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Riociguat in children with pulmonary arterial hypertension: The PATENT-CHILD study

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Abstract

Riociguat, a soluble guanylate cyclase stimulator, is approved for treatment of adults with pulmonary arterial hypertension (PAH). The safety, tolerability, and pharmacokinetics (PK) of oral riociguat in a pediatric population with PAH was assessed in PATENT-CHILD (NCT02562235), a multicenter, single-arm, 24-week, open-label, Phase 3 study. Patients aged 6–17 years in World Health Organization functional class (WHO-FC) I–III treated with stable endothelin receptor antagonists and/or prostacyclin analogs received riociguat equivalent to 0.5–2.5 mg three times daily in adults, as either oral pediatric suspension or tablets, based on bodyweight. Primary outcomes were safety, tolerability, and PK of riociguat. Twenty-four patients (mean age 12.8 years), 18 of whom were in WHO-FC II, were enrolled. Adverse events (AEs), mostly mild or moderate, were reported in 20 patients (83%). Four patients (17%) experienced a serious AE; all resolved by study end and two (8%) were considered study-drug related. Hypotension was reported in three patients and hemoptysis in one (all mild/moderate intensity). Riociguat plasma concentrations in pediatric patients were consistent with those published in adult patients. From baseline to Week 24, mean $\pm$ standard deviation increase in 6-minute walking distance was 23 ± 69 m ($n = 19$), and mean decrease in NT-proBNP was -66 ± 585 pg/ml ($n = 14$). There was no change in WHO-FC. Two patients experienced clinical worsening events of hospitalization for right heart failure. PK results confirmed a suitable riociguat dosing strategy for pediatric patients with PAH. The data suggest an acceptable safety profile with potential efficacy signals.

KEYWORDS

pediatrics, pharmacokinetics, pulmonary arterial hypertension, riociguat, treatment outcome

INTRODUCTION

Pulmonary arterial hypertension (PAH), characterized by increased pulmonary vascular resistance and pulmonary artery pressure, is a rare condition in infants and children that results in substantial morbidity and mortality (5-year survival $\sim 75\%$).^{1,2} PAH etiologies in children are distributed quite differently compared with adults, with idiopathic PAH, heritable PAH, and PAH associated with congenital heart disease (PAH-CHD) being more common in children; nonetheless, the disease characteristics are alike.^{1,3–5} Targeted pulmonary PAH therapies in children are primarily based on data from adult studies,⁶ resulting in clinical development issues of defining the correct therapeutic dose and determining long- and short-term safety in pediatric patients. As pediatric studies have inherent limitations that prevent

recruitment of large cohorts, extrapolation from adult data can be used as an approach to generate evidence to support regulatory assessment or marketing authorization of a targeted treatment if pathology and pharmacology are translatable.⁷

Targeted treatments for pediatric PAH include endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5i), and parenteral prostacyclin analogs (PCAs).^{1,8–10} Recent recommendations acknowledge that early (up-front or add-on) combination therapy may be considered,¹ and early therapy with two oral PAH-targeted drugs in newly diagnosed children with PAH in World Health Organization functional class (WHO-FC) II–III is considered reasonable.¹¹ Consequently, dual therapy is becoming more commonplace in clinical practice, except in PAH-CHD, where evidence of the benefits of combination therapy is more limited.

However, while bosentan, sildenafil, and ambrisentan are approved by the European Medicines Agency (EMA) for pediatric use, the Food and Drug Administration in the United States released a warning in 2012 against the (chronic) use of sildenafil for pediatric patients with PAH. This was updated in 2014 to clarify that there may be some situations in which the sildenafil risk:benefit profile might be acceptable in individual children.⁸ In July 2021 the EMA approved ambrisentan for use in pediatric PAH for children aged 8 to <18 years after a 41-patient study evaluated the safety, tolerability, and efficacy of a low and high dose, based upon the principles of extrapolation from adults (not approved for use in the United States).^{12,13}

Riociguat is a stimulator of soluble guanylate cyclase (sGC), the enzyme responsible for generating cGMP,^{14–16} and acts by directly stimulating sGC and by independently increasing the sensitivity of sGC to stimulation by nitric oxide (NO). In adults with PAH, riociguat, individually adjusted to a maximum dose of 2.5 mg three times daily (TID) has a positive benefit:risk ratio and was associated with significant improvements in exercise capacity, WHO-FC, hemodynamic parameters, time to clinical worsening, and Borg dyspnea scale after 12 weeks compared with placebo.¹⁷ Short-term improvements were maintained at 2 years, with no additional safety signals.¹⁸

To date, riociguat has not been formally evaluated in children in interventional clinical studies. PATENT-CHILD was designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of riociguat in children and adolescents aged 6–17 years.

METHODS

Study design

PATENT-CHILD (ClinicalTrials.gov: NCT02562235) is a single-arm, open-label study conducted in 16 study centers in nine countries (Colombia, Germany, Hungary, Italy, Japan, Mexico, Poland, Taiwan, and Turkey) (the initial 24-week treatment ran from 29 October 2015 to 7 March 2020; long-term extension [LTE] study ongoing). Initially, adolescents (age 12–17 years) were enrolled, with enrollment opened to children aged 6–11 years only when an optimal dose had been received in the first five adolescent patients and recommendation to proceed was given by an independent Data Monitoring Committee.

Patients received riociguat for 24 weeks, including an 8-week dose-adjustment period followed by 16 weeks of maintenance therapy. Patients who completed 24 weeks

of riociguat treatment were eligible for an ongoing LTE study, and safety follow-up was to be performed 60 ($\pm$ 8) days after the last riociguat dose for patients who did not enter the LTE or who stopped riociguat prematurely. Riociguat was administered TID as an oral suspension reconstituted from granules in patients with bodyweight <50 kg at baseline, and as oral tablets in patients with bodyweight $\geq$ 50 kg. Participants could switch between formulations, depending on their bodyweight. Adult doses were used for patients with $\geq$ 50 kg bodyweight.¹⁹ Patients <50 kg at baseline received a bodyweight-adjusted dose of riociguat to achieve a similar exposure to that observed in adults with PAH receiving riociguat (Supporting Information: Table 2). The starting dose was 1.0 mg or bodyweight-adjusted equivalent TID and was adjusted to a maximum of 2.5 mg or bodyweight-adjusted dose equivalent TID. The maintenance dose for each patient was individually determined based on monitoring of systolic blood pressure, wellbeing, and clinical status.

Patients and treatment

Eligible patients were children and adolescents aged 6–17 years with PAH diagnosed by right heart catheterization (at any time before enrollment) in WHO-FC I–III. Patients were receiving standard-of-care PAH treatment (i.e., an ERA and/or a PCA) for $\geq$ 12 weeks before the baseline visit.

Previous treatment with sildenafil and tadalafil was allowed (up to 24 h and 3 days, respectively), before the start of riociguat treatment. Patients receiving PDE5i or nonspecific PDE inhibitors, nitrates, or NO donors at baseline were excluded. Full exclusion/inclusion criteria are shown in Supporting Information: Table 1.

Outcomes and assessments

The primary outcomes of the study were safety, tolerability, and PK of riociguat. Safety was assessed by electrocardiogram, vital signs, and laboratory assessments. Hand X-rays (left hand) were used to monitor bone development. Adverse events (AEs) of special interest were defined as symptomatic hypotension, hemoptysis, and bone and/or growth abnormalities. Bone age and bone morphology were determined centrally by a specialist. Assessments made by physical examination, growth chart evaluation, and pubertal development using the Tanner scale were performed to assess overall development. These assessments were repeated at the discretion of the investigator if bone and/or growth anomalies were suspected.

Efficacy of riociguat in children was evaluated by exploratory secondary outcomes, including 6-minute walking distance (6MWD), WHO-FC, *N*-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) or BNP (sites were guided that, when both tests were available, NT-proBNP should be chosen over BNP and the same parameter then measured at each visit), quality of life (Short-Form 10 [SF-10] Child Health Questionnaire; Pediatric Quality of Life Inventory [PedsQL]), echocardiographic parameters (assessed by a central reader), and time to clinical worsening. Clinical worsening was defined as any of the following: death from any cause; hospitalization for right heart failure; lung transplantation; Potts' anastomosis or atrioseptostomy; or worsening of PAH symptoms (see Supporting Information for additional details). The taste and texture of the oral riociguat suspension formulation were assessed by use of a questionnaire with four initial questions ("Do you like the look of the drink?", "Do you like the taste of the drink?", "Do you like the drink?", "Would you like to drink this again?"). Patients who responded "No" to the third and fourth questions were asked additional questions about the taste and texture.

Study visits took place at baseline and at Weeks 2, 4, 6, 8, 12, 16, 20, and 24. AEs were assessed at each visit and X-ray, efficacy, and quality of life outcomes, and taste assessments were assessed at baseline and Week 24. Any AEs starting >2 days after the visit at Week 24 were not included.

Concentrations of riociguat and its metabolite M-1 in plasma were assessed using high-performance liquid chromatography/mass spectrometry. Measurements were made at baseline (30–90 min and 2.5–4 h postdose) and at Weeks 4 and 8 (predose).

Statistical analyses

No formal sample size calculation was carried out. Based on an evidence-based feasibility assessment and the proposed PK evaluation, enrollment of 20 patients was considered appropriate to assess the safety and characterize PK. Four PK samples per patient were required to allow accurate PK evaluation in a reasonable time frame. Every effort was made to enroll equal numbers of patients in the two age cohorts (12–17 and 6–11 years).

All safety and efficacy variables were analyzed by descriptive statistical methods in the safety analysis set, defined as all patients who received at least one dose of study medication. Analyses were carried out using SAS software version 9.4 (SAS Institute Inc.). Kaplan–Meier plots were generated to assess the time to clinical worsening.

Descriptive statistics were generated for riociguat plasma concentration in patients with a valid PK value

(see Supporting Information for additional details including handling of missing data).

Patient and public involvement

This study did not have patient or public involvement in its design, participant recruitment, or conduct; however, patient-reported outcomes were included as exploratory secondary outcomes. Study results were not shared with participants on study completion; results will be submitted for public posting on <https://clinicaltrials.gov>.

RESULTS

Patients and treatment

In total, 24 patients received at least one dose of riociguat and were included in the analyses. Three patients withdrew from the study because of AEs and 21 patients completed the 24-week study and entered the LTE (Figure 1). Of the 24 patients, 18 were aged 12–17 years and 6 were aged 6–11 years. There was one patient in the group aged 12–17 years with trisomy 21. Baseline demographics and disease characteristics are shown in Table 1. Before the study, 100% of patients were treated with ERAs (63% bosentan, 21% macitentan, and 17% ambrisentan), 75% with PDE5i (38% sildenafil, 21% tadalafil, 13% sildenafil citrate, and 4% dipyridamole), and 38% with PCAs (13% epoprostenol sodium, 8% each for selexipag and treprostinil, and 4% each for iloprost and iloprost trometamol). The most frequently used prior PAH-approved medications were bosentan (63%) and sildenafil (38%). PDE5i were discontinued before the first dose of riociguat. All patients received riociguat with concomitant ERAs; 15 patients (63%) received ERAs only, and nine patients (38%) received concomitant PCAs in addition to the ERAs.

Median (range) riociguat treatment duration was 24.0 (0.9–25.1) weeks, with 22 patients (92%) receiving at least 16 weeks of treatment. Median (range) cumulative riociguat exposure was 649 (4–1212) mg, with 46% of patients receiving a cumulative riociguat dose of 400–800 mg. Of the 22 patients in the study at the end of the 8-week dose-adjustment phase, 16 patients (73%) were receiving a bodyweight-adjusted dose equivalent to the maximum adult dose of 2.5 mg TID, three patients (14%) were receiving an adjusted dose equivalent to 0.5 mg TID, and one patient each (4.5%) was receiving a dose equivalent to 1.0, 1.5, and 2.0 mg TID. Details of the individual dosing of each patient are shown in Supporting Information: Figure 1.

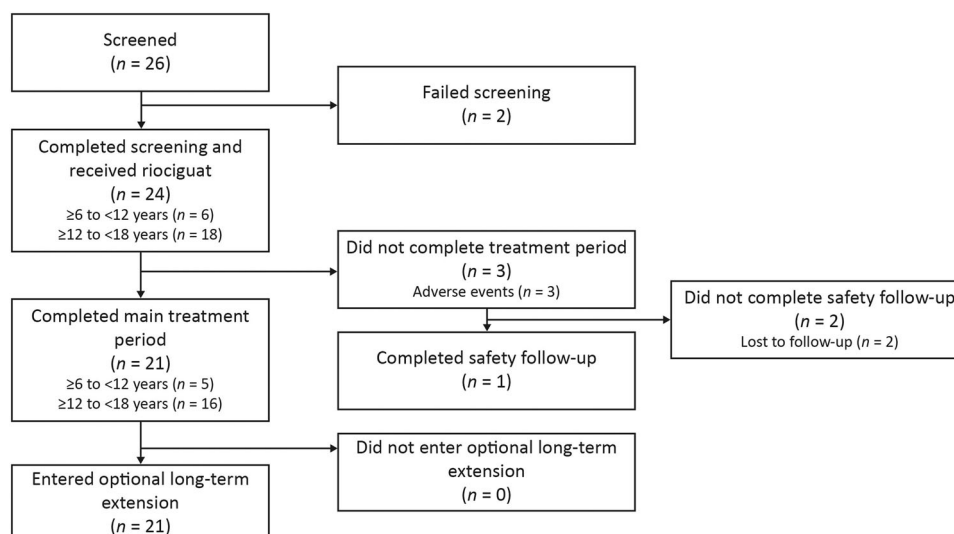


FIGURE 1 Patient disposition adverse events leading to discontinuations were hypotension ($n = 2$) and right ventricular failure ($n = 1$)

Safety

During riociguat treatment, 20 patients (83%) experienced at least one AE (Table 2), most of which were mild or moderate in intensity and were consistent with the known safety profile in adults. Other than headache (29%; $n = 7$), the most frequently occurring AEs were common childhood conditions, including abdominal pain, nasopharyngitis, and upper respiratory tract infections (all 17%; $n = 4$) (Table 2). Four patients (17%) experienced a serious AE (SAE). The only SAE reported in more than one patient was right ventricular failure (8%; $n = 2$). The investigator considered two SAEs (right ventricular failure and hypotension) to be study drug-related and all SAEs were resolved or recovered by the end of the study. No clinically significant abnormalities of laboratory parameters, heart rate, or heart rate-related AEs were reported, and no deaths occurred during the study. No bone or growth anomalies were reported during the study, and no clinically significant changes in left hand bone age or morphology compared with baseline were observed.

Four patients (17%) reported AEs of special interest: mild or moderate symptomatic hypotension ($n = 3$); moderate hemoptysis ($n = 1$). Symptomatic hypotension was considered study drug-related in two of these patients. For those with symptomatic hypotension, riociguat was continued unchanged, with a reduced dose, and discontinued in one patient each. No dose change or discontinuation was recorded for the patient who experienced hemoptysis, and the event was not considered to be study drug-related.

Pharmacokinetics

Observed individual plasma concentrations of riociguat and metabolite M-1 in pediatric patients are shown in Figure 2 and were in the range of those observed in adult studies with riociguat. Within-subject variability of riociguat and M-1 plasma concentrations was high (Supporting Information: Table 3).

Exploratory analysis of efficacy

Consistent with EMA guidelines for clinical studies in pediatric PAH,⁶ PATENT-CHILD was not powered to assess efficacy. Mean (standard deviation [SD]) 6MWD was 23 (69) m longer ($n = 19$) at Week 24 in the overall population (Figure 3; Supporting Information: Figure 2); results for the two age cohorts, and in the subgroups receiving ERA and ERA + PCA are shown in Supporting Information: Figure 3. Most patients (75%) were in WHO-FC II at baseline and no patient had changed WHO-FC at Week 24. Evaluated in 14 patients, mean (SD) NT-proBNP was 66 (585) pg/ml lower at Week 24 compared with baseline (Figure 3; Supporting Information: Figure 2). In six patients in whom BNP was evaluated, levels were increased in three patients and remained stable in three (Supporting Information: Figure 2); overall, there was a mean increase of +7.5 pg/ml from baseline to Week 24 (Figure 3).

Echocardiographic parameters are presented in Table 3.

TABLE 1 Baseline demographics and disease characteristics

	All patients (n = 24)
Age, years	12.8 (2.8)
Female sex, n (%)	11 (46)
Weight, kg	46.4 (15.9)
Range	12.4–80.9
≥50, n (%)	7 (29)
Height, cm	155.1 (17.8)
Heart rate, bpm	84.5 (19.0)
Concomitant PAH medication, n (%)	
ERA only	15 (63)
PCA only	0 (0)
ERA + PCA	9 (38)
PAH diagnosis, n (%)	
Idiopathic	18 (75)
PAH-CHD	4 (17)
Heritable	1 (4)
Other ^a	1 (4)
6MWD, m	442.1 (109.7) ^b
WHO-FC, n (%)	
I	1 (4)
II	18 (75)
III	5 (21)
NT-proBNP, pg/ml	982.7 (1595.8) ^c
BNP, pg/ml	10.5 (9.1) ^d
Mean pulmonary artery pressure, ^e mmHg	59.5 (22.3) ^f
Systolic pulmonary artery pressure, ^e mmHg	90.0 (30.0) ^f
Diastolic pulmonary artery pressure, ^e mmHg	44.3 (19.4) ^g
Pulmonary capillary wedge pressure, ^e mmHg	8.3 (3.0) ^f
Pulmonary vascular resistance, ^e dyn·s·cm ⁻⁵	1088.5 (684.1) ^g
Cardiac index, ^e L/min/m ²	3.5 (1.5) ^g
Cardiac output, ^e L/min	4.6 (2.6) ^g
Bone age, years	14.2 (3.0) ^b
Bone age, ^h n (%)	
Delayed	1 (4)
Consistent with chronologic age	12 (50)
Advanced	10 (42)

TABLE 1 (Continued)

	All patients (n = 24)
Bone morphology, n (%)	
Normal	23 (96) ^b

Note: Data are mean (SD) unless stated otherwise.

Abbreviations: BNP, brain natriuretic protein; CHD, congenital heart disease; ERA, endothelin receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PCA, prostacyclin analog; SD, standard deviation; WHO-FC, World Health Organization functional class.

^aOne patient with pulmonary hypertension as the result of developmental abnormalities did not have PAH and was enrolled despite not meeting the inclusion criteria for the study, and thus was recorded as an important protocol deviation.

^bn = 23.

^cn = 15.

^dn = 7.

^eLast observed value before start of study treatment.

^fn = 22.

^gn = 20.

^hBone age and morphology missing in one patient.

Two patients reported clinical worsening events of hospitalization for right heart failure (see Supporting Information for additional details). Of these two patients, one patient was hospitalized for right heart failure the day after a 2-day interruption of concomitant bosentan treatment during riociguat dose adjustment. The patient recovered 9 days after hospitalization and completed the 24-week study on riociguat 2 mg. The other patient received riociguat 1 mg after low systolic blood pressure occurred with the 1.5 mg dose; worsening of right heart failure occurred during Week 17 of treatment; riociguat was withdrawn and the patient recovered. The number of patients with events was too low to produce valid Kaplan–Meier estimates for the time to clinical worsening.

Quality of life

Mean (SD) SF-10 Physical and Psychosocial summary scores improved slightly, from 31.0 (13.3) and 48.8 (8.3), respectively, at baseline, to 36.4 (14.6) and 49.5 (9.2) at Week 24 (Supporting Information: Table 4). Mean (SD) PedsQL total score improved from 69.8 (16.3) at baseline to 74.0 (14.8) at Week 24 (Supporting Information: Table 4). Improvements were also seen in the Physical Health and Psychosocial Health summary scores, from 64.4 (15.8) to 70.6 (14.1) and 72.6 (19.2) to 75.8 (17.6), respectively. Improvements in SF-10 and PedsQL scores were also seen across the age and concomitant PAH medication subgroups (data not shown).

TABLE 2 Safety summary and most frequently occurring adverse events

	All patients (n = 24)
Any AE	20 (83.3)
Most common AEs reported in >1 patient	
Headache	7 (29.2)
Abdominal pain	4 (16.7)
Nasopharyngitis	4 (16.7)
Upper respiratory tract infection	4 (16.7)
Hypotension	3 (12.5)
Pyrexia	3 (12.5)
Dizziness	2 (8.3)
Gastroenteritis	2 (8.3)
Right ventricular failure	2 (8.3)
Any severe AE	2 (8.3)
Any drug-related AE	7 (29.2)
Any SAE	4 (16.7)
Right ventricular failure	2 (8.3)
Asthma	1 (4.2)
Hypotension	1 (4.2)
Skin pain	1 (4.2)
Skin swelling	1 (4.2)
Vascular device infection	1 (4.2)
Any drug-related SAE	2 (8.3)
Any AE leading to discontinuation	3 (12.5)
Death	0 (0.0)

Note: Data are presented as n (%). AEs reported are those occurring after the first dose of riociguat and up to 2 days after the end of riociguat treatment; one child reported a pretreatment AE of tonsillitis.

Abbreviations: AE, adverse event; SAE, serious adverse event.

Taste assessment

Of patients who received at least one dose of the riociguat oral suspension and answered the taste and texture questionnaire (baseline: $n = 16$; Week 24: $n = 14$), most responded positively or indifferently concerning the appearance, smell, and taste of the suspension (Supporting Information: Table 5). Only 1/16 patients at baseline and 4/14 at Week 24 responded that they did not like the drink or would not like to drink it again. There were no discontinuations due to the smell or taste of the riociguat oral suspension.

DISCUSSION

PATENT-CHILD is the first interventional exploratory study of riociguat conducted in a pediatric population, designed in line with EMA guidelines.⁶ Riociguat was well tolerated in children and adolescents aged 6–17 years with PAH, with no new safety signals observed and with the suspension considered palatable. AEs were consistent with clinical trials of riociguat in adults,^{17,18,20} with those expected in a population of this age with PAH, and with the mechanism of action of riociguat. PK results confirmed that the riociguat weight-based dosing strategy established in the PATENT-CHILD study resulted in comparable drug exposures to those seen in adults, and individual plasma concentrations in pediatric patients overlapped with those measured in adult patients with PAH.²¹ The high variability in intraindividual riociguat PK can be explained in part by the metabolic pathways involved in riociguat metabolism and the heterogeneity of the disease leading to additional interindividual PK variability. Exploratory analyses of efficacy suggested positive trends, including modest increases in 6MWD and decreases in NT-proBNP, and a relatively low incidence of clinical worsening events, consistent with studies of riociguat in adults with PAH.^{17,18,20} Although these positive trends were modest, mild improvements may be seen as clinically relevant since the prognosis of pediatric PAH is often poor, progressive, and fatal. However, PATENT-CHILD was not powered to formally assess efficacy, as agreed with the EMA. This study was based upon the premise that efficacy could be extrapolated from adults if similar systemic exposures were achieved, as seen previously with the EMA approval of ambrisentan.^{12,13} Although this study was the only pediatric clinical study required under the pediatric investigation plan, further investigator-initiated studies or registry data could enhance the valuable information gained from this study about riociguat in pediatric patients with PAH.

Despite the availability of various treatment options for adult patients with PAH, few have been rigorously evaluated and then approved for pediatric use. In particular, PK and safety data cannot be extrapolated from data in adults.²² Both bosentan and sildenafil are now approved by the European Medicines Agency for pediatric use (in children aged older than 1 year); however, sildenafil is not recommended in the United States, although the risk:benefit profile may be acceptable in some individual children.⁸ The constant hormonal and metabolic changes associated with growth and development mean that specifically designed, age-appropriate studies are necessary for pediatric

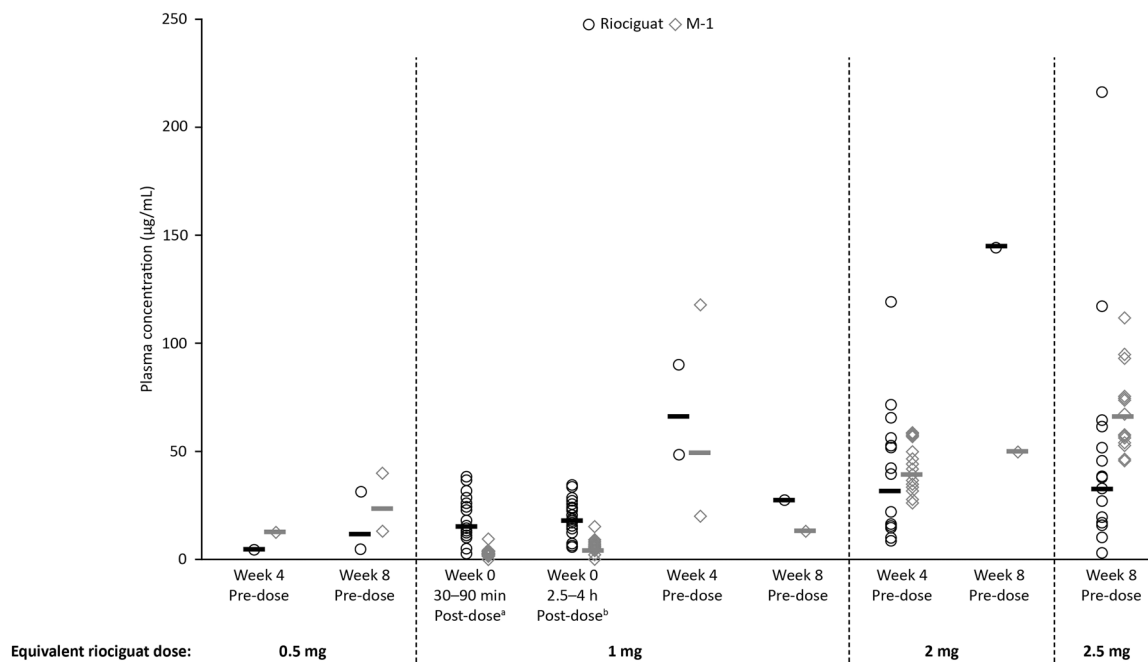


FIGURE 2 Observed individual and mean plasma concentrations in pediatric patients with pulmonary arterial hypertension. Mean is shown by the horizontal lines (black for riociguat and gray for the metabolite, M-1). ^aThirteen values were below the lower limit of quantification; ^bfour values below the lower limit of quantification.

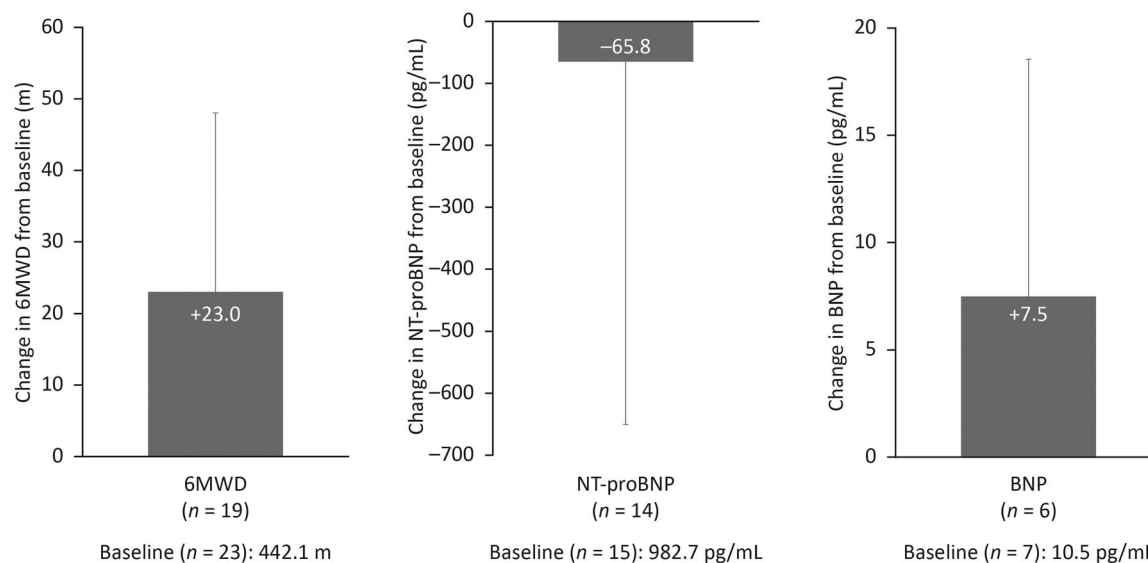


FIGURE 3 Mean (standard deviation) change from baseline to Week 24 in 6MWD, NT-proBNP, and BNP. 6MWD, 6-minute walking distance; BNP, brain natriuretic protein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

populations.^{23,24} Previous data regarding the use of riociguat in children have been limited to isolated case reports.²⁵ The PATENT-CHILD study provides valuable preliminary evidence to start to fill this gap. As preclinical studies suggested bone changes possibly associated with increased sGC activity,²² we investigated growth and bone development and found no evidence of any adverse effects of 24-week treatment with riociguat.

The main limitations of the study were the difficulties in design and recruitment resulting from the contraindication of concomitant riociguat and PDE5i, leading to the recruitment of only 24 patients over 5 years. It should also be noted that PATENT-CHILD was designed as a small, open-label, PK and safety study and was therefore not powered to detect statistically significant changes in endpoints. The lack of a placebo control

TABLE 3 Echocardiographic parameters

	Baseline	Week 24	Change
Right atrial pressure, mmHg	9.3 (3.4) ^a	9.0 (4.0) ^b	−0.6 (3.6) ^c
Left ventricular eccentricity index	2.1 (1.3) ^d	2.1 (1.0) ^a	+0.0 (1.0) ^e
Pericardial effusion, mm	1.3 (0.2) ^f	2.2 (—) ^g	+1.0 (—) ^g
Pulmonary artery acceleration time, ms	91.6 (36.9) ^d	83.7 (24.1) ^d	−7.8 (35.9) ^e
Right ventricular cardiac index, L/min/m ²	4.3 (1.6) ^c	4.3 (1.9) ^c	+0.2 (2.1) ^h
Right ventricular cardiac output, L/min	5.5 (2.1) ^c	6.0 (3.4) ^c	+0.5 (3.1) ^h
Right atrial diastolic area, cm ²	16.9 (11.1) ^a	17.8 (10.3) ^b	+1.1. (3.3) ^c
Right atrial diastolic area index	12.8 (7.0) ^a	12.6 (6.9) ^b	+0.6 (2.3) ^c
Right atrial systolic area, cm ²	12.0 (9.4) ^a	12.4 (9.6) ^b	+0.4 (3.8) ^c
Right atrial systolic area index	9.0 (6.0) ^a	8.8 (6.8) ^b	+0.3 (2.4) ^c
Right ventricular fractional area change (%)	25.7 (8.5) ^d	23.5 (6.7) ⁱ	−4.3 (7.3) ^e
Right ventricular diastolic area, cm ²	27.2 (12.0) ^d	28.5 (10.1) ⁱ	+0.6 (4.5) ^e
Right ventricular diastolic area index	20.7 (6.6) ^d	20.5 (6.2) ⁱ	+0.5 (3.6) ^e
Right ventricular systolic area, cm ²	20.2 (9.3) ^d	22.0 (8.6) ⁱ	+1.7 (3.8) ^e
Right ventricular systolic area index	15.6 (5.7) ^d	15.8 (5.6) ⁱ	+1.2 (3.3) ^e
Systolic pulmonary artery pressure, mmHg	117.2 (51.6) ^j	105.5 (25.7) ^k	+5.7 (49.0) ^l
Tricuspid annular plane systolic excursion, mm	18.8 (4.2) ^d	17.7 (3.4) ^b	−1.3 (3.9) ^e
Tricuspid regurgitation peak velocity, m/s	4.9 (1.1) ^m	4.6 (0.8) ⁿ	−0.1 (0.7) ^o

Note: Data are presented as mean (standard deviation) unless stated otherwise.

^an = 18.

^bn = 20.

^cn = 16.

^dn = 17.

^en = 15.

^fn = 2.

^gn = 1.

^hn = 13.

ⁱn = 19.

^jn = 6.

^kn = 4.

^ln = 3.

^mn = 11.

ⁿn = 14.

^on = 10.

group and associated randomization and blinding are typical limitations in pediatric studies of a rare and serious condition such as PAH.

Additionally, there are challenges relating to selecting appropriate endpoints for studies in children with PAH. The most relevant endpoints include long-term “hard” outcomes such as transplantation and hospitalization¹ that are difficult to measure in short-term studies. Moreover, the standard endpoints used in studies in adults with PAH, such as 6MWD and hemodynamic outcomes, may be more challenging in young children,

while surrogate endpoints such as weight, echocardiography, and NT-proBNP have not been validated in children.^{1,24} In this small study, wide variation and better baseline values than commonly seen in adult patients in 6MWD and serum NT-proBNP/BNP highlight additional challenges in interpretation of the exploratory efficacy data. Additionally, most echocardiographic parameters were not performed in all patients, making any interpretation difficult. Confirming efficacy results in larger studies is of interest; however, due to these limitations, alternative Bayesian approaches such as

extrapolating data from adults to children may facilitate the development of pediatric PAH medicines.

In conclusion, results from this single-arm study demonstrate a suitable dosing strategy for riociguat in children and adolescents with PAH. Although the study was not powered for assessing efficacy, positive trends were seen. The EMA requirements to support extrapolation of efficacy from adults are supported by the similarities in PAH pathology and pharmacology of riociguat in children and adults. The results of the data from the LTE phase of the study are awaited with interest.

AUTHOR CONTRIBUTIONS

Humberto García Aguilar, Matthias Gorenflo, D. Dunbar Ivy, Shahin Moledina, Biagio Castaldi, Hidekazu Ishida, Paweł Cześniewicz, Jacek Kusa, Oliver Miera, Joseph Pattathu, Ken-Pen Weng, Laszlo Ablonczy, Christian Apitz, Marta Katona, Kenichi Kurosaki, Tomas Pulido, Hiroyuki Yamagishi, Kazushi Yasuda, Damien Bonnet, and Matthias Gorenflo were involved in the collection of the data. Galia Cisternas, Matthias Gorenflo, Susanne Lippert, Anna Radomskyj, Soundos Saleh, Stefan Willmann, and Gabriela Wirsching were involved in the design of the study and/or analysis of the data. Maurice Beghetti was coordinating investigator and Matthias Gorenflo was appointed clinical trial director according to German Drug Law. All authors reviewed the data, provided comments on the different versions, and approved the final version of the manuscript.

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CONFLICTS OF INTEREST

H. G. A. reports fees for lectures and member of advisory boards for Bayer and Janssen. D. D. I. reports the University of Colorado contracts with Acceleron, Actelion/Janssen, Altavant, Bayer, Eli Lilly, GlaxoSmithKline, and United Therapeutics for D. D. I. to be a consultant and perform clinical trials. S. M. reports consultancy from Actelion/Janssen and GlaxoSmithKline. J. P. reports fees for lectures and/or consultancy from

Actelion/Janssen. T. P. reports fees for lectures, member of advisory boards, and research grants from Actelion/Janssen, Bayer, GlaxoSmithKline, and Pfizer. H. Y. reports research grants and lecture fees from Actelion, AbbVie, and Teijin Pharma; research grants from Tanabe-Mitsubishi; lecture fees from Bayer, GE Healthcare Japan, Merck Sharp and Dohme, Novo Nordisk, Nihon Seiyaku, Nihon Shinyaku, Pfizer, and Termo. G. C., M. G., S. L., A. R., S. S., S. W., G. W. are employees and stockholders of Bayer AG. D. B. is a steering committee member for Eli Lilly and Company, and steering committee and advisory board member for Actelion Pharmaceuticals, Bayer, and Novartis. M. B. reports fees for lectures and/or consultancy from Acceleron, Actelion/Janssen, AOP, Bayer, Eli Lilly, GlaxoSmithKline, and Gossamer; unrestricted research grants from Actelion and Bayer. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation guideline E6: Good Clinical Practice. The design of the study was discussed and agreed upon with the European Medicines Agency and experts, and according to the EU reflection paper on data extrapolation.⁷ The protocol and amendments were reviewed and approved by each site's Independent Ethics Committee or Institutional Review Board before the start of the study. All patients, or their legally authorized representative, provided written informed consent before any study procedures were conducted. Child assent was also obtained where applicable. Ethics approvals for PATENT-CHILD study (Protocol BAY 63-2521/15681) were obtained from: Medical Research Council EC for Clinical Pharmacology, Budapest, Hungary; Comitato Etico Sperimentazione Clinica Provincia Padova, Padova Italy; Komisja Bioetyczna przy Dolnoslaskiej Izbie Lekarskiej, Wroclaw, Poland; Hacettepe Universitesi Klinik Arastirmalar Etik Kurulu, Ankara, Turkey; Universitätsklinikum Heidelberg, Ethikkommission der Med. Fakultät Heidelberg, Heidelberg, Germany; National Cerebral and Cardiovascular Center, Institutional Review Board, Osaka, Japan; Osaka University Hospital Institutional Review Board, Osaka, Japan; Keio University Hospital Institutional Review Board, Tokyo, Japan; Aichi Children's Health and Medical Center Institutional Review Board, Aichi, Japan; IPS Centro Médico Imbanaco de Cali S.A., Comité de Ética en Investigación del Centro Médico Imbanaco, Cali, Colombia; Instituto Nacional de Cardiología "IgnacioChávez", Ciudad de Mexico, Mexico; Comité de Ética en Investigación Operadora de Hospitales Ángeles, Huixquilucan,

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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