the pediatric granules for oral suspension formulation dosing in children with PAH aged 6 to less than 18 years with bodyweight < 50 kg is supported. Due to delays in the technical transfer of the manufacturing of the granules formulation to a commercial manufacturing facility, the Applicant has decided to separate the submission of type II variation to add a paediatric indication to tablets (for children ⩾50 kg) (previous type II application; EMEA/H/C/002737/II/0037) from that of the granules for oral suspension (for children < 50 kg) submission (current line extension application).

Therefore, clinical data on granules-for-oral suspension formulation for patients with PAH aged 6 to less than 18 years with bodyweight < 50 kg was already included and assessed in the previous application (EMEA/H/C/002737/II/0037).

No new clinical data are provided within this application, but for clarity a short summary of the design and results of the PATENT-CHILD study is described below. For a detailed overview and assessment reference is made to the assessment reports of the previous Type II extension of the indication application (EMEA/H/C/002737/II/0037).

2.6.3.1. Dose response study(ies)

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.

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

PATENT-CHILD was a study in 24 pediatric participants designed to evaluate PK, safety and tolerability with exploratory efficacy endpoints over a time period of 24 weeks.

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.

Treatments

Study 15681 was composed of two parts:

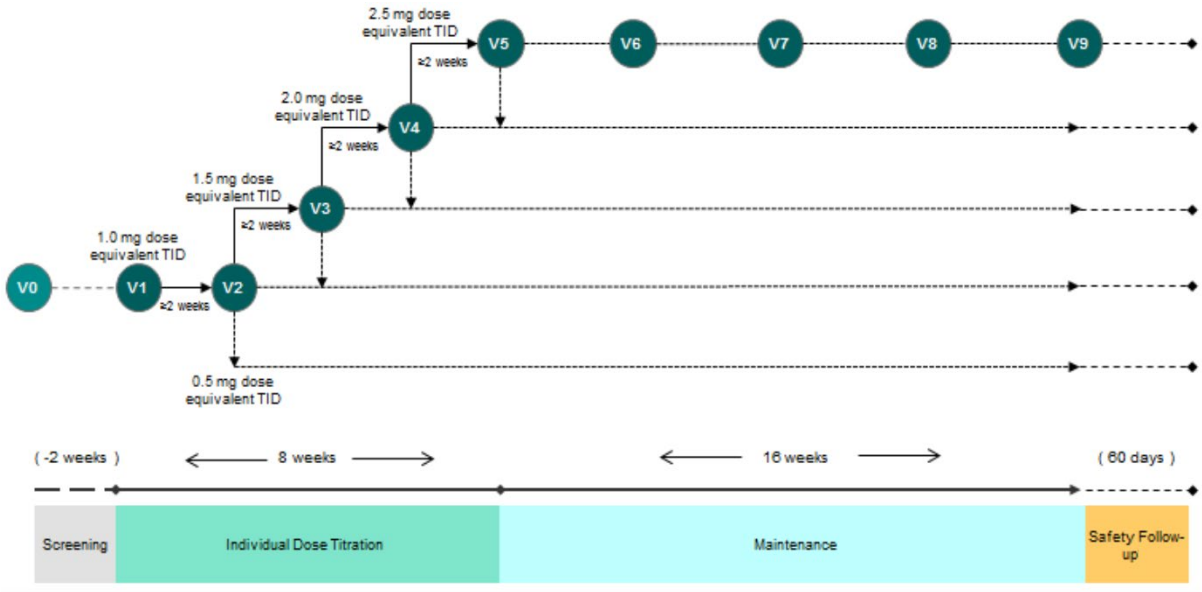
- Main study part (**Figure 2**):

- 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 2. 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 6**). 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 4. 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.

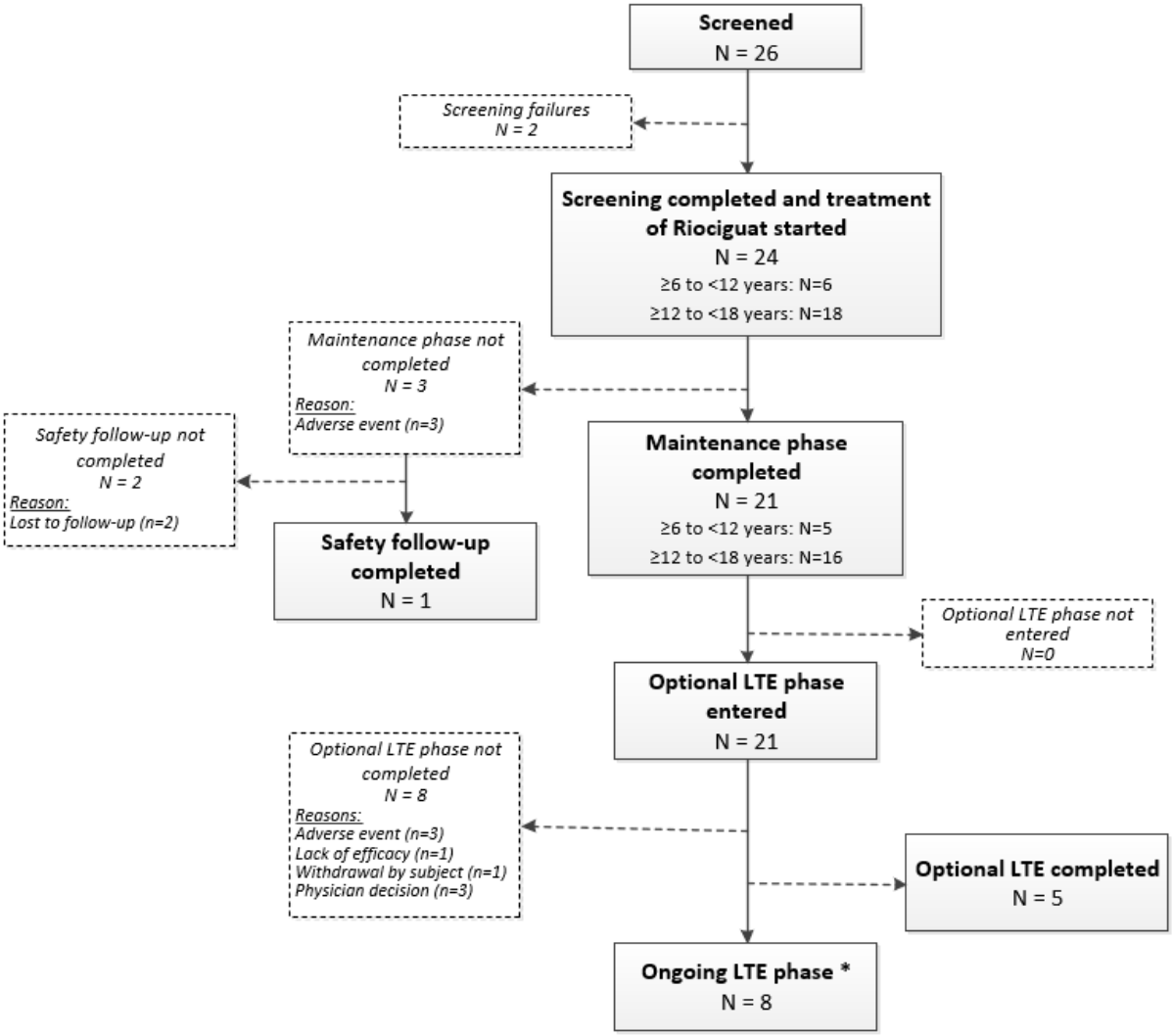
Results

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 3**). 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 3. 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.

Baseline data

Demographics and baseline characteristics were generally balanced across concomitant PAH medications groups.

Table 5. 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 6. 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

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%). 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 7. 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%)

	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%)
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

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 . 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 8. 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

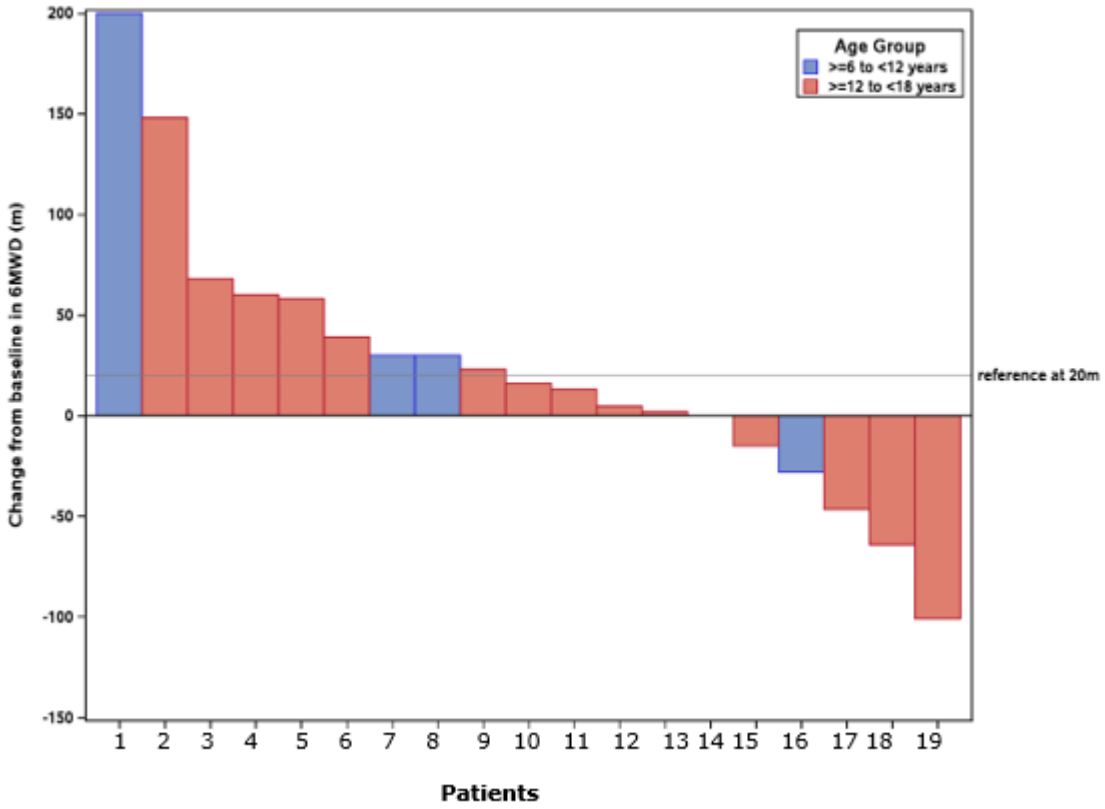
ERA = endothelin receptor antagonists; Max = maximum; Min = minimum; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogue; SD = standard deviation, SAF = safety analysis set

Source: Module 5.3.5.2 Report PH-41307 (15681), Table 14.2.2/1 to Table 14.2.2/3

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 4**). 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 4. 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 . 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.

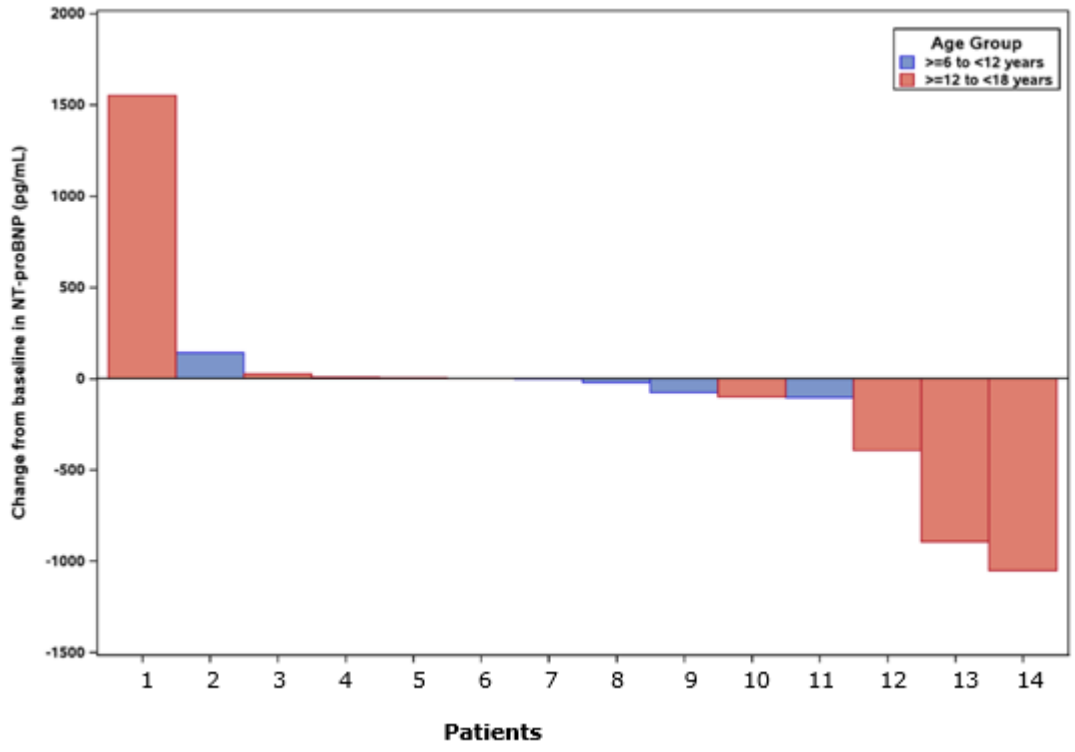
Table 9. Summary statistics for NT-proBNP (pg/mL) by age group and concomitant PAH medication (SAF)

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



Discussion on clinical efficacy

For a detailed discussion on efficacy reference is made to the assessment reports of the previous Type II extension of the indication application (EMEA/H/C/002737/II/0037).

2.6.4. Conclusions on the clinical efficacy

Overall, it has been concluded that 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 Applicant 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.

2.6.5. 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.

1.1.1.1. 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. 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).

At the cut-off date of the LTE phase of PATENT-CHILD (07 JAN 2022), 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.

1.1.1.2. Adverse events

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. 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 10. 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%)

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%)
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%). 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 11. 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.

1.1.1.3. Serious adverse events, deaths, and other significant events

Serious adverse events

Serious TEAEs were reported for 4 (16.7%) subjects in total. 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.

Deaths

In the initial paediatric dossier, no deaths were reported. Since the cut-off date 07 Jan 2022, one death case has been reported during the ongoing LTE phase of the PATENT-CHILD study, which was evaluated and considered as unrelated to study drug.

1.1.1.4. 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 . 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 12. 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

1.1.1.5. 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).

1.1.2. Discussion on clinical safety

For a detailed discussion on safety reference is made to the assessment reports of the previous Type II extension of the indication application (EMEA/H/C/002737/II/0037).

1.1.3. Conclusions on clinical safety

Overall, it can be concluded that riociguat was well-tolerated in the paediatric population. All in all, tolerability can be considered similar to the adult population.

2.7. Risk Management Plan

2.7.1. Safety concerns

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

2.7.2. Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities **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**				
Ongoing	To evaluate safety, tolerability, and pharmacokinetics of oral riociguat treatment in children 6 to <18 years of age with PAH.	Bone safety in patients <18 years old	Final report	Six months after LPLV (EOS as per protocol)

2.7.3. Risk minimisation measures

None

2.7.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 9.3 is considered acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

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

3. Benefit-Risk Balance

The application introduces a new formulation i.e. granules for oral suspension with the intention to extend the indication to paediatric patients of 6 years and older without a bodyweight restriction. The paediatric indication has been approved in 2023 in procedure EMEA/H/C/002737/II/0037, although with a body weight restriction. An oral suspension had been used in the pivotal paediatric PATENT-CHILD study in paediatric patients weighing < 50 kg in that procedure. However, the granules for suspension were not available for commercial purposes at that time as the development of this formulation was delayed.

This line extension is supported by a full Quality dossier on the new formulation and by five new non-clinical toxicity studies, all covering impurities found in the newly formulated drug product.

No new clinical data have been provided as they were already assessed in procedure EMEA/H/C/002737/II/0037.

The already authorised Adempas 0.5 mg; 1 mg; 1.5 mg, 2.0 mg and 2.5 mg strengths (film-coated tablets) allow uptitration from 0.5 mg up to the maximal dose of 2.5 mg TID in subjects ≥50 kg. Adempas 0.15 mg/ml granules for oral suspension was developed to achieve a dosing regimen for children aged between 6 and <18 years < 50 kg that results in riociguat exposures similar to levels observed in adult PAH patients dosed with 1 to 2.5 mg tablets TID.

The drug product is immediate release granules for oral suspension. Riociguat granules 0.3% for oral suspension is reconstituted with 200 mL non-carbonated drinking water prior to use to result in a suspension for oral application.

The drug product is a brown glass bottle of 250 ml, filled with 10.5 g ± 0.2 g white to off-white granules. The bottle is closed with a PP white opaque child resistant screw cap. The drug product will be provided with a syringe (100 ml) for reconstitution and pipettes (5 and 10 ml; liquid dosing device) and a suitable adapter.

The proposed drug product is acceptable from a quality point of view; all outstanding quality issues have been resolved.

Regarding the Non-Clinical dossier the impurities and leachables are acceptable from a toxicological point of view. No potential risk of riociguat to the environment is expected.

In conclusion, the overall benefit /risk balance of Adempas 0.3 mg/ml granules for oral suspension is positive.

3.1. Conclusions

The overall benefit/risk balance of Adempas is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Adempas is not similar to Winrevair (Sotatercept) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Adempas 0.15 mg/ml granules for oral suspension is favourable in the following indication(s):

Adempas is indicated for the treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 6 to less than 18 years with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists (see section 5.1).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Adempas subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The 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.

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

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0289/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, the film coated tablets presentations are updated, as a consequence, to accommodate the new pharmaceutical form.