Document Type:	Study Protocol
Official Title:	Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with pulmonary arterial hypertension (PAH)
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Cover Page of Integrated Study Protocol

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)

This protocol version is an integration of the following documents / sections:

- **Original protocol,** Version 1.0, dated 13 MAR 2015
- **Amendment 03** (global amendment described in Section 17.1) forming integrated protocol Version 2.0, dated 24 NOV 2015
- **Amendment 05 (**global amendment described in Section 17.2) forming integrated protocol Version 3.0, dated 31 MAY 2016
- **Amendment 06** (global amendment described in Section 17.3) forming integrated protocol Version 4.0, dated 9 JAN 2017
- **Amendment 09** (global amendment described in Section 17.4) forming integrated protocol Version 5.0, dated 13 MAR 2018
- **Amendment 12** (global amendment described in Section 17.5) forming integrated protocol Version 6.0, dated 23 AUG 2019
- **Amendment 14** (global amendment described in Section 17.6) forming integrated protocol Version 7.0, dated 20 JUL 2020

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol.

- **Amendment 01** dated 25 AUG 2015 (local amendment valid for UK only)
- **Amendment 02** dated 3 NOV 2015 (local amendment valid for Poland only)
- **Amendment 04** dated 8 MAR 2016 (local amendment valid for Japan only)
- **Amendment 07** dated 7 MAR 2017 (local amendment valid for Japan only)
- **Amendment 08** dated 3 NOV 2017 (local amendment valid for Germany only)
- **Amendment 10** dated 29 MAY 2018 (local amendment valid for Taiwan only)
- **Amendment 11** dated 05 APR 2019 (local amendment valid for Romania only)
- **Amendment 13** dated 17 OCT 2019 (local amendment valid for Germany only)

This document integrates the original protocol and all global amendments.

Title page - amended

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)

Riociguat in children with PAH

PATENT-CHILD

Test drug:	BAY 63-2521 / Riociguat		
Study purpose:	Safety		
Clinical study phase:	3	Date:	**20 JUL 2020**
Registration:	EudraCT: 2014-003952-29	Version no.:	**7.0**
Sponsor's study no.:	BAY 63-2521 / 15681		
Sponsor: *(Note: Sponsor info was updated according to Amendment 6, see Section 17.3.1.10.)*	**Bayer AG, D-51368 Leverkusen, Germany** **US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA**		
Sponsor's medical expert: (*Note: Study medical expert was changed according to Amendment 3, see section 17.1.1.16. The contact details were updated according to Amendment 5, see Section 17.2.1.8. Study medical expert was changed according to Amendment 9, see Section 17.4.1.13. Study medical expert was changed according to Amendment 14, see Section 17.6.)*	PPD Bayer U.S. LLC Pharmaceuticals, Pharmaceuticals Study Medical Experts 100 Bayer Boulevard Whippany NJ 07981 United States Tel: PPD Cell: PPD		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol amendment as presented.

Name: PPD Role: GCL (Global Clinical Lead)

Date: 22.07.2020 Signature: PPD

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol amendment as presented.

Name:

Affiliation:

Date: Signature:

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

List of abbreviations - amended

6MWD	6-minutes-walking-distance
AE(s)	adverse event(s)
Alb	albumin
ALT	alanine aminotransferase (also known as SGPT)
APAH	associated PAH
ASD	atrial septal defect
AST	aspartate aminotransferase (also known as SGOT)
AUC	area under the curve
BCRP	breast cancer resistance protein
BP	blood pressure
BUN	blood urea nitrogen
BW	body weight
Ca	calcium
CBC	complete blood count
CCDS	Company Core Data Sheet
cGMP	cyclic guanosine monophosphate
CHD	congenital heart disease
CHMP	Committee for Medicinal Products for Human Use
C_{max}	maximum concentration
CSR	Clinical Study Report
CTEPH	chronic thromboembolic pulmonary hypertension
CTS	clinical trials simulations
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ERA	endothelin receptor antagonist
ESC	European Society of Cardiology
EU	European Union
EU-SmPC	Summary of Product Characteristics (EU)
FAS	Full analysis set
FC	Functional class
FPAH	Familial PAH
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
HPAH	Hereditable PAH
IB	investigator's brochure
ICH	International Council on Harmonization
IDMS	isotope dilution mass spectrometry
IDT	individual dose titration
IEC(s)	Independent Ethics Committee(s)
INN	International non-proprietary name
IPAH	Idiopathic PAH
IRB(s)	Institutional Review Board(s)
IxRS	interactive voice / web response system
K	potassium
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
Na	sodium

NO	nitric oxide
NT-proBNP	N-terminal pro–brain natriuretic peptide
P	phosphate
OS-ASD	ostium secundum atrial septal defect
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PAP_{mean}	mean pulmonary artery pressure
PASP	pulmonary arterial systolic pressure
PBPK	physiologically based pharmacokinetic
PCA	prostacyclin analogue
PD	pharmacodynamic
PDE	Phosphodiesterase
P-gp	P-glycoprotein
PFO	patent foramen ovale
PH	pulmonary hypertension
PIP	pediatric investigation plan
PK	Pharmacokinetic
PTC	Product Technical Compliant
PVR	pulmonary vascular resistance
QoL	quality of life
RHC	right heart catheter
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	Steering Committee
SCr	serum creatinine
sGC	soluble guanylate cyclase
SUSARs	suspected unexpected serious adverse reaction(s)
TAPSE	tricuspid annular plane systolic excursion
T-Bil	total bilirubin
TEAE(s)	treatment-emergent adverse event(s)
TID	three times a day
TOPP	Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension
TTCW	time to clinical worsening
UA	uric acid
WHO	World Health Organization

(*Note: Changes to this section were applied according to Amendment 3, see Section 17.1.1.16. Changes to this section were applied according to Amendment 5, see Section 17.2.1.8. Changes to this section were applied according to Amendment 9, see Section 17.4.1.13.*)

Synopsis - amended

Title	Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with pulmonary arterial hypertension (PAH)
Short title	Riociguat in children with PAH
Acronym	PATENT-CHILD
Clinical study phase	3
Study objective(s)	Primary objectives: • To evaluate safety, tolerability and pharmacokinetics of oral riociguat treatment. Secondary objectives: • Exploratory efficacy.
Test drug(s)	Riociguat (BAY 63-2521)
Name of active ingredient	Methyl-N-[4,6-diamino-2-[1-[(2-fluorphenyl)methyl]-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl]-N-methyl-carbaminate
Dose(s) *(Note: For ensuring the correct dosing, the text was clarified by Amendment 3, see Section 17.1.1.6.)*	For children with body-weight <50 kg at screening, body-weight adjusted dose equivalent to the exposure of (0.5 mg) 1.0 - 2.5 mg three times a day (TID), individual dose titration (IDT) in adults treated for PAH. Doses of 1.0 to 2.5 mg TID will be applied for children ≥50 kg at screening The individual optimal (maintenance) dose is to be determined based on patients' monitoring of systolic blood pressure, well-being and clinical status.
Route of administration	Oral
Duration of treatment	Active treatment period: 24 weeks (titration phase: 8 weeks, maintenance phase: 16 weeks)
Reference drug(s)	N/A
Background treatment *(Note: the wording was modified according to Amendment 6, see Section 17.3.1.2.)*	Patients must be on standard of care PAH medications, allowing Endothelin Receptor Antagonists (ERA) and/or Prostacyclin Analogues (PCA), for at least 12 weeks prior to baseline visit.
Indication	Pulmonary arterial hypertension

Diagnosis and main criteria for inclusion /exclusion *(Note: This part was modified according to Amendment 3, see Section 17.1.1.16.This part was modified according to Amendment 6, see Sections 17.3.1.2 and 17.3.1.5.)*	Children from 6 years to less than 18 years of age with PAH Main inclusion criteria: • PAH, diagnosed by right heart catheterization (RHC) (for patients with closed shunts – RHC no less than 4 months after surgery). • Patients must be on standard of care PAH medications, allowing ERA and/or PCA, for at least 12 weeks prior to baseline visit. • Two groups of patients will be included: Prevalent: Patients currently on PAH medication (allowing ERA and/or PCA) who need additional treatment (discretion of the investigator) Incident: Treatment naïve patients initiated on PAH medication (allowing ERA and/or PCA) and then riociguat added once patients are stable on standard of care. • WHO functional class I-III. Main exclusion criteria: • Concomitant use of the following medications: phosphodiesterase 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific phosphodiesterase (PDE) inhibitors (theophylline, dipyridamole), nitrates or NO donors (such as amyl nitrite) in any form. • Pretreatment with NO donors (e.g. nitrates) within the last 2-weeks before visit1. • Active state of hemoptysis or pulmonary hemorrhage, including those events managed by bronchial artery embolization.
Study design	Open-label, single arm, individual dose titration
Methodology *(Note: For ensuring the correct dosing, the text was clarified by Amendment 3, see Section 17.1.1.6.)*	This study is designed to evaluate the safety, tolerability, pharmacodynamics and pharmacokinetics of riociguat in children from ≥6 to less than 18 years with pulmonary arterial hypertension (PAH) group 1. For children with body weight < 50 kg at screening, body weight adjusted doses of 1.0 mg, 1.5mg, 2.0 mg, and 2.5 mg TID will be applied. For children with body weight ≥50 kg, doses of 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg TID will be applied. The study consists of two phases: titration phase up to 8 weeks and a maintenance phase

	up to 16 weeks.
Type of control	N/A
Data Monitoring Committee	A Data Monitoring Committee will provide the Steering Committee and the sponsor with recommendations related to the protection of the children's safety, including stopping recruitment and study treatment.
Number of subjects *(Note: the wording was modified according to Amendment 6, see Section 17.3.1.2.)*	Children on treatment with ERAs and/or PCAs can be enrolled. At least 20 children on treatment with bosentan or other Endothelin Receptor Antagonists (ERA) must be enrolled.
Primary variable(s) *(Note: the wording was modified according to Amendment 9, see Section 17.4.1.13)*	• Change from baseline to end of treatment (week 24) of safety and tolerability assessed by incidence of adverse events and serious adverse events, recording of vital signs and left-hand x-ray. • Pharmacokinetics/Pharmacodynamics analyses. Blood samples will be taken for pharmacokinetic and pharmacodynamic measurements from all participants treated with riociguat. The number of pharmacokinetic (PK) blood samples to be taken will be determined using physiologically based pharmacokinetic (PBPK) modelling predictions. It is intended to collect the minimum amount of blood needed for adequate analysis (sparse sampling).

Main secondary variable(s) *(Note: this part was modified according to Amendment 5, see Sections 17.2.1.3 and 17.2.1.7. This part was modified according to Amendment 6, see Section 17.3.1.6 This part was modified according to Amendment 9, see Section 17.4.1.7 and 17.4.1.13.)*	Change from baseline to end of treatment (week 24) of: • 6-Minute Walking Distance (6MWD). • WHO functional class. • N-terminal prohormone brain-type natriuretic peptide or brain-type natriuretic peptide. When both tests are available, N-terminal pro–brain natriuretic peptide (NT-proBNP) should be chosen over BNP and the same test should be performed at every required visit. • Quality of Life scores (parent questionnaire and in children able to understand questions). • Echocardiographic assessment of the following: o pulmonary arterial systolic pressure (PASP), o tricuspid annular plane systolic excursion (TAPSE), o pericardial effusion, o left ventricular eccentricity index, o estimated right atrial pressure, o right ventricular pressure by tricuspid regurgitant jet velocity, o acceleration time of pulmonary flow, o right heart dimensions, and o cardiac output Time to clinical worsening defined as: o hospitalization for right heart failure, o death, o lung transplantation, o Pott's anastomosis and atrioseptostomy, o worsening of PAH symptoms, which must include either ▪ an increase in WHO functional class, OR ▪ appearance/worsening symptoms of right heart failure AND need for additional PAH therapy.

Time point/frame of measurement for primary variable(s)	Timeframe of measurement for primary variable: 24 weeks Time points of assessment: *Assessment of adverse events* o at baseline, o at all visits in the titration phase and maintenance phase, and o every 3-4 months in the extension phase. *Left hand x-ray* o at baseline o at end of study treatment period (week 24) o every 12 months in the extension phase until growth plates are closed. *Exploratory efficacy* o at baseline o at end of study treatment period (week 24) o every 3 to 4 months in the extension phase.
Plan for statistical analysis	A descriptive analysis of the safety and efficacy parameters will be performed.

Study flow chart - amended

Table 0–1: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
Informed consent/assent	•														
In-/exclusion criteria	•	•													
Demographics	•														
Medical history	•														
Concomitant medication		•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant PAH specific medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Physical examination [m]	•	• [d]	•	•	•	•	•	•	•	•	•	•	•	•[h]	•
Obtain lab test	•[i]					•				•		•			
Pregnancy test [a]	•	•		•		•	•	•	•	•		•	•	•	•
Dispense study medication		•	•	•	•	•	•	•	•	•	(•)			•	
Instruct how to take study drug		•	•	•	•	•	•	•	•	•	(•)			•	

Table 0–1: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
Provide study guidelines		•													
Vital signs	•	•[d]	•	•	•	•	•	•	•	•	•	•	•	•	•
ECG	•	•[d]								•		•			
Echocardiogram		•								•		•		•	
RHC data [o]	•[o]														
WHO functional class		•								•		•		•	
6MWD		•								•		•		•	
NT-proBNP or BNP[p]		•								•		•		•	
Left hand x-ray		•[j]								•				•[e]	
Adverse events [n]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Drug accountability			•	•	•	•	•	•	•	•		•		•	
PK blood sample[b]		•		•		•									
Child Health Questionnaire (SF-10 and PedsQL)	•									•		•		•	

Table 0–1: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
Check the systolic BP monitoring form if applicable			•	•	•	•	•	•	•	•					
Tanner scale [c]	•									•		•		• [e]	
Taste assessment questionnaire		•								•		•			

Table 0-1: Flow chart - amended

a Urine or serum pregnancy test for women of childbearing potential, in the LTE pregnancy testing is to be performed in 4-weekly interval; also actively request the results of the home urinary pregnancy test as soon as this test is due

b A minimum volume of 1.0 mL per sample is needed. Accurate adherence to time points is essential and has to be documented, see Table 0–2

c Scale of physical development in children and adolescents

d At Visit 1 blood pressure, heart rate and ECG pre-dose, 2 and 4 hours after first dose (see Table 0–2)

e Every 12 months until growth velocity is plateauing and growth plates are closed (see section 6.1.6)

f ±2 days for Visits 1 to 4, ±4 days for Visit 5, ±5 days for Visits 6 to 9

g Visit 1 is considered the baseline visit

h Including monitoring of growth velocity

i Obtain blood samples if AST and ALT, creatinine, BUN, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC are not available within 30 days prior to Visit 0. Record the same laboratory parameters to eCRF when obtained as medically required according to a local package insert of bosentan or other ERAs, or medical practice at the study site at any time.

j If no historical data (not older than 30 days) of x-ray is available
k Home visits (only at week 12 and/or 20 of maintenance phase) at the discretion and responsibility of the investigator
l For subjects dropping off the protocol at any time after V1 and before V9
m Including height and weight
n Including AEs of special interest
o In case RHC has been performed for a study subject before enrollment, record most recent RHC parameters to the eCRF on V0 (timing of RHC not limited to the period of Day -14 to -1). Additionally, if RHC is conducted on medical reasons during the study, the RHC data should be recorded to the eCRF.
p When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit

(Note: The table was modified according to protocol Amendment 3, see Sections 17.1.1.1, 17.1.1.15. The table was modified according to Amendment 5, see Sections 17.2.1.1 and 17.2.1.2.The table and footnotes were modified according to Amendment 6, see Sections 17.3.1.2, 17.3.1.3, 17.3.1.6, 17.3.1.7, and 17.3.1.8. The table was modified according to Amendment 9, see Sections 17.4.1.8, 17.4.1.12, and 17.4.2.4.)

Table 0–2: Visit details - amended

		Visit 1 (Baseline visit)						Visit 3 and 5	
		Detailed study activities at pre-dose and after the first study medication dose intake						Study activities before first study medication dose intake	
Order of procedures	Time interval (h)	pre-dose	0:00	0:30 to 1:30	2:00	2:30 to 4:00	4:00	-1:00 to 0:00	0:00
↓	Pharmacokinetic blood sample			•		•		•	
	Blood sample for NT-proBNP or BNP[b]	•							
	Blood sample for safety laboratory							• [a]	
	Blood pressure, heart rate	•			•		•		
	ECG	•			•		•		
	WHO functional class	•							
	Left hand x-ray	•							
	Echocardiogram	•							
	Administration study drug		•						•

a. Obtain blood sample for safety parameters on Visit 5 only.
b. When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit

Abbreviations: ECG = electrocardiogram

(Note: Visit details were modified according to Amendment 3, see Section 17.1.1.16.The table for visit details was modified according to Amendment 5, see Section 17.2.1.8. The table for details was modified according to Amendment 6, see Section 17.3.1.6. The table for visit details was modified according to Amendment 9, see Section 17.4.1.12 and 17.4.2.4.)

Protocol Amendment Summary of Changes Table

Amendment 14, forming integrated protocol Version 7.0 (20 JUL 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The purpose of this amendment is to modify the definition of End of Study.

Section number and name	Description of (wording) change	Brief rationale
3.1 Study description	End of Study definition was modified from LPLV of the main study to LPLV of the long-term extension (LTE).	For clarification and to avoid interruption of the ongoing LTE
6.3 Efficacy/ Pharmacodynamic/ Other outcomes – amended	Wording for time of assessment for **Taste and texture of the pediatric formulation(s)** was modified.	For consistency with the wording given in the protocol “Change from baseline to end of treatment (week 24)” and the timepoints indicated in the Study flow chart
6.1 Study visits	Wording describing study periods was modified.	To align with wording in Study flow chart and other sections and keep consistent with PIP
Title page Sponsor’s medical expert	The Study Medical Expert was changed.	Administrative change

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1. Introduction - amended

Pulmonary arterial hypertension (PAH) is a chronic disorder of the pulmonary vasculature, characterized by a progressive increase in pulmonary vascular resistance leading to right heart failure and death. Pulmonary Hypertension (PH) according to the current European Society of Cardiology (ESC) guidelines (Galie et al., 2009) is defined by a mean pulmonary artery pressure (PAP) ≥25 mmHg at rest, which is still consistent with the definition of the 5th World Symposium on Pulmonary Hypertension, which took place in Nice, 2013 (Simonneau et al., 2013). The definitions for adults have been applied to children without any modification of the values (Donti et al., 2007, Ivy et al., 2013, Widlitz and Barst, 2003, Park, 2008).

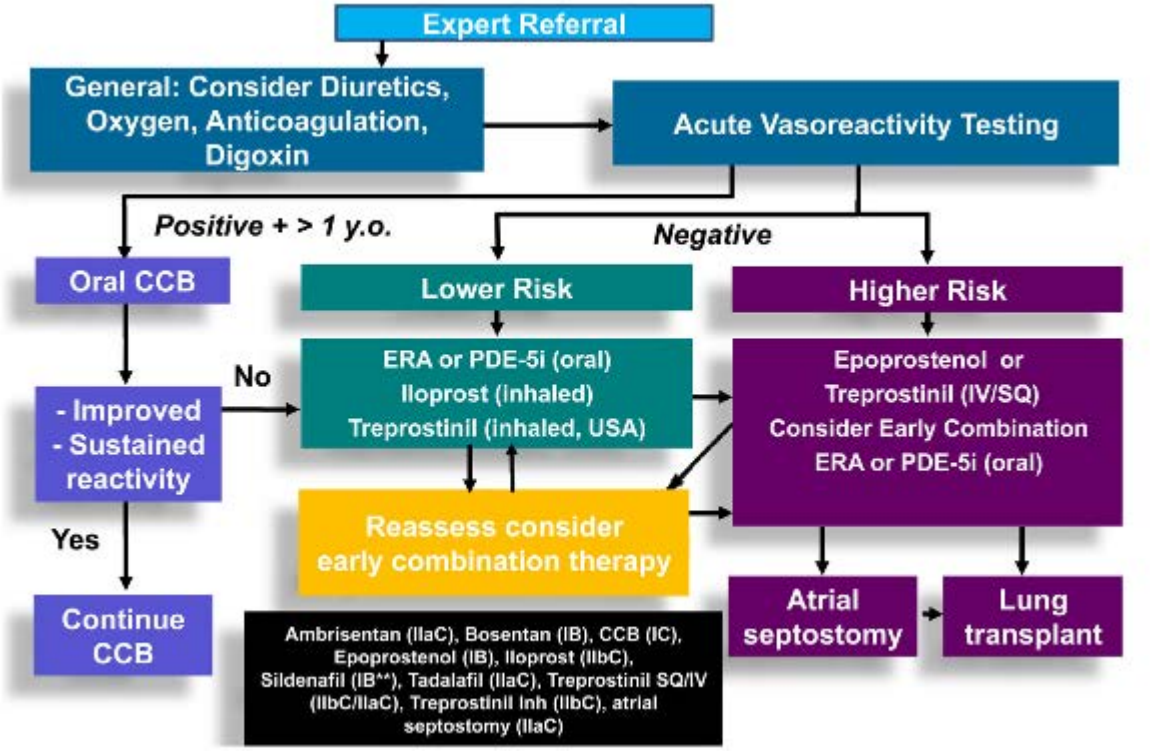
Pulmonary hypertension (PH) can present at any age from infancy to adulthood. Data on pediatric epidemiology remain scarce and the exact incidence and prevalence of PH in children is not known. In the French registry, the estimated prevalence for PAH in children was 3.7 cases/million (Fraisse et al., 2010). The distribution of etiologies in children is quite different than that of adults, in children, idiopathic PAH (IPAH), heritable PAH, and APAH-CHD (PAH associated with congenital heart disease) constitute the majority of cases, whereas cases of PAH associated with connective tissue disease are relatively rare (Fraisse et al., 2010, Barst et al., 2012, Barst et al., 2011, Berger et al., 2012, Takatsuki et al., 2011, Haworth and Hislop, 2009). Large registries of pediatric PH, including the TOPP (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension) registry (Berger et al., 2012) and the combined adult and pediatric U.S. REVEAL (Registry to Evaluate Early and Long- Term PAH Disease Management) registry, have been described (Barst et al., 2012).

Without appropriate treatments, median survival rate after diagnosis of children with IPAH appears worse when compared with that of adults with an estimate median survival in children of only 10 months (D'Alonzo et al., 1991, McLaughlin et al., 2002, Barst et al., 1999).

Although many treatment goals and endpoints for clinical trials are similar in adults and children, there are also important differences. As in adults, clinically meaningful endpoints include clinically relevant events such as death, transplantation, and hospitalization for PAH. Further parameters that directly measure how a patient feels, functions, and survive are meaningful and include functional class and exercise testing; however, there are no acceptable surrogates in children (Ivy et al., 2013). Although World Health Organization (WHO) functional class is not designed specifically for infants and children, it has been shown to correlate with 6-min walk distance and hemodynamic parameters (Fraisse et al., 2010, Barst et al., 2012, van Loon et al., 2011, Moledina et al., 2010, Haworth and Hislop, 2009).

The prognosis of children with PAH has improved in the past decade owing to new therapeutic agents and aggressive treatment strategies. However, the use of targeted PAH therapies in children is almost mainly based on experience and data from adult studies, rather than evidence from clinical trials in pediatric patients. Treating physicians propose a pragmatic treatment algorithm based on the strength of expert opinion that is most applicable to children with IPAH (Ivy et al., 2013) (Figure 1–1).

Figure 1–1: Pediatric IPAH/FPAH treatment algorithm



Note: Use of all agents is considered off-label in children aside from sildenafil in Europe. **Dosing recommendations per European approved dosing for children
Abbreviations: CCB = calcium channel blocker; ERA = endothelin receptor antagonist; HPAH = hereditary pulmonary arterial hypertension; inh = inhalation; IPAH = idiopathic pulmonary arterial hypertension; IV = intravenous; PDE-5i = phosphodiesterase 5 inhibitor; SQ = subcutaneous, FPAH = Familial PAH
Source: (Ivy et al., 2013)

The recommended treatment scheme for pediatric populations is similar to that of adult populations and in general obtained by extrapolation of adult experience (Galie et al., 2004, Beghetti, 2009, Galie et al., 2009). In general, children will undergo a vasoreactivity test, which tests the acute response to short-acting vasodilators. Based on current literature children show a better response compared to adult patients permitting more children to be treated with calcium channel blockers and also translating into a better prognosis for those children who respond. On the other hand non-responders in pediatric age have a worse prognosis than adult patients with severe disease (Galie et al., 2004). The guideline of the European Society of Cardiology has been updated recently to reflect the recommendations of the World Conference on Pulmonary Hypertension in Nice (Simonneau et al., 2013). Thus, due to the rarity of the disease and the limited treatment data gained from pediatric populations (with the exception of STARTS 2) there is also paucity of internationally recommended treatment guidelines. The use of targeted pulmonary PAH therapies in children is almost exclusively based on experience and data from adult studies, rather than evidence from clinical trials in pediatric patients.

Revatio (sildenafil) and bosentan are PAH-specific drugs approved for children in European Union. The medical treatment recommendations of Tracleer (International non-proprietary

name [INN]: bosentan) in pediatric populations with PAH in the European Union (EU) are mainly based on extrapolation from experience in adult populations (EMA, 2012b). Data from clinical studies in pediatric patients are derived from retrospective cohort studies (without control-group) in mono-therapy and combination therapy, (Hislop et al., 2011, Ivy et al., 2010, Maiya et al., 2006, Rosenzweig et al., 2005), from clinical studies in pediatric patients with PAH and focus on pharmacokinetics (PK) (without control group) (Beghetti, 2009, Barst et al., 2003), from a European non-interventional post-marketing surveillance database (Beghetti et al., 2008), and from a double-blind placebo controlled study in patients > 12 years of age with Eisenmenger's syndrome (Galie et al., 2006). These studies showed encouraging results for the benefit of the pediatric population but still indicate that improvement in medical treatment is needed. Recent expert guidelines suggest the use of endothelin receptor antagonists (ERA) or phosphodiesterase 5 (PDE5) inhibitors and, when children deteriorate on use of any of these medications, additional agents may be considered, either in an up-front approach or sequential add-on (Ivy et al., 2013).

There is a paucity of combination therapy data in children with PAH. In the recent Nice guidelines, it is stated that combination therapy should be considered for children who deteriorate on either ERA or phosphodiesterase 5 (PDE5) inhibitors. Indeed, it is suggested that patients may benefit from early (up-front) combination therapy. At the international European Respiratory Society meeting 2014, the results of the randomized, double-blind AMBITION study were presented (Galie et al., 2014). This study investigated the first-line treatment of PAH in adults with the combination of ambrisentan 10 mg and tadalafil 40 mg (compared to the pooled ambrisentan and tadalafil monotherapy arm). The combination therapy reduced the risk of clinical failure by 50% compared to pooled ambrisentan and tadalafil monotherapy arm (hazard ratio = 0.502; p=0.0002). This study may support the direct treatment of affected patients with combination therapy, which is recommended by Ivy et al. as primary approach for children with higher risk PAH (Galie et al., 2014). In addition, the study supports the concept to add another PAH specific drug when clinically necessitated as stated in the ESC adult guidelines (Galie et al., 2009) and in the treatment recommendations of the 5th World Symposium on Pulmonary Hypertension at Nice, 2013 (Galie et al., 2013). The results of the AMBITION study corroborate the findings of the PATENT-1 study (Ghofrani et al., 2013), where the addition of riociguat to treatment with ERA or prostanoids resulted in further beneficial effects for adults with PAH.

Taking into account the current treatment options and the bad prognosis for the pediatric patients, a new medication with a novel mechanism of action may offer another treatment option to this population. This might be especially true of riociguat because of its different mode of action in the nitric oxide pathway and distinctive from currently used drugs, i.e. direct soluble guanylate cyclase (sGC) stimulation as it has been shown in adult PAH patients (Schermuly et al., 2008).

(Note: The text was modified according to the Amendment 3, see Section 17.1.1.10. The text was modified according to Amendment 5, see Section 17.2.1.5. The text was modified according to Amendment 6, see Section 17.3.1.10.)

1.1 Riociguat

Riociguat is the first of a new class of drugs, the soluble guanylate cyclase (sGC) stimulators that acts in the nitric oxide pathway and is being developed for the treatment of pulmonary hypertension (PH). Riociguat has a dual mode of action: it sensitizes sGC to the body's own

nitric oxide (NO) and can also increase sGC activity in the absence of NO, causing vasorelaxation, anti-proliferation and anti-fibrotic effects. Riociguat is approved for adults in over 40 countries for the treatment of PAH and chronic thromboembolic pulmonary hypertension (CTEPH). Recent data presented has demonstrated long-term (2-year) safety and tolerability data in adult patients with PAH and CTEPH (Rubin et al., 2015, Simonneau et al., 2014).

1.2 Rationale of the study and risk-benefit assessment - amended

There is an unmet medical need for children with group 1 PAH. Riociguat would be a new class of drugs tested in this patient population, and may provide a safe and effective drug for this life-threatening disease, as seen in adults.

sGC is an important regulator in the cardiovascular system and is present in vascular cells and platelets. The endogenous activator of sGC is endothelial cell-derived NO, which acts in paracrine fashion. In smooth muscle cells and in platelets NO activates sGC, resulting in an increased intracellular cyclic guanosine monophosphate (cGMP) level which induces vasorelaxation, and inhibition of cell proliferation and fibrotic effects. By increasing the sGC activity in the absence of NO, riociguat causes vasorelaxation, anti-proliferation and anti-fibrotic effects.

PATENT-1 was the pivotal study that led to the approval of riociguat (Adempas) for adults with PAH. The PATENT-1 study was a phase 3, double-blind study where 443 adult subjects with symptomatic PAH were randomly assigned to treatment and actually received placebo, riociguat in individually adjusted doses of up to 2.5 mg three times daily (2.5 mg–maximum group), or riociguat in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg–maximum group). The 1.5 mg–maximum group was included for exploratory purposes, and the data from that group were analyzed descriptively. Subjects who were receiving no other treatment for pulmonary arterial hypertension and subjects who were receiving endothelin-receptor antagonists or (non-intravenous) prostanoids were eligible. The primary end point was the change from baseline to the end of week 12 in the distance walked in 6 minutes. Secondary endpoints included the change in pulmonary vascular resistance, N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, World Health Organization (WHO) functional class, and time to clinical worsening, score on the Borg dyspnea scale, quality-of-life variables, and safety. By week 12, the 6-minute walk distance had increased by a mean of 30 m in the 2.5 mg–maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% confidence interval, 20 to 52; $P<0.001$). Important for this current study, prespecified subgroup analyses showed that riociguat improved the 6-minute walk distance both in subjects who were receiving no other treatment for the disease AND in those who were receiving endothelin-receptor antagonists or prostanoids. There were significant improvements in pulmonary vascular resistance ($P<0.001$), NT-proBNP levels ($P<0.001$), WHO functional class ($P = 0.003$), time to clinical worsening ($P = 0.005$), and Borg dyspnea score ($P = 0.002$). The most common serious adverse event in the placebo group and the 2.5 mg–maximum group was syncope (4% and 1%, respectively). In conclusion, riociguat significantly improved exercise capacity and secondary efficacy end points in subjects with pulmonary arterial hypertension (Ghofrani et al., 2013). In PATENT-1, riociguat improved the 6-minute walk distance in both patients who were receiving no therapy for the disease and patients who were receiving endothelin-receptor antagonists or prostanoids.

Further details can be found in the latest available version of the investigator's brochure, which contains comprehensive information on the study drug.

Based on the positive results of riociguat in adult subjects with PAH, children with PAH may also benefit from treatment with riociguat, e.g. those pre-treated with bosentan.

As previously discussed, Revatio (INN: sildenafil) is approved in Europe and has now become standard of care. Riociguat and PDE5 inhibitors such as sildenafil act on the NO-sGC-cGMP signaling pathway. Thus, an additive effect on pulmonary and systemic circulation may be expected. Non-clinical studies in animal models showed an additive systemic blood pressure lowering effect when riociguat was combined with either sildenafil or vardenafil. With increased doses, more than additive effects on systemic blood pressure were observed in some cases. The interaction of riociguat and PDE5i was investigated in a clinical study (PATENT-Plus; study 15096). PATENT-Plus was designed as an interaction study to evaluate changes in blood pressure following 1, 1.5, 2, and 2.5 mg riociguat TID (i.e., the IDT regimen) compared to placebo treatment on the background of stable sildenafil pre-treatment in subjects with symptomatic PAH.

On the basis of the safety, tolerability and efficacy data available, and in particular the apparent high rate of discontinuations due to hypotension and a lack of overall clinical benefit in the patient population studied, a positive benefit risk assessment could not be established and therefore riociguat should not be used in combination with sildenafil. After a review of the above data, the long-term extension phase of Patent-Plus was discontinued. Based on these considerations and in agreement with the CHMP (Committee for Medicinal Products for Human Use) (Adempas_EMEAHC2737) riociguat on top of sildenafil (Revatio in Europe) is contraindicated in the EU-SmPC. Accordingly, use of PDE5 inhibitors is a key exclusion criterion in this current study.

In general, treatment with riociguat is expected to cause comparable mode of action related side effects in children and adolescents as in adults. In growing rats, morphological changes (widening of the growth plates, increase of bone mass) of the bones have been found as additional adverse effects related to mode of action. Although the regulation of bone homeostasis via the NO-sGC-cGMP-PKG pathway holds true for all species including humans, the effect of sGC stimulation on the growing bone is yet unclear. Considering the severity and prognosis of PAH and the fact that the bone findings in rats were seen at 3-4 fold of human exposure, and that the findings were reversible and can be monitored in the clinical setting, the preclinical bone findings are considered as not prohibitive for the initiation of a clinical study in children.

The protocol was developed in accordance with ICH Good Clinical Practice, and other ICH/EMA guidelines for conducting clinical trials in pediatric population, in particular the ICH Topic E 11 (Clinical Investigation of Medicinal Products in the Pediatric Population) and the guideline on Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population.

The necessity of minimizing any possible burden and any potential risk for participating child and adolescent patients was taken into consideration and addressed during the development of this protocol. In order to provide guidance for investigators this protocol describes use of all study procedures, as well as outlines any potential related burden for participating patients, whenever applicable, in the respective chapters. In terms of the IMD administration the titration phase has been implemented (as described in the Section 5.1.1 “Body-weight

adjusted individual dose titration regimen"), as well as a dosing pipette for administration of oral suspension will be used. Educational material for training on the dosing pipette use and dose administration for study site staff, as well as for the patients and their caregivers, to ensure adequate dosing pipette use and treatment compliance will be distributed.

The study design includes standard procedures for pediatric PAH management, and only a few additional, study specific procedures have been included wherever absolutely necessary to ensure the study conduct, and monitoring of safety of enrolled patients. Study-specific procedures are: ECGs, Echocardiogram, urine or serum pregnancy testing for female patients of childbearing potential, selected blood sampling, and the left-hand X-ray for monitoring of bone growth. The above listed study specific procedures are non-invasive, standard medical care procedures. Laboratory samples will be restricted to the selected laboratory tests at screening (only if historical data is not available), visit 1, 5 and 9. Pharmacokinetic samples and blood sampling for study purposes will be aligned with clinically required blood tests whenever possible in order to avoid additional burden of a painful procedure and blood volume taken (see the subchapter "Laboratory parameters" in Section 6.2). Blood samples for pharmacokinetic analysis will have the blood volume minimized to 1 ml per sample. All blood samples collection will be performed by pediatric specialist staff and will be performed with the use of techniques like distraction and local anesthetic techniques, if applicable, to reduce the burden for patients. The left hand X-ray for monitoring of bone growth will be performed and assessed according to the established method. The rare periodicity of this X-ray examination, as well as the standard precautions will ensure minimal and therefore acceptable exposure to radiation (Section 6.2 Safety outcomes).

Investigators are mandated and trained to report adverse events, and all the respective definitions, criteria for qualifying AEs, and their reporting, as well as a description of pharmacovigilance procedures are included in a separate section of this protocol (Section 8.8). The monitoring of safety of participating patients by investigators and the sponsor is ensured by adherence to pharmacovigilance regulations and implementation of study specific monitoring measures (e.g. observation and evaluation of potential AEs of special interest, patients' growth and bone growth monitoring). Close monitoring and ongoing medical review will be performed by the sponsor. An independent Data Monitoring Committee (DMC, which will be acting according to a DMC Charter) will meet periodically to review the safety data of enrolled patients, as well as the scientific merit of the trial. In addition a Steering Committee (SC) will ensure a scientifically sound and safe conduct of the study. Both, the DMC and the SC, are described in a separate subsection of this protocol (6.6 Study committees").

The expected benefit-risk balance of riociguat is considered positive if used in adherence to this clinical trial protocol and in accordance with the recommendations and guidance given in the Investigator's Brochure.

(Note: The section was widened according to Amendment 3, to better describe the minimization of burden degree of pediatric subjects, see Sections 17.1.1.5 and 17.1.1.16.The section was modified according to Amendment 6, see Section 17.3.1.8.)

2. Study objectives - amended

The primary objectives:

- To evaluate safety, tolerability and pharmacokinetics of oral riociguat treatment

Secondary objectives:

- Exploratory efficacy. To characterize the pharmacodynamic profile of riociguat comprising the following exploratory parameters: time to clinical worsening (TTCW), exercise capacity (6MWD test), functional capacity (measured by WHO FC), laboratory biomarkers (NT-proBNP or BNP), Quality of Life (QoL) measurements (SF-10, PedsQL), echocardiographic variables

Other objective is:

- To assess taste and texture of the pediatric formulation(s) by use of a questionnaire

(Note: The text was modified according to Amendment 3, see Section 17.1.1.3.The text was modified according to Amendment 5, see Section 17.2.1.7.The section was modified according to Amendment 6, see Sections 17.3.1.2 and 17.3.1.6.)

3. Study design

This is an international, multicenter, single-arm, open-label study to evaluate the safety, tolerability and pharmacokinetics of a body-weight adjusted riociguat regimen in subjects aged between ≥6 years old and <18 years old who have been diagnosed with idiopathic PAH, hereditable PAH, or PAH associated with connective tissue disease or congenital heart disease with shunt closure. These subjects must be on stable treatment with PAH medications (ERA and/or PCA) prior to receiving the first dose of riociguat (EMA, 2009, EMA, 2012a, eMC, 2015a, eMC, 2015b).

(*Note: The Section was modified according to Amendment 6, see Section 17.3.1.2.)*

3.1 Study description - amended

After providing written informed consent and assent (if applicable) subjects will undergo a screening evaluation to determine their eligibility. Eligible subjects – once on stable background treatment with PAH medications (ERA and/or PCA) - will start body-weight adjusted individual dose titration (IDT) regimen as described in section 5.1.1. After the individual titration phase of maximum of 8 weeks, subjects will enter the 16-week maintenance phase. The last dose administered at Visit 4 will be regarded as individual optimal dose and subject will receive that treatment during the maintenance phase.

Subjects of the older age cohort (≥12 to <18 years) will be treated first. After 5 patients of this age cohort have reached their optimal dose and received this dose until assessment of their first control x-ray of left hand at week 24, an independent Data Monitoring Committee (DMC) will give recommendations to the Steering Committee (SC) whether to continue with enrolment in this age cohort and open enrollment in the subsequent lower age cohort (≥6 to <12 years).

Children who require treatment with riociguat for more than 24 weeks will be offered participation in an extension study and continuation until market approval of riociguat for the

pediatric population or until they are 18 years of age (whatever comes first). Subjects reaching adulthood can be transitioned to commercially-available Adempas.

The primary objective is the evaluation of safety and tolerability as well as the pharmacokinetic properties of riociguat in the pediatric population. The DMC will monitor the subjects' safety on an ongoing basis and give recommendations to the SC.

For all subjects, visits are scheduled at regular time points (see Table 0–1). Subjects who prematurely discontinue study drug or do not consent to participate in the long-term extension phase will be seen at the safety follow-up visit. During all contacts, the treatment and clinical course of the subject will be evaluated. Subjects with suspected safety concerns (for safety outcomes see section 6.2) will undergo confirmatory testing as per standard of care. Blood samples for PK will be taken at defined time points (see Table 0–2).

The reason why subjects did not pass the screen of in- and exclusion criteria after obtaining informed consent/child assent will be documented.

Primary completion

The primary completion event for this study is when the last visit of the last subject for all centers has occurred after 24 weeks of treatment.

End of study

The end of the study will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (EU and non-EU).

A clinical study report (CSR) will be written after the primary completion. A separate CSR will be prepared after completion of the optional long-term extension (LTE).

(Note: The wording in Primary completion and in End of the study was modified according to Amendment 3, see Section 17.1.1.2.The Section was modified according to Amendment 6, see Section 17.3.1.2. The wording in End of the study was modified according to Amendment 14, see Section 17.6.)

4. Study population

4.1 Planned number of subjects - amended

Children on treatment with ERAs and/or PCAs can be enrolled. At least 20 children on treatment with bosentan or other Endothelin Receptor Antagonists (ERA) must be enrolled in the study.

The sponsor commits to put efforts in enrolling equal number of subjects in each of the ≥12 to <18 year and the ≥6 to <12 year age cohort overall. Enrolment will be started with children from 12 to less than 18 years of age.

After 5 patients in the ≥12 to <18 years old group have reached their optimal dose, have been treated on their maintenance dose and obtained the control x-ray of left hand at week 24, their data will be evaluated by DMC. Only after obtaining positive safety and efficacy data in the first 5 patients, enrolment in the group from 6 to less than 12 years of age will be started.

The sponsor will make every effort to facilitate an equal distribution between the two age cohorts with a minimum of 5 patients in each age cohort. In case of inadequate availability of patients in the age group ≥6 to <12 years total enrolment will be stopped only if at least 5 patients of this younger age group have been enrolled.

(Note: The Section was modified according to Amendment 6, see Section 17.3.1.2. The Section was modified according to Amendment 9, see Section 17.4.1.9)

4.2 Inclusion criteria – amended

1. Children from 6 years to less than 18 years of age with pulmonary arterial hypertension (PAH)
2. Diagnosed with PAH :
   - Idiopathic (IPAH)
   - Hereditable (HPAH)
   - PAH associated with (APAH)
     - Connective tissue disease
     - Congenital heart disease with shunt closure more than 6 months ago (no open shunts, confirmed by RHC no less than 4 months after surgery)

   Regardless of the type of PAH, the following findings are not exclusionary:
     - Patent foramen ovale (PFO) and asymptomatic, isolated, ostium secundum atrial septal defect (OS-ASD) ≤ 1 cm (both confirmed by echocardiogram) and not associated with hemodynamic alterations indicative of significant shunt, e.g. Qp/Qs ratio less <1.5:1 are not exclusionary
3. Pulmonary arterial hypertension (PAH), diagnosed by right heart catheterization (RHC) at any time prior to enrolment (for patients with closed shunts – RHC no less than 4 months after surgery)
4. Pulmonary arterial hypertension confirmed by a RHC at any time prior to start of study, with mean pulmonary artery pressure (PAP_{mean}) ≥25 mmHg at rest, pulmonary capillary

wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg, and pulmonary vascular resistance (PVR) >240 dyn•sec•cm^{-5} (i.e., ≥3.0 wood units•m^2)

5. Patients must be on standard of care PAH medications, allowing Endothelin Receptor Antagonists (ERA) and/or Prostacyclin Analogues (PCA), for at least 12 weeks prior to baseline visit.

   Two groups of patients will be included:

   - Prevalent: Patients currently on PAH medication (allowing ERA and/or PCA) who need additional treatment (discretion of the investigator)
   - Incident: Treatment naïve patients initiated on PAH medication (allowing ERA and/or PCA) and then riociguat added once patients are stable on standard of care

6. WHO functional class I-III
7. Adolescent females of childbearing potential can only be included in the study if a pregnancy test is negative. Adolescent females of childbearing potential must agree to receive sexual counseling and use effective contraception as applicable. 'Effective contraception' is defined as progestogen-only hormonal contraception associated with inhibition of ovulation (implant), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), or any combination of adequate methods of birth control (e.g. condoms with hormonal contraception). Agreement to use contraception is required from the signing of the informed consent form up until 4 weeks after the last study drug administration.
8. Young men must agree to use adequate contraception when sexually active.
9. Written inform consent provided and if applicable child assent provided

(Note: The text was modified according to Amendment 3, please see Section 17.1.1.16. The Section was modified according to Amendment 6, see Section 17.3.1.2. The Section was modified according to Amendment 9, see Section 17.4.1.1, 17.4.1.2, and 17.4.1.3)

4.3 Exclusion criteria - amended

- Concomitant use of the following medications: phosphodiesterase (PDE) 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific phosphodiesterase (PDE) inhibitors (theophylline, dipyridamole), nitrates or NO donors (such as amyl nitrite) in any form [a]

[a] Pretreatment with the phosphodiesterase (PDE) 5 inhibitor Sildenafil is allowed up to 24 h prior to start of riociguat treatment (Visit 1). Pretreatment with the phosphodiesterase (PDE) 5 inhibitor tadalafil is allowed up to 3 days prior to start of riociguat treatment (Visit 1). Patients are not expected to be withdrawn from treatment with PDE5i for the purpose of entering into this trial. During the period without PDE5i, patients who received treatment with PDE5i are expected to be on stable clinical condition and receiving standard of care treatment with ERA and/or PCAs.

(Note: The footnote was added by Amendment 6, see Section 17.3.1.4. The footnote text was modified according to Amendment 9, see Section 17.4.1.4)

- Pretreatment with NO donors (e.g. nitrates) within the last 2 weeks before visit 1. The use of any drug including NO acutely for testing during catheterization is not an exclusion criterion.

- Active state of hemoptysis or pulmonary hemorrhage, including those events managed by bronchial artery embolization or any history of bronchial artery embolization or massive hemoptysis within 3 months prior to screening
- Systolic blood pressure (SBP) more than 5 mmHg lower than the age-, sex- and height-adapted level of the 50th SBP percentile (NHBPEP, 2004) see Table 4–1 and Table 4–2 and appendix 18.5.

Table 4–1: Age- and sex-adapted SBP (Boys)

Age (year)	BP percentile	Systolic BP (mmHg)						
		← Percentile of Height →						
		5TH	10TH	25TH	50TH	75TH	90TH	95TH
6	50th	91	92	94	96	98	99	100
7	50th	92	94	95	97	99	100	101
8	50th	94	95	97	99	100	102	102
9	50th	95	96	98	100	102	103	104
10	50th	97	98	100	102	103	105	106
11	50th	99	100	102	104	105	107	107
12	50th	101	102	104	106	108	109	110
13	50th	104	105	106	108	110	111	112
14	50th	106	107	109	111	113	114	115
15	50th	109	110	112	113	115	117	117
16	50th	111	112	114	116	118	119	120
17 *	50th	114	115	116	118	120	121	122

Note: Age will be rounded down if age is x years and <6 months and rounded up if x years and ≥6 months.

* Rounding up does not apply for those subjects older than 17 years and 6 months.

Table 4–2: Age- and sex-adapted SBP (Girls)

Age (year)	BP percentile	Systolic BP (mmHg)						
		← Percentile of Height →						
		5TH	10TH	25TH	50TH	75TH	90TH	95th
6	50th	91	92	93	94	96	97	98
7	50th	93	93	95	96	97	99	99
8	50th	95	95	96	98	99	100	101
9	50th	96	97	98	100	101	102	103
10	50th	98	99	100	102	103	104	105
11	50th	100	101	102	103	105	106	107
12	50th	102	103	104	105	107	108	109
13	50th	104	105	106	107	109	110	110
14	50th	106	106	107	109	110	111	112
15	50th	107	108	109	110	111	113	113
16	50th	108	108	110	111	112	114	114
17 *	50th	108	109	110	111	113	114	115

Note: Age will be rounded down if age is x years and <6 months and rounded up if x years and ≥6 months.

* Rounding up does not apply for those subjects older than 17 years and 6 months.

- History of left-sided heart disease, including valvular disease or heart failure
- Pulmonary hypertension related to conditions other than specified in the inclusion criteria
- WHO functional class IV
- Pulmonary veno-occlusive disease
- Screening aspartate transaminase (AST) and/ or alanine transaminase (ALT) more than 3 times the upper limit of normal (ULN)
- Non-stable disease status, e.g., signs and symptoms of decompensated right heart failure
- Severe bronchial asthma
- Severe restrictive lung disease
- Severe congenital abnormalities of the lung, thorax, and diaphragm
- Clinically relevant hepatic dysfunction (especially Child Pugh C)
- Renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73m^2 e.g. calculated based on Schwartz formula, for detailed calculation instructions, see 18.6)
- Subject with hypersensitivity to the investigational drug or any of the excipients
- Active smoking of tobacco of any type or quantity. Smoking marijuana is also not permitted.
- Subjects with any other condition that is not recommended with riociguat
- Previous assignment to treatment during this study

- Previous (within 30 days) or concomitant participation in another clinical study with investigational medicinal product(s)
- Any condition that, according to treating physician, might jeopardize subject's participation and compliance with procedures indicated in this protocol.
- PH associated with idiopathic interstitial pneumonia (PH-IIP)

(Note: The section was modified according to Amendment 3, see Sections 17.1.1.16 and 17.1.1.9.The section was modified according to Amendment 5, see Section 17.2.1.6.The Section was modified according to Amendment 6, see Sections 17.3.1.1, 17.3.1.2, 17.3.1.4, and 17.3.1.5. The Section was modified according to Amendment 9, see Sections 17.4.1.4 and 17.4.1.11.)

4.4 Concomitant medication - amended

Concomitant medication includes either continuation of a treatment started before study entry or addition of a new treatment during the study.

Co-administration of riociguat with the following concomitant medications is not allowed during the study:

- PDE inhibitors: PDE5 inhibitors (such as sildenafil, tadalafil, vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline) because of increased risk of hypotension
- Nitrates: Nitrates or NO donors (such as amyl nitrite) in any form (e.g. nitrates, molsidomine, sodium nitroprusside) because of increased risk of hypotension

Other concomitant medication considerations:

- Strong multi pathway cytochrome P450 (CYP) and P-glycoprotein 1(P-gp)/breast cancer resistance protein (BCRP) inhibitors: Concomitant use of riociguat with strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV (human immunodeficiency virus) protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg TID equivalent when initiating riociguat in subjects on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors and monitor for signs and symptoms of hypotension. A dose reduction should be considered in subjects who may not tolerate the hypotensive effect of riociguat.
- Strong CYP1A1 inhibitors and strong P-gp inhibitors: The concomitant use of riociguat with strong CYP1A1 (CYP family 1, subfamily A, polypeptide 1) inhibitors, such as the tyrosine kinase inhibitor erlotinib or the reverse-transcriptase inhibitor abacavir, and strong P-gp inhibitors, such as the immunosuppressive agent cyclosporine A, may increase riociguat exposure. In *vitro,* abacavir, rilpivirine, efavirenz, ritonavir, cobicistat and elvitegravir inhibited CYP1A1 and the metabolism of riociguat in the order listed with abacavir as the strongest inhibitor. Concomitant administration of HAART combinations with the drugs listed before led to an increase in riociguat mean AUC of up to about 160%. All these drugs should be used with caution. Blood pressure should be monitored and dose reduction of riociguat considered.

- Strong CYP3A4 inducers: The concomitant use of riociguat with strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may lead to decreased riociguat plasma concentration.
- Antacids: Co-administration of the antacid aluminum hydroxide / magnesium hydroxide reduced riociguat mean area under the curve (AUC) by 34% and mean maximum concentration (C_{max}) by 56%. Antacids should be taken at least 1 hour after riociguat.
- Omeprazole: Pre- and co-treatment with the proton pump inhibitor omeprazole (40 mg once daily) reduced riociguat mean AUC by 26% and mean C_{max} by 35%. This is not considered clinically relevant.

Clarithromycin: Co-administration of clarithromycin (500 mg twice daily), classified as strong and selective CYP3A4 inhibitor and also reported to be a weak-to-moderate P-gp inhibitor, moderately increased riociguat mean area under the curve (AUC) by 41% without significant change in C_{max}. This is not considered clinically relevant.

(Note: The Section was modified according to the Amendment 3, see Section 17.1.1.16.)

5. Treatment groups and regimens

5.1 Method of treatment allocation

Allocation to treatment dose will be done centrally by an interactive voice / web response system (IxRS). All subjects will be allocated to riociguat body-weight adjusted, individual dose titration (IDT).

The investigator will provide the IxRS with study center identification, the subject's date of birth (year) and age, gender, and weight. Further details are contained in the IxRS manual.

5.1.1 Body-weight adjusted individual dose titration regimen - amended

Riociguat must be provided to all patients using an individual dose titration scheme according to a body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for PAH (Figure 5–1). The individual optimal (maintenance) dose is to be determined based on patient's monitoring of systolic blood pressure, well-being and clinical status. For children with <50 kg body weight at baseline, a body weight adjusted dosing will be applied. Children with ≥ 50kg body weight will receive adult doses.

In subjects with a body-weight below 50 kg at baseline, riociguat will be administered as oral suspension TID with or without food. Subjects with a body-weight ≥50 kg at baseline will receive riociguat as tablet formulation.

The body weight-adjusted riociguat dosing schedule is provided in Table 5–2.

The following tablet strengths will be available: 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg. An oral suspension formulation of 0.15 mg/mL will also be available.

The treatment administration of riociguat oral suspension requires the use of a 5 mL or 10 mL dosing pipette. These dosing pipettes will be calibrated to the required volume of the weight adjusted dose and are manually operated. Each subject will be provided with a new reusable dosing pipette at each drug dispense.

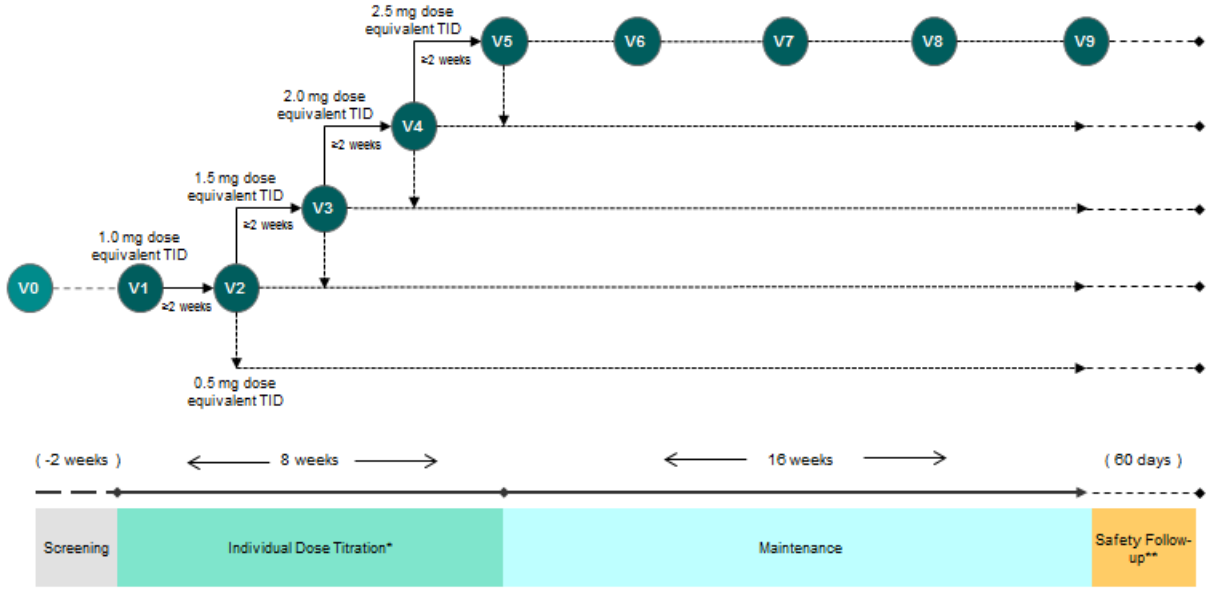
Recommended study medication handling process must be followed.

Educational material for training on the dosing pipette and dose administration for study site staff as well as for the subjects to ensure adequate dosing pipette use and treatment compliance will be distributed.

Subjects with <50 kg body weight will start with body-weight adjusted riociguat dose equivalent to the exposure of 1.0 mg TID in adults. Subjects with ≥ 50kg body weight will start with dose 1.0 mg TID. During the individual titration period, the dose will be up-titrated every 2 weeks (±2 days) at the discretion of the investigator, based on subject's peripheral systolic blood pressure and general tolerability measured at trough before intake of the next higher dose of riociguat. The maximum dose is the dose equivalent to the exposure of 2.5 mg in adults TID. Dose reductions for safety reasons are allowed at any time. The individual dose titration period will not exceed 8 weeks.

Dosing steps and dose equivalents in adults are shown in Figure 5–1.

Figure 5–1: Titration scheme for main study treatment phase



At each titration visit, the individual dose will be assigned based on the following algorithm where peripheral systolic blood pressure (SBP) will be measured (by oscillometry with the same calibrated oscillometry unit in each center) at trough before intake of the first dose of the day.

(Note: The description of the dosing of riociguat was clarified according to Amendment 3, see Sections 17.1.1.6, 17.1.1.13, and 17.1.1.16.The Section wording was modified according to Amendment 5, see Section 17.2.1.8.The Section was modified according to Amendment 6, see Section 17.3.1.2.)

Dose titration algorithm

- If systolic blood pressure (SBP) is less than 5 mmHg lower than the age-, sex- and height-adapted level of the 50th SBP percentile (NHBPEP, 2004) (see appendix 18.5), increase riociguat dose (+0.5 mg dose-equivalent TID)

- If SBP is ≥ 5 mmHg but less than 10 mmHg lower than the age-, sex- and height-adapted level of the 50th blood pressure (BP) percentile, maintain dose of riociguat.
- If SBP is ≥ 10 mmHg lower than the age-, sex- and height-adapted level of the 50th BP percentile, reduce riociguat dose (- 0.5 mg dose-equivalent TID)
- If any SBP is ≥ 5 mmHg lower than the age-, sex- and height-adapted level of the 50th BP percentile, with clinical symptoms of hypotension such as dizziness or presyncope, stop study treatment; restart after 24 hours with reduced dose - 0.5 mg dose-equivalent TID).

Down-titration of riociguat is possible for safety reasons at any time point. If at any time, the subject has symptoms of hypotension, temporarily stop the medication and restart after 24 hours with a reduced dose (decrease dosage by 0.5 mg dose-equivalent TID).

The sex- and age-adapted height percentile will be determined using standard height charts (see 18.1, Appendix 1). Age-, sex- and height-adapted levels of the 50th BP percentile will be determined according to Table 4–1 and Table 4–2.

If at any time, the subject has symptoms of hypotension, decrease the dosage by 0.5-mg dose equivalent TID.

At the end of the individual titration period (Visit 4), the subjects should have reached their individually adjusted dose (maximum equivalent dose of 2.5 mg riociguat TID). The established individual equivalent dose will then be taken as optimal dose to be administered during the 16-week maintenance period. Dose reductions for safety reasons are allowed in the maintenance phase, but a subsequent re-increase is not possible. During the LTE phase the dose may be up-titrated at the investigator's discretion.

Subjects not tolerating the body-weight adjusted riociguat 0.5 mg TID will be withdrawn from study.

The respective decision (increase, maintain, decrease) will be entered into the IxRS system. The study medication for the next 2-4 weeks will be dispensed to the subjects.

Dose interruptions

In the case an interruption takes place during the ***individual dose titration period*** and lasts longer than 3 consecutive days (9 doses missed), it is not allowed to restart the study medication again (respective subjects must be withdrawn from the trial).

In case an interruption takes place after completion of the titration period and lasts longer than 14 consecutive days, it is not allowed to restart the study medication again. In case of shorter interruptions, study medication can be restarted at the discretion of the investigator. Dose interruptions will be communicated to the DMC and/or SC.

(Note: The dose titration algorithm, dose up-titration in the LTE phase, and wording under dose interruptions were clarified according to Amendment 9, see Sections 17.4.1.10, 17.4.1.6 and 17.4.1.9.)

5.2 Subject identification

At screening Visit 0 and after having obtained informed consent and, if applicable, child assent has been provided, each subject will be assigned a unique 9-digit subject identification (SID) number by IxRS for unambiguous identification. The first 2 digits represent the country

code, the next 3 digits represent the center code, and the last 4 digits represent a sequential number assigned to each subject.

Subject identification numbers must be used in sequence and no number should be skipped, substituted or re-used.

5.3 Duration of study treatment - amended

During the individual dose titration period with a maximum duration of 8 weeks, the individual maximum equivalent dose will be established. Subjects will be treated on this body-weight adjusted dose level during the 16-week maintenance period as long as well tolerated. Subjects who have completed 24 weeks of treatment will be offered participation in the Long Term Extension (LTE) phase.

(Note: Wording describing the LTE in this section was modified according to Amendment 3, see Section 17.1.1.1.)

5.4 Formulation and dose - amended

Riociguat will be provided by Bayer as film-coated tablets and granules for reconstitution in an oral suspension (0.15 mg/mL), see Table 5–1. The following tablet strength will be available: 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg. For the application of the oral suspension, two sizes of dosing pipettes, manufactured by Raumedic, which are considered medical devices (therefore also called LDD- Liquid Dosing Device), are available and certified. These dosing pipettes are designed to deliver between 1 mL and 5 mL with 0.25 mL dosing increments as well as 2 mL to 10 mL with 0.5 mL dosing increments. These increments were chosen to enable accurate bodyweight-adjusted dosing. Further details on the dose-measuring pipettes for the oral suspension formulation are given in detail in the suspension manual.

Tablets and oral suspension will be administered orally in a TID regimen.

Subjects <50 kg at baseline will receive riociguat oral suspension during the initial 24-week treatment phase.

Subjects ≥50 kg at baseline will receive oral tablets. If the BW decreases below 50 kg, then the IXRS will deliver the oral suspension.

During the long-term extension phase, subjects receiving stable dose of 1.0 mg, 1.5 mg, 2.0 mg, or 2.5 mg TID as oral suspension, can switch to the tablet formulation according to the discretion of the investigator provided the body weight is ≥ 50 kg (for details on tablet and suspension body-weight adjusted equivalent dosing, see Table 5–2.)

(Note: The text was modified according to Amendment 3, see Section 17.1.1.13.)

Table 5–1: Identity of investigational product

International non-proprietary name (INN)	Riociguat	
Sponsor's internal reference number	BAY 63-2521	
Formulation	Film-coated tablets	Oral suspension
Galenical form	Round immediate-released tablets, diameter 6 mm	Granules
Composition	Active ingredient: *Methyl-N-[4,6-diamino-2-[1-[(2-fluorphenyl)methyl]-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl]-N-methyl-carbaminate* Empirical formula: $C_{20}H_{19}FN_8O_2$ Molar mass: 422.42 g/mol (molarity)	
	Excipients: lactose, microcrystalline cellulose, magnesium stearate, crospovidone, hypromellose, and sodium lauryl sulphate *Coating*: hydroxypropyl cellulose, hypromellose, propylene glycol, iron oxide (red and yellow), and titanium dioxide.	*Excipients*: mannitol, microcrystalline cellulose and carmellose sodium, hypromellose, sodium benzoate, citric acid, xanthan gum, sucralose, strawberry flavor
Strength	0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg	0.15 mg/mL
Material numbers	83296470 BAY 63-2521 TABL 0.5 mg 511 COAT 83296535 BAY 63-2521 TABL 1.0 mg 512 COAT 83296543 BAY 63-2521 TABL 1.5 mg 513 COAT 83296578 BAY 63-2521 TABL 2.0 mg 504 COAT 83296608 BAY 63-2521 TABL 2.5 mg 515 COAT	84367923 BAY 63-2521 GRAN SUSP 0.3%
Packaging	High-density polyethylene bottles	Brown glass bottles

Abbreviation: TABL = tablet

All subjects will receive body-weight-adjusted dose of riociguat. The starting dose will be the body weight-adjusted equivalent of the 1.0-mg dose in adults. Guidelines on how to prepare the oral suspension are provided to the subjects/parents.

The body-weight-adjusted riociguat dosing schedule is provided in Table 5–2.

Table 5–2 : 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).

(Note: The table was modified according to Amendment 3, see Section 17.1.1.6.)

5.5 Packaging, labeling, and storage

All study medication will be labeled according to local law and legislation. Also, a system of numbering in accordance with Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study medication can be traced back to the respective bulk ware of the ingredients. Further details are provided in a separate manual.

A complete record of batch numbers and expiry dates of all study medication provided by Bayer, as well as the labels, will be maintained in the study file.

All study medication need to be stored at the site according to the labeled storage advice in accordance with Good Clinical Practice (GCP) and GMP requirements.

The study drug is to be kept in a secure area. The responsible site personnel will confirm receipt of study medication via IxRS and will use the study medication only for this study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study medication must be properly documented according to specified procedures.

5.6 Treatment assignment - amended

After enrolment, the subject identification number will be recorded on the corresponding electronic case report form (eCRF). The subject identification number will also have to be recorded on the label of the study medication.

In case bosentan or other ERA and/or PCA is/are provided locally, the compound's name, dose, quantity and batch number, or a copy of the prescription has to be included in the subject's files.

(Note: The text was modified according to Amendment 3, see Section 17.1.1.11.The text was modified according to Amendment 6, see Section 17.3.1.9.)

5.7 Study treatment delivery and compliance assessment

All empty packaging and unused study drug will be returned at all study visits. All non-used study medication will be kept securely in a designated locked container. Tablets and suspension volumes will be counted for a compliance check. The investigator should ensure adequate subject compliance.

6. Study procedures

6.1 Study visits - amended

The main study part comprises 3 periods:

- Pre-treatment period (Screening): up to 2 weeks. This period is to identify potential eligibility of subjects who have been diagnosed with PAH. This visit will take place up to 2 weeks before Visit 1 (baseline visit).
- Main study (Active) treatment period: 24 weeks (titration phase: 8 weeks, maintenance phase: 16 weeks):
  - The individual titration phase comprises 4 visits 2 weeks (±2 days) apart.
  - The maintenance phase comprises 5 visits 4 weeks (±5 days) apart.

- Follow-up period: at least 60 days for serious adverse events (SAEs). (Only for patients who do not enter the long-term extension study or who stop the study medication prematurely.)

Subjects who have completed 24 weeks of treatment will be offered participation in an optional long term extension phase. Subjects not entering the LTE phase will perform the safety follow-up visit (see section 6.1.4). Subjects completing the optional LTE will also perform the safety follow up visit after 60 + 8 days after LTE. Subjects dropping-off the protocol any time after Visit 1 and before Visit 9 will perform an end-of-treatment visit (see section 6.1.3).

The titration visits have to be performed at the study site. Only visits at Week 12 and/or Week 20 (Visit 6 and/or Visit 8) might be performed as home visits by an experienced nurse/ healthcare practitioner in close contact with the treating investigator, when no further titration is scheduled and subjects are on stable dose. The decision to delegate the responsibility to visit the subject is at the discretion of the investigator, must be consistent with regional medical practice, and in accordance with regional legal requirements. The responsibility must be documented on the delegation log and signed by the investigator. At the end of the titration phase (Week 8, Visit 5) patients will have reached riociguat doses between 0.5 mg TID and 2.5 mg TID.

(Note: The wording describing LTE was modified according to the Amendment 3, see Section 17.1.1.1.The Section was modified according to Amendment 6, see Section 17.3.1.2.)

6.1.1 Pre-treatment phase (Visit 0, Day -14 to -1) - amended

The parents/legal guardians and children will be given an explanation about the study and will be given sufficient time to consider their participation in the study and to ask any questions. Afterwards, informed consent and, if applicable, assent will be obtained (see section 11.2). Collection of AEs starts after informed consent is signed. If the subject passes the screen of inclusion and exclusion criteria, the subject will be eligible to enter the study. The following procedures will be performed if no historical data (not older than 30 days) are available:

- Obtain demographics (incl. smoking status) and medical history
- Record concomitant PAH specific medication
- Perform physical examination (incl. height, weight, vital signs and pubertal assessment using Tanner scale [see section 18.3])
- Obtain blood sample if AST, ALT, creatinine, blood urea nitrogen (BUN), gamma-glutamyltransferase (GGT), uric acid (UA), total bilirubin (T-Bil), Albumin (Alb), Sodium (Na), potassium (K), Calcium (Ca), P and complete blood count (CBC) are not available within 30 days prior to screening visit
- Perform ECG (electrocardiogram)
- Pregnancy test for females of childbearing potential
- Child Health Questionnaire (SF-10 and PedsQL Generic Core Scales self-report) (section 18.2 and 18.7)
- In case RHC has been performed for a study subject before enrollment, record the most recent RHC parameters to the eCRF (timing of RHC not limited to the period of Day -14 to -1)

(Note: The text was modified according to Amendment 3, see Sections 17.1.1.8 and 17.1.1.16. The Section was modified according to Amendment 5, see Sections 17.2.1.1 and 17.2.1.2. The Section was modified according to Amendment 6, see Sections 17.3.1.2 and 17.3.1.3. The Section was modified according to Amendment 9, see Section 17.4.1.8.)

6.1.2 Main study treatment period - amended

6.1.2.1 Individual titration phase (Visit 1 – Visit 4) - amended

At Visit 1, subjects should come to the hospital for the riociguat morning dose. At Visits 2 and 4, subjects are allowed to take the riociguat morning dose up to midday. The following procedures will be performed during the titration period:

- Procedures and assessments for the baseline visit (Visit 1) should be completed within the span of one day
- Re-confirm in-/exclusion criteria (Visit 1 only, prior to study drug intake)
- Record concomitant medication incl. concomitant PAH specific medication
- Perform physical examination (incl. height, weight and vital signs)
- Pregnancy test for females of childbearing potential (at Visit 1 and Visit 3)
- Decide on the next dose based on the titration algorithm and dispense study medication
    - Instruct how to take study drug
    - Provide study guidelines for dosing/suspension (Visit 1 only)
- Determine WHO functional class (Visit 1 only)
- Perform echocardiogram (Visit 1 only)
- Perform electrocardiogram (Visit 1 only)
- X-ray of left hand for determination of bone age (Visit 1 only: if no historical data [not older than 30 days] are available)
- Perform 6MWD test (Visit 1 only)
- Collect PK sample (Visit 1 and 3), for details see Table 0–2
- Collect NT-proBNP or BNP (Visit 1 only; when both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit)
- Check adverse events including adverse events of special interest
- Check the systolic BP monitoring form provided by the patients at the visit, if applicable (Visit 2 – 4)
- Check drug accountability (Visit 2 – 4)
- Taste assessment questionnaire (Visit 1 only) (section 18.4)
- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a

local package insert of bosentan or other ERA, or medical practice at the study site at any time.

- In case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF

(Note: The Section was modified according to Amendment 3, see Sections 17.1.1.8 and 17.1.1.16. The Section was modified according to Amendment 5, see Sections 17.2.1.1 and 17.2.1.2.The section was modified according to Amendment 6, see Sections 17.3.1.2 and 17.3.1.6. The section was modified according to Amendment 9, see Section 17.4.1.5.)

6.1.2.2 Maintenance phase (Visit 5 - Visit 9) - amended

Subject should take the riociguat morning dose at home as usual, except of Visit 5, where the morning dose will be taken at the hospital. The following procedures will be performed during the maintenance period:

- Record concomitant medication incl. concomitant PAH specific medication
- Perform physical examination (incl. height, weight, vital signs and at Visit 9 only, pubertal assessment using Tanner scale)
- Collect PK sample (Visit 5 only, for details see Table 0–2)
- Pregnancy test for females of childbearing potential
- Dispense study medication
    - Instruct how to take study drug
- Check adverse events including adverse events of special interest
- Check the systolic BP monitoring form provided by the patients at the visit, if applicable
- Check drug accountability
- Determine WHO functional class (Visit 9 only)
- Perform echocardiogram (Visit 9 only)
- Perform electrocardiogram (Visit 9 only)
- Perform 6MWD (Visit 9 only)
- Collect NT-proBNP or BNP (Visit 9 only; when both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit)
- X-ray of left hand for determination of bone age (Visit 9 only)
- Child Health Questionnaire (SF-10 and PedsQL Generic Core Scales self-report) (Visit 9 only)
- Taste assessment questionnaire (Visit 9 only)
- Obtain laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) at Visits 5 and 9 as well as record the same parameters when

obtained as medically required according to a local package insert of bosentan or other ERA, or medical practice at the study site at any time

- In case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF

(Note: The Section was modified according to Amendment 3, see Sections 17.1.1.8, 17.1.1.14, and 17.1.1.16. The Section was modified according to Amendment 5, see Sections 17.2.1.1 and 17.2.1.2. The section was modified according to Amendment 6, see Sections 17.3.1.2, 17.3.1.3, and 17.3.1.6. This section was modified according to Amendment 9, see Section 17.4.1.13.)

6.1.3 End-of-treatment visit - amended

For all subjects dropping-off the protocol at any time after V1 and before V9, an end-of-treatment visit has to be performed.

The same procedures as at Visit 9 will be performed with the exception of the x-ray of left hand.

In case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF.

(Note: The Section was modified according to Amendment 3, see Section 17.1.1.16.
The Section was modified according to Amendment 5, see Section 17.2.1.2. This section was modified according to Amendment 9, see Section 17.4.1.13.)

6.1.4 Safety follow-up visit - amended

For all subjects stopping study medication either at the end of treatment or prematurely discontinuing the study at any time, a follow-up visit 60 days (±8 days) after last study medication intake has to be performed.

For subjects directly proceeding with treatment in the long-term extension phase, a safety follow-up visit 60 days (+8 days) will be scheduled either at the end of optional LTE phase, when patient's transition to approved and commercially available riociguat in the respective country is possible, or when prematurely discontinuing LTE phase at any time.

The following procedures will be performed:

- Record concomitant medication incl. concomitant PAH specific medication
- Perform physical examination (incl. height, weight and vital signs)
- Pregnancy test for females of childbearing potential
- Check adverse events including adverse events of special interest
- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or other ERA, or medical practice at the study site at any time
- In case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF

(Note: The safety follow up visit added to concern all subjects as well as the wording was changed according to Amendment 3, see Section 17.1.1.4. The Section was modified

according to Amendment 5, see Sections 17.2.1.1 and 17.2.1.2.The section was modified according to Amendment 6, see Section 17.3.1.2.)

6.1.5 Unscheduled visit - amended

If deemed necessary, it is at the investigator's discretion to arrange additional visits. The following procedures will be performed:

- Record concomitant medication incl. concomitant PAH specific medication
- Perform physical examination (incl. height, weight and vital signs)
- Dispense study medication (if required)
    - Instruct how to take study drug
- Check adverse events including adverse events of special interest
- Update eCRF
- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or other ERA, or medical practice at the study site at any time
- In case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF

(Note: The Section was modified according to Amendment 5, see Sections 17.2.1.1 and 17.2.1.2.The Section was modified according to Amendment 6, see Section 17.3.1.2.)

6.1.6 Optional long-term extension phase (until adulthood or approval in the indication and commercial availability) - amended

Children who require treatment with riociguat for more than 24 weeks will be offered participation in the optional extension phase. Subjects who become ≥18 years of age will continue to receive their individually optimal dose of riociguat (drug) from the clinical supply for up to 6 months to allow the transition to commercial product to complete as locally applicable.

The following procedures will be performed:

Every 3 (± 14 days) months

- Record concomitant medication incl. concomitant PAH specific medication
- Pregnancy test for females of childbearing potential
  Pregnancy testing is to be performed in 4-weekly intervals starting at Visit 1 until 4 weeks after the patient stops intake of study drug. If the interval falls on a visit date pregnancy testing is to be performed locally while at all other dates the patient is to perform a urine dipstick test at home. The results are to be documented in the eCRF and in the patient file. The result of every home urine pregnancy test should be actively requested by the site as soon as the test is due. The patient must report a positive result to the site without delay. The results are to be documented in the eCRF and in the patient file in a timely manner. It is not acceptable to obtain the result only at the next scheduled visit at the site.

- Perform physical examination (In the long term extension phase the physical examination includes monitoring of growth velocity in addition to the. height, weight and vital signs)
- Dispense study medication
    - Instruct how to take study drug
- Check drug accountability
- Check adverse events including adverse events of special interest
- Exploratory efficacy (6MWD test, WHO FC, NT-proBNP or BNP[when both tests are available, NT-pro-BNP should be chosen over BNP and the same test should be performed at every required visit], QoL [SF-10 and PedsQL Generic Core Scales self-report], echocardiography, TTCW)
- If needed and to reduce burden, 6MWD test and echocardiography can be performed at every second visit in LTE at the discretion of the investigator
- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or other ERA, or medical practice at the study site at any time
- In case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF
- X-ray of the left hand will be performed every 12 months until growth plates are closed
- Pubertal assessment using Tanner scale will be performed every 12 months
- Perform the Child Health-related Questionnaire (SF-10) and PedsQL. The age version used must match with subject´s actual age at time of completing the questionnaire.

(Note: The wording was modified according to Amendment 3, see Sections 17.1.1.1 and 17.1.1.14. The Section was modified according to Amendment 5, see Sections 17.2.1.1 and 17.2.1.2.The Section was modified according to Amendment 6, see Sections 17.3.1.2, 17.3.1.3, and 17.3.1.6. The Section was modified according to Amendment 9, see Section.17.4.1.13.)

6.2 Safety outcomes - amended

During the course of the study treatment-emergent adverse events (TEAEs), ECGs, bone age x-ray of left hand, laboratory tests, vital signs, body weight and frequency of premature discontinuations will be assessed.

The primary safety outcome is described as:

- The change from baseline (V1, Day 0) to the end of treatment (V9, week 24) of:
    - Heart rate
    - Blood pressure

- Bone age x-ray of left hand
- Laboratory parameters (see description in respective section below)

- The assessment of:
  - Incidence of treatment-emergent adverse event
  - Incidence of treatment-emergent serious adverse events

Other safety outcomes are the changes from baseline (V1, Day 0) to the end of treatment (V9, week 24) of:

- ECG parameters

Bone monitoring

Skeletal development will be assessed throughout the study trial.

During the main study period, x-ray of left hand will be performed before study drug intake (Visit 1) and at week 24 (Visit 9). For those patients entering the extension phase, the x-ray of left hand will be performed every 12 months until growth velocity is plateauing and growth plates are closed.

Bone age and also bone morphology will be determined centrally by a specialist. Every 12 months until growth velocity is plateauing and growth plates are closed, the subject's overall development will also be assessed by physical examination, growth chart evaluation and pubertal development using Tanner scale, and at the discretion of the investigator in case of clinical suspicion for bone and/or growth anomalies.

This data will be reviewed on an ongoing basis by the DMC.

Laboratory parameters

Laboratory parameters will be collected at V0 (if no historical data is available), V5 and V9.

Hematology: CBC

General Chemistry: AST, ALT, Creatinine, BUN, GGT, UA, T-Bil, Alb, Na, K, Ca, and P

Afterwards; any additional collection of laboratory parameters will be obtained in case medically required according to a local package insert of bosentan, or other ERA, or medical practice at the site at any time point and will be captured in the eCRFs.

Echocardiograph

Echocardiographic parameters will be evaluated centrally by a specialist during the main study phase and optional long term extension. Details are specified in the respective Imaging documents.

(Note: The paragraph Laboratory parameters was added by Amendment 3, see Section 17.1.1.7. The paragraph was modified according to Amendment 5, see Sections 17.2.1.1 and 17.2.1.4.The Section was modified according to Amendment 6, see Section 17.3.1.2.)

6.3 Efficacy/Pharmacodynamic/Other outcomes - amended

Main secondary endpoints will be assessed as:

Change from baseline to end of treatment (week 24) of:

- 6-Minute Walking Distance (6MWD)
- WHO functional class
- Lab N-terminal prohormone brain-type natriuretic peptide or brain-type natriuretic peptide (when both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit)
- Quality of Life scores (parent questionnaire and in children 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, and computing of cardiac output.

Time to clinical worsening

- Hospitalization for right heart failure
- Death
- Lung transplantation
- Pott's anastomosis and atrioseptostomy
- Worsening of PAH symptoms, which must include either:
  - an increase in WHO FC

    OR
  - appearance/worsening symptoms of right heart failure

    AND

    need for additional PAH therapy.

Other endpoints assessed in the study will be:

- Taste and texture of the pediatric formulation(s) must be assessed by use of a questionnaire at the beginning and at the end of treatment (week 24).
- Right heart catheterization

  A change in RHC parameters (if available) obtained from RHC performed before study enrollment and during study conduct.

(*Note: The paragraph was modified according to Amendment 5, see Sections 17.2.1.2, 17.2.1.3 and 17.2.1.7.The Section was modified according to Amendment 6, see Sections 17.3.1.2, 17.3.1.3, and 17.3.1.6. This section was modified according to Amendment 9, see Sections 17.4.1.7 and 17.4.1.13.*)

6.4 Pharmacokinetics/Pharmacodynamics analyses - amended

Blood samples will be taken for pharmacokinetic and pharmacodynamic measurements from all participants treated with riociguat.

The number of PK blood samples to be taken has been optimized using physiologically based pharmacokinetic (PBPK) modelling predictions in conjunction with clinical trials simulations (CTS) in order to only collect the minimum amount of blood needed for adequate analysis (sparse sampling).

Based on these evaluations the following measures to minimize pain and distress have been included: the number of blood samples in children from 6 to less than 18 years of age for PK analysis must not exceed four, and the minimum amount of blood needed for adequate analysis of each sample is 1.0mL of blood.

The following blood samples will be taken:

Visit 1: 2 PK samples will be taken: the first at 0.5 to 1.5 h and the second at 2.5 to 4 h post-dose. Preferred proposal is to have both post-dose samples at the first visit. (To ensure having PK samples in case of drop-outs, both “early post-dose” samples should be collected at the first visit. If this is not feasible, the second post-dose sample can be taken at any visit.)

Visit 3 and Visit 5: Trough samples should be collected -1 to 0 hours before the morning dose at both visit 3 and visit 5, which is approx. 5 to 15h after the evening dose.

For all visits in the main study phase, the exact time of three riociguat dosings (current and the previous two doses) and time of PK blood sampling will be documented in the eCRF.

If, for any reason, PK samples are taken outside of the pre-specified time window, the exact time that the sample was taken should be recorded and not the pre-defined time window. If riociguat was temporarily stopped prior to a PK sample collection visit, sampling of blood for PK analysis according to this visit's schedule should be postponed until riociguat treatment has been restarted and sustained for 3 days.

If PK samples are collected at an unscheduled visit or at a visit not foreseeing PK collection, the previous riociguat doses and the time of sampling should be documented like described above. Those samples may be included in the analysis.

Primary PK outcome measure:

Pre- and post-dose blood samples for PK characterization of riociguat and its active metabolite BAY 60-4552 will be collected during the titration and the maintenance phase of the study. For details, see section 7.4.3.

(Note: Wording in this Section was changed according to Amendment 3, see Section 17.1.1.16. The wording was modified according to Amendment 6, see Section 17.3.1.2. This section was modified according to Amendment 9, see Section 17.4.1.13.)

6.5 Study guidelines for parents and children - amended

Parents/children will receive study guidelines, specifying:

- The local medical contact person and local emergency telephone number
- The dates of hospital visits and telephone calls, if applicable
- Instructions to return empty medication packages and unused study medication

- Instructions on signs and symptoms of hypotension (systolic BP monitoring form).
- How to take riociguat tablets or suspension
- Calendar to track the date, time of study drug intake

(Note: This section was modified according to Amendment 9, see Section 17.4.1.13.)

6.6 Study committees

6.6.1 Steering Committee

The Steering Committee (SC) has the overall scientific responsibility of the study. Its tasks and responsibilities are:

- To facilitate and approve the final protocol
- To help select the investigators network
- To support and organize the national logistics in the initiation and conduct of the study
- To ensure a scientifically sound and safe conduct of the study
- To consider the DMC recommendations
- To monitor progress of study enrollment
- To assist in the analysis and presentation of the results
- To decide on the publication and presentation policy of final results.

6.6.2 Data Monitoring Committee

This independent committee has the responsibility to provide the SC and the sponsor with recommendations related to the protection of the subjects safety, including stopping recruitment and study treatment. For that purpose, the DMC will regularly review all incidences of serious adverse events and adverse events of special interest. Organizational aspects, responsibilities, and processes will be described in the DMC charter.

For all subjects reaching week 24 of the main study treatment phase and all subjects continuing in the LTE, the left hand x-rays will be evaluated by the DMC. The DMC will be provided with all relevant documentation on an ongoing basis.

After 5 patients in the ≥12 to <18 years old group have reached their optimal dose, have been treated on their maintenance dose and obtained the control x-ray of left hand at week 24, their data will be evaluated by DMC. After agreement of the DMC, the enrolment of patients in the age group ≥6 to <12 years will start.

All cases of clinical worsening (as defined in protocol section 6.3) that occur after intake of first dose of study medication in the main study treatment phase - including the 60 day safety follow-up period (only for those patients not entering the LTE) - will be evaluated by the DMC. After the completion of the main study, the DMC will be provided with all relevant documentation related to the cases.

Organizational aspects, responsibilities, and processes will be described in the DMC charter. DMC results will be included in the final analyses of the main study.

7. Statistical and analytical methods

7.1 General considerations

The plan described in the following sections will be detailed in a Statistical Analysis Plan (SAP). The SAP will accommodate protocol amendments. Any revision will be clearly identified in the final SAP, issued prior to data base lock. All efforts will be taken to avoid missing data in important baseline characteristics and post baseline data. Missing data proportions will be reported.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables using frequency tables and continuous variables by sample statistics, i.e. mean, standard deviation, minimum, median, quartiles and maximum.

Statistical analyses will be performed using SAS; the version used will be specified in the statistical analysis plan (SAP).

7.2 Analysis sets

Safety analysis set (full analysis set, FAS): this population will include all subjects assigned to receive study medication who received at least one dose of study medication.

Listing only set (LOS): this population includes all screening failures.

7.3 Demographic and other baseline characteristics

Demographic and baseline characteristics, medical history, concomitant PAH medications and patient disposition will be summarized for the FAS population. For continuous measurements, the mean, standard deviation, range and median will be computed; for categorical values, the frequency and percent will be provided. Medical history findings (i.e. previous diagnoses, diseases or surgeries) will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms.

7.4 Analyses

A descriptive analysis of the safety and efficacy parameters will be performed.

(Note: The section was modified according to Amendment 6, see Section 17.3.1.2.)

7.4.1 Safety analysis - amended

The primary objective is to evaluate the safety and tolerability of riociguat in children with PAH. Primary endpoint of the study is: Change from baseline to end of treatment (week 24) of safety and tolerability assessed by incidence of adverse events and serious adverse events, recording of vital signs and left-hand X-ray and laboratory panel.

The safety evaluation of adverse event (AE) data will include:

- The incidence of treatment-emergent AEs (TEAEs). Adverse events are considered to be treatment-emergent if they have started or worsened after first application of study drug up to 2 days after end of treatment with study drug.
- Tables of serious and/or drug-related treatment-emergent AEs, treatment-emergent AEs leading to discontinuation of study drug and AEs of special safety interest.

- The incidence of AEs during pre-treatment and during follow-up (i.e. AEs occurring more than 2 days after end of treatment with study drug).
- Listings of serious adverse events (SAEs), AEs leading to discontinuation of study drug and AEs of special safety interest.
- Descriptive summaries of mortality in the study.
- Listing of deaths in the study period, including day of death relative to start and stop of study drug and cause of death.

The safety evaluation of laboratory data will include:

- Incidence rates of treatment-emergent laboratory values outside of normal range
- Incidence rates of pre-specified laboratory data abnormalities
- Descriptive analysis of laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) and their corresponding changes from baseline

Other evaluations of safety data will include:

- Descriptive analysis of body weight, vital signs, ECG parameters, left hand x-ray and their corresponding changes from baseline.
- Tabulation of ECG status pre-dose, 2 and 4 hours post treatment-initiation.
- Incidence rates of treatment-emergent ECG abnormalities.

Time points of assessment: Assessment of adverse events at baseline, at all visits in the titration phase and maintenance phase, and every 3-4 months in the extension phase. Left hand x-ray at baseline, end of study treatment period (week 24) and every 12 months until growth plates are closed.

For details on safety variables, see section 6.2.

(Note: The wording in this section was modified according to the Amendment 3, see Section 17.1.1.8. The wording in this section was modified according to Amendment 5, see Section 17.2.1.1.The Section was modified according to Amendment 6, see Section 17.3.1.2.)

7.4.2 Efficacy analysis - amended

Other objectives are to characterize the pharmacodynamic profile of riociguat using the following parameters: time to clinical worsening (TTCW), exercise capacity (6MWD test), functional capacity (measured by WHO FC), laboratory biomarkers (NT-proBNP or BNP [when both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit]), echocardiographic parameters and QoL measurements (SF-10 and PedsQL Generic Core Scales self-report).

Continuous efficacy parameters will be analyzed descriptively by sample summary statistics. Time points of efficacy assessment: Exploratory efficacy at baseline and week 24 and every 3 to 4 months in the extension phase.

Categorical efficacy parameters will be analyzed descriptively by frequency tables.

RHC parameters (if available) will be analyzed descriptively by summary tables.

For details on the exploratory efficacy variables, see section 6.3.

(*Note: The section was modified according to Amendment 5, see Section 17.2.1.2. The Section was modified according to Amendment 6, see Sections 17.3.1.2, 17.3.1.3, and 17.3.1.6.)*

7.4.3 Pharmacokinetic analysis - amended

The number of blood samples to be taken for the assessment of pharmacokinetic parameters was determined using clinical trial simulation (CTS) based on the physiology based PK (PBPK) modeling predictions. In order to minimize pain and distress for the patient population, the number of PK samples was kept to the minimum. The minimum amount of blood needed for adequate analysis for each sample 1.0 mL of blood. For investigation of exposure behavior, plasma concentrations of BAY63-2521 and its active metabolite M1 (BAY 60-4552) will be analyzed descriptively.

PK analyses using population approaches will be used to describe the pharmacokinetics of riociguat, including potential influence relevant subject covariables (e.g. age, gender, serum creatinine, etc.) and to relate pharmacodynamic parameters with riociguat plasma concentrations (PK/PD evaluations). Details will be given in a separate detailed PK/PD evaluation plan and will be reported separately.

(Note: *This section was modified according to Amendment 9, see Section 17.4.1.13.)*

7.4.4 Interim analyses

There is no interim analysis planned for this study.

7.4.5 Analyses - amended

The study results will be reported once all the pediatric subjects have completed their main study treatment period of 24 weeks. Thereafter only descriptive summaries of study data from the ongoing subjects will be provided.

(Note: The text was modified according to the Amendment 3, see Section 17.1.1.2.)

7.5 Determination of sample size - amended

Children on treatment with ERAs and/or PCAs can be enrolled. At least 20 subjects on treatment with bosentan or other Endothelin Receptor Antagonists (ERA) must be enrolled in the study. The sample size does not originate from a formal sample size calculation, but is based on an evidence-based feasibility assessment. Based on the results of the evidence-based feasibility survey (Davie, 2014) and the proposed PK evaluation (see section 7.4.3), 20 patients will permit an accurate PK evaluation and feasibility of the study in a reasonable time frame. Every effort will be made to enroll equal numbers of patients in both age cohorts (see section 4.1).

(Note: The Section was modified according to Amendment 6, see Section 17.3.1.2. This section was modified according to Amendment 9, see Section 17.4.1.13.)

8. Adverse events

Individual listings of adverse events will be provided. The incidence of treatment-emergent adverse events will be summarized, using MedDRA preferred terms, grouped by primary system organ class.

8.1 Definitions

8.1.1 Adverse event (AE) - amended

An AE, including AE in relation to a medical device (i.e. Raumedic dosing pipette), is any untoward medical occurrence in a subject administered with a pharmaceutical product and does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not considered related to the drug. AE associated with the use of a drug, whether or not considered drug-related, includes AE occurring in the course of the use of a drug, from an overdose whether accidental or intentional, from drug abuse, from drug withdrawal, or if there is a reasonable possibility that the event occurred purely as a result of participation in the study, even if it is not related to the drug. AEs were considered to be treatment-emergent if they had started or worsened after the first dose of study medication up to 2 days after end of treatment with study medication. The clinical manifestation of any failure of expected pharmacological action is not recorded as an AE, if it is already reflected as an outcome captured in the eCRF, except if the event fulfills the criteria for a “serious” AE.

A surgical procedure or intervention that was planned prior to the study should not be recorded as an AE. Conditions, including abnormal physical examination findings, symptoms, and diseases will be recorded as medical history, if they started before providing written informed consent/assent. If the condition started or deteriorated after providing written informed consent/assent, it will be documented as adverse event.

Medical device related event is any occurrence or information the investigator becomes aware of regarding a medical device used in the study. Typical examples are:

- Malfunction, failure or deterioration in the characteristics or performance,
- An inaccuracy in the labeling or instructions for use,
- Use error.

(Note: The text was modified according to the Amendment 3, See section 17.1.1.13.)

8.1.2 Serious adverse event (SAE)

An SAE is any untoward medical occurrence that at any dose is resulting in death, is life-threatening (i.e. the subject was at risk of death at the time of the event), requires hospitalization or prolongation of existing hospitalization unless the admission results in a hospital stay of less than 12 hours, is pre-planned (e.g. to perform routine RHC), or is not associated with an AE (i.e. social hospitalization for purposes of respite care), results in persistent or significant disability/incapacity. In addition, SAE is a congenital anomaly or a birth defect or an important medical event, including associated invasive treatment, as judged by the investigator. For reporting of a SAE, local regulations take precedence if more stringent definitions are applicable.

8.1.3 Unexpected AEs

An unexpected AE is any adverse drug event whose specificity or severity is not consistent with the investigator brochure or package inserts for marketed products. Also, reports which add significant information on specificity or severity of an already documented AE constitute unexpected AEs, e.g. an event more specific or more severe than described in the investigator

brochure would be considered “unexpected”. Specific examples would be 1) acute renal failure as a labeled adverse event with a subsequent new report of interstitial nephritis and 2) hepatitis with a first report of fulminant hepatitis.

8.2 Relationship of AE to study drug

The assessment of the causal relationship between an AE and the use of study drug is a decision to be made by the investigator based on all available information at the time of the completion of the eCRF and is based on whether there was a "reasonable causal relationship" to the study drug. An assessment of "no" would include the existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site, or non-plausibility, e.g. the subject while on a bike is struck by an automobile when there is no indication that the study drug caused disorientation that may have caused the event. An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study drug. Factors in assessing the relationship of the AE to study drug include the temporal sequence from drug administration (the event should occur after the study drug is given) and the length of time from study drug exposure, recovery on study drug discontinuation (de-challenge), and recurrence on study drug re-introduction (re-challenge), underlying, concomitant, or intercurrent diseases should be evaluated in the context of the natural history and course of any disease the subject may have, concomitant medication or treatment and, finally, the pharmacology and pharmacokinetics of study drug.

8.3 Causal relationship to protocol-required procedure

The assessment of a possible causal relationship between the AE and protocol-required procedure is based on the presence of a reasonable relationship.

8.4 Intensity of an AE, action taken and outcome

The intensity of an AE is assessed as mild (usually transient in nature and generally not interfering with normal activities), moderate (sufficiently discomforting to interfere with normal activities), and severe (prevents normal activities).

Any action on study drug to resolve the AE is to be documented as either: study drug withdrawn, interrupted, dose increased, dose not changed, dose reduced, not applicable or unknown. Other specific treatment(s) of AEs will be documented as: none, remedial drug therapy or other. The outcome of the AE is documented as: recovered/resolved, recovering/ resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal or unknown.

8.5 Assessment and documentation of adverse events

After signing the informed consent, documentation of AEs including the AEs related to the medical device, must be supported by an entry in the subject’s file. A laboratory test abnormality considered clinically relevant, e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates, severity, relationship to study drug, action taken and outcome. When assigning the cause of death, "death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

8.6 Reporting of serious adverse events

All investigators will be thoroughly instructed and trained on all relevant aspects of the reporting obligations for SAEs including the SAEs related to the medical device. This information, including all relevant contact details, is summarized in the investigator site file and will be updated as needed.

SAEs occurring after enrolment up to 30 days after the last study drug administration must be reported within 24 hours of the investigator's awareness. Reports should be as complete as possible, and must be followed up until resolution or stabilization. When required, and according to local law and regulations, SAEs must be reported to the ethics committee and regulatory authorities. If reported, SAEs occurring after the protocol-defined observation period will be processed by Bayer according to all applicable regulations (i.e. notification of Independent Ethics Committees/Institutional Review Boards [IECs / IRBs] and other authorities).

Bayer will inform all investigational sites about the occurrence of suspected unexpected serious adverse reaction/s (SUSARs) according to all applicable regulations.

8.7 Expected AEs

The applicable reference document is the most current version of the investigator's brochure (IB) / Company Core Data Sheet (CCDS). Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, it will be integrated into an update of the IB and distributed. The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

8.8 Adverse events of special interest

The following AEs are of special interest:

- Symptomatic hypotension
- Hemoptysis
- Bone and/or growth anomalies

Symptomatic hypotension, hemoptysis as well as bone and/or growth anomalies have been defined as adverse events of special interest and must be documented accordingly in the corresponding adverse events of special safety interest pages in the electronic case report form (eCRF). Events of special interest should not automatically be upgraded by the reporting Investigator to serious. Declaration of an event as serious should only occur when one or more of the serious criterion (as defined in Section 8.1.2) is applicable.

8.9 Premature discontinuation of study medication

Subjects must be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative at any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result

- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being.
- If any AE occurred which is not acceptable in the opinion of the investigator and / or participating parent(s)/legal representative(s) or subject
- Occurrence of adverse drug reactions, which have from the investigator's point of view, a negative impact on the subject's individual risk-benefit ratio.
- If treatment is interrupted for more than 3 days during any individual dose titration phase
- If treatment is interrupted for more than 14 consecutive days during the maintenance phase.
- In case a female subject of childbearing potential is not compliant with pregnancy testing
- In case of lung transplantation
- In case of pregnancy or breast feeding
- In case that the subject fulfills one of the stopping criteria specified in Section 5.1.1
- Subject does not tolerate the lowest possible riociguat dose (0.5 mg TID)
- Patient with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP)

Discontinuation of bosentan or other ERA treatment (i.e. due to elevated liver enzymes) during the course of the study does not mandate withdrawal of the subject from the study. Also, discontinuation PCA treatment, during the course of the study, does not mandate withdrawal of the subject from the study. The final decision of withdrawal will be the responsibility of the investigator.

The DMC may recommend stopping the trial due to an unfavorable risk benefit assessment during the course of the trial. The final decision to terminate will be the responsibility of the Sponsor.

If the subject or parent(s)/legal representative(s) withdraw(s) consent to treatment with study drug, the investigator will ask to continue with study visits as planned, only with the aim to collect potential study outcomes and AEs. If the subject/parent(s)/legal representative(s) state to the investigator that they no longer authorize to continue to obtain outcome data, this will be respected and documented in the source records, and no further study data will be collected.

In all subjects who prematurely discontinue study drug for other reasons than withdrawal of informed consent, study visits will take place as planned to collect potential study outcomes and AEs.

(Note the section was modified according to Amendment 6, see Sections 17.3.1.1 and 17.3.1.2.)

8.10 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a study subject, or in the study subject's partner, during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother or child should be reported. For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent. For all reports, the forms provided are to be used.

8.11 Appropriateness of procedures/measurements

The diagnostic methods to document safety and efficacy outcomes are standard methods in clinical practice and are used and generally recognized as reliable, accurate and relevant.

8.12 Device malfunction or failure and medical device related events reporting - amended

Any device malfunction or failure including use errors or inadequacy in the labeling will be recorded by the clinical/investigational site, including all relevant device information, using the Product Technical Compliant (PTC) form, and forwarded within 24 hours to the Sponsor or Sponsor's designee for evaluation and investigation.

A PTC is any report about a potential or alleged failure of a product in its quality (including the identity, durability, reliability, safety, efficacy or performance) or suspect counterfeit. The complaint may or may not represent a potential risk to the patient.

There are three different situations, in which a PTC form might need to be filled out by the investigator.

1. When an AE is recorded, the investigator needs to check if a device malfunction or failure might be associated with the recorded AE.
2. When a device malfunction or device failure occurs, the investigator needs to assess whether an AE might have occurred in relation to the device complaint.
3. When a device malfunction, device failure, or use error occurs, without any associated AE, this also needs to be captured in the form, especially if it classifies as a near incident, and immediately forwarded to the sponsor for product technical complaints (PTC) investigation.

There are three different categories of medical related events (specified in the PTC form).

Incident

Any malfunction or deterioration in the characteristics and / or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, led, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Any event which meets all three basic reporting criteria (a-c) is considered an incident and must be reported to the relevant National Competent Authority. The criteria are that:

a) An event has occurred

b) The suspension dosing device is suspected to be a contributory cause of the Incident.

c) The event led, or might have led, to death or serious deterioration in state of health of a patient, or user, or other person

Other Reportable Incident (Near Incident)

Any incident that did not lead to death or serious deterioration in health, but it might do if it occurred again under less fortunate circumstances or without intervention of healthcare personnel. This may include cases without any medical event reported.

Non-Incident

Any device related case that does not fulfill all the three basic incident criteria a-c listed in the definition of an "Incident" above. This includes reports of:

- Deficiencies of a device which are always detected prior to its use
- Event is caused by the patient's condition
- Service life or shelf life of the device is expired
- Events which did not lead to serious deterioration in state of health or death, because a design feature protected against a fault becoming a hazard.
- Events where the risk of a death or serious deterioration in state of health has been quantified and found to be negligibly small.

In case of an incident and other reportable incident a technical complaint form always needs to be completed.

Serious deterioration in state of health (=serious injury) is any AE in relation to a medical device if it:

- Resulted in a life-threating illness or injury, or
- Resulted in a permanent impairment of a body structure or a body function, or
- Required in-patient hospitalization or prolongation of existing hospitalization, or
- Resulted in medical or surgical intervention to prevent life-threating illness, or permanent impairment of a body function or damage to a body structure, or
- Led to fetal distress, fetal death or congenital abnormality or birth defect.

The details of the malfunction and medical circumstances will be captured on a PTC form and the eCRF for device-related events by the investigator and then returned to the sponsor or sponsor's designee. The processing and reporting of all reportable device events (incidents / other reportable incidents) to the authorities will be done by the sponsor according to all applicable regulations. The final determination of reportability is made by the sponsor and not the clinical/investigational site based on the medical circumstances surrounding the event. The device manufacturer may recommend reporting an incident based on investigations, but the final determination of reportability is made by the sponsor.

Incidents / Other reportable incidents occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for incidents and serious public health threats related to

the suspension dosing device. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The sponsor will inform the device manufacturer about any incident or trend report and the manufacturer will then perform further evaluation and investigation of the device, as necessary, and exchange any significant information with the sponsor. The device manufacturer will inform the sponsor about necessary trend reports and will provide the required documentation after completing the respective investigation and statistical analysis. The sponsor will then notify the authorities of any trend reports according to all applicable regulations.

All devices that have malfunctioned or failed will be inventoried and returned to the device manufacturer. The devices should be stored in a hermetically sealed bag and labeled with the respective case reference. In cases where an AE is recorded in connection with the device malfunction or failure, the device should be sent immediately per courier to the device manufacturer. If any of the devices need to be replaced, the reason(s) will be documented. Additional clinical devices are provided for this purpose.

(*Note: The section was modified according to Amendment 5, see Section 17.2.1.8.*)

9. Data handling and quality assurance

For all data entered into the eCRF, source documentation should be available at the site. A source document checklist will be used to identify the source data for all data points collected. In accordance with GCP and Bayer's/CRO's procedures, monitors will review the protocol, study requirements, and responsibilities with the site staff, including identification and documentation of source data items. Sponsor and designee personnel will monitor the site to verify that data are authentic, accurate, and complete and that the safety and rights of participating subjects are being protected. In addition, they will assess if the study is conducted in accordance with the latest version of the protocol and study agreements. The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.1 Data processing

The data collection tool for this study will be a validated electronic system called RAVE and data will be entered into a validated database or data system (Tools for Syntactic Corpus Analysis [TOSCA]). Study data management will be performed in accordance with applicable Bayer's/CRO's standards. This is applicable for data recorded on eCRF as well as for data from other study sources. Internationally recognized and accepted dictionaries will be used for data coding.

9.2 Audit and inspection

Bayer's (or a designated contract research organization's) quality assurance unit may conduct an audit to ensure compliance with GCP and regulatory requirements. The investigator/institution will be informed of the audit outcome. In addition, inspections by regulatory health authority representatives, ethic committees, and/or institutional review boards might occur and the site will notify Bayer immediately. The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate

time to the auditor/inspector to discuss any findings. Audits and inspections may occur at any time during or after completion of the study.

9.3 Archiving

Study documents will be archived safely and securely in such a way that they are readily available upon authorities' request. Subject and related hospital files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. If the archiving procedures do not meet the minimum timelines required by Bayer, alternative arrangements will be made to ensure the availability of the source documents for the required period. The investigator/institution will notify Bayer if a change in archival arrangements occurs. The investigator site file will not be destroyed without Bayer's approval. The investigator's institution contract will contain all regulations relevant for the study center.

10. Premature termination of the study

The investigator has the right to terminate participation in the study at any time.

Bayer has the right to close this study or study sites at any time, which may be due but not limited to the following reasons:

- If the risk-benefit ratio becomes unacceptable due to, for example,
  - safety or efficacy findings from this study
  - results of parallel clinical studies.
- If study conduct (e.g. recruitment rate; dropout rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties
- All affected institutions must be informed, as applicable, according to local law.

All study materials will be returned to Bayer, except documentation that has to remain stored at the site. This documentation can only be destructed with approval from Bayer.

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that Bayer and investigator abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to Bayer. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply Bayer, upon request, a list of the IEC/IRB members involved in the

vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either Bayer or the investigator without agreement by both parties. However, the investigator or Bayer may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to the trial subjects without prior IEC/IRB/Bayer approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/Bayer. Any deviations from the protocol must be explained and documented by the investigator.

11.2 Child information and consent

All relevant study information will be summarized in an integrated subject information sheet, an informed consent and an informed assent form provided by Bayer or the study center. A sample child information and informed consent and assent form are provided as documents separate to this protocol. Consent will be asked from the parent(s)/ legal representative(s) and, if appropriate as determined by local regulation, age and individual subject capability, will be asked from the subject, according to country-specific regulations.

The investigator or designee will explain all relevant aspects of the study to the parent(s)/legal representative(s) and the subject, if applicable, prior to entry into the study.

The parent(s)/legal representative(s) and the subject, if applicable, will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for their decision.

The subject can only enter the study if the parent(s)/legal representative(s) voluntarily agree to sign and date the informed consent and the subject provides informed consent or assent, as appropriate and determined by local regulation, age and individual subject capability, and have done so. Then the investigator or designee will sign and date the forms. The parent(s)/legal representative(s) and the subject, if applicable, will receive a copy of the signed and dated form(s).

The signed informed consent and the assent form will remain in the investigator site file or, if locally required, in the subject’s file.

The informed consent/assent form and any other written information provided to the subject/parent(s)/legal representative(s) will be revised whenever important new information becomes available that may be relevant to the subject's consent, or if there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written informed consent/assent form. The investigator will inform the subject/parent(s)/legal representative(s) of changes in a timely manner and will ask the parent(s)/legal representative(s) and the subject, if applicable, to confirm participation in the study by signing the revised informed consent, and, if applicable, will ask the subject to provide informed assent as documented on the revised assent form. Revised informed consent/assent form and the subject information sheet must receive the IEC's/IRB's approval before implementation.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

12. Investigators and other study participants

The principal investigator of each site must sign the protocol signature sheet before recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center. A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the Bayer study file. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13. Publication policy

Bayer is committed to publication of the results of every study it performs. The SC will be responsible for the publication and presentation strategy. All publications will be based on data released or agreed by Bayer, verified by the SC. The study protocol has been made publicly available at www.clinicaltrials.gov.

14. Insurance for subjects

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

15. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to Bayer. Only the subject's study number will be recorded in the eCRF. If the subject's name appears on any other document, it will be anonymized. Study data stored in a computer will be handled in accordance with local data protection laws. As part of the informed consent process, the children/parents/legal guardians will be informed in writing that representatives of Bayer, IEC/IRB, or regulatory authorities may inspect their medical records to verify collected information and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects to be identified.

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(A reference Weber et al. for Modification 6 was added to the reference list according to Amendment 6, see Section 17.3.1.6).

17. Protocol amendments

17.1 Amendment 3

Amendment 3 is the first global amendment dated 24 NOV 2015.

In order to consider medical practice according to feedback from investigators, Health Authorities, and Ethical Committees as well as ensure consistency and clarity, the global amendment was generated.

17.1.1 Overview of changes to the study

17.1.1.1 Modification 1: Change in the wording in describing the Long Term Extension part of the study

According to the original protocol, the subjects who completed the 24-week main study treatment phase, and require further treatment with riociguat, will be offered to participate in a long-term extension (LTE) study and continue until market approval of riociguat for the pediatric population or until they are ≥18 years of age (whatever comes first). The wording ***study*** is replaced with wording ***phase***, and a word ***optional*** is added for the description of LTE. Modifications clarify that the subjects can volunteer to participate to the long-term extension, and that the LTE is a part of this study 15681.

Sections affected by this modification are:

Study flow chart

Section 5.3 Duration of study treatment

Section 6.1 Study visits

Section 6.1.6 Long-term extension phase (until adulthood or approval in the indication and commercial availability)

17.1.1.2 Modification 2: Clarification of primary completion and end of study

According to the original protocol, the primary completion event is when the last visit of the last subject for all centers has occurred. The wording in **Primary completion** is modified for clarification that primary completion day is the day, when last visit of the last subject for all centers has occurred after main study treatment phase, after 24 weeks of treatment.

End of the study is determined in original protocol to be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (EU and non-EU). The wording in **End of the study** is modified for clarification to describe that the end of the study will be reached as soon as the last visit of the subject has been reached in all centers of all participating countries after 24 weeks of treatment. In addition, wording in **End of the study** highlights that long term extension phase is not a part of the main study phase as well as gives timing for CSR writing.

Sections affected by this modification are:

Section 3.1 Study description

Section 7.4.5 Analyses

17.1.1.3 Modification 3: Changes to the text describing primary objective

Original protocol described pharmacodynamics as a primary and secondary objective in section 2.0, but elsewhere in the protocol pharmacodynamics was described as secondary/other objective. To keep consistency, the pharmacodynamics is deleted from primary objective. Furthermore, with the limited blood sample volume, a throughout pharmacokinetics/pharmacodynamics (PK/PD) analysis might not be feasible. Therefore PK and PD will be addressed separately, and handled as separate objectives, not as one PK/PD.

Section affected by this change is:

Section 2 Study objectives

17.1.1.4 Modification 4: Addition of safety follow up visit for subjects participating to the long- term extension phase

Original protocol describes no safety follow up visit for subjects directly enrolling to the long-term extension phase. As all subjects should end study properly, the correction for the description is made, and the safety follow up visit is added as well as the time is specified, regardless of end of the study in main study phase, or in long-term extension phase.

Sections affected by this modification are:

Study flow chart

Section 6.1.4 Safety follow up visit

17.1.1.5 Modification 5: Widening the Section 1.2 to better describe the minimization of burden degree of pediatric subjects

In order to response to the feedback received from German Federal institute for Drugs and medical devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArm), the ***section 1.2 Rationale of the study and risk-benefit assessment*** is widened. The new text address following points: the low burden and risk of study subjects, definitions of the burden degree, continuous monitoring as well as the description of how the burden degree and threshold of risks shall be continuously monitored.

Section affected by this modification is:

Section 1.2 Rationale of the study and risk-benefit assessment

17.1.1.6 Modification 6: Clarification for the body weight adjusted dosing

For preventing potential riociguat dosing mistakes, a new, more accurate wording for body weight adjusted dosing is presented. In addition, two tabular descriptions (table 5-2 of original protocol and Appendix 1of original protocol) of riociguat dosing schedule are integrated.

The integration would help the health care professionals (HCPs) to figure out which dose, as well as which corresponding volume of suspension should be administered. Providing all necessary data in one table would also help to prevent possible errors in prescribing a proper dose, which could occur if the two separate tables would be used (one for a dose calculation, and another one for a corresponding volume of the suspension). Such tables, although complex, are widely used by pediatricians. Clear graphic differentiation between doses in mg and volumes in ml should be used for preventing of potential dosing mistakes (however, the

doses in mg are in the majority of cases not as “round” as the volumes of suspension, as well as the units of a scale on the suspension dosing devices are 0.25 ml and 0.50 ml respectively, what would in fact prevent dosing mistakes from occurring).

Sections affected by this modification are:

Synopsis

Section 5.1.1 Body-weight adjusted individual dose titration regimen

Section 5.4 Formulation and dose

Appendix 18.1

17.1.1.7 Modification 7: Addition of a paragraph of Laboratory parameters

A new paragraph is added to the section 6.2 to describe the laboratory tests obtained during screening and Visits 5 and 9 as well as in case medically required.

New paragraph is added to:

Section 6.2 Safety outcomes

17.1.1.8 Modification 8: Addition of blood sampling in study visits 0, 5 and 9

Blood sampling is added to the study visits 0, 5, and 9. There is no indication for drug-induced laboratory parameter changes attributable to riociguat in the adult studies. However, our study population will be in use of Bosentan for at least 12 weeks and this medication has been associated with cases of anemia and increases in liver enzymes. Therefore, an evaluation of results of historical laboratory tests, as well as a collection of blood samples for CBC, BUN, creatinine, AST, and ALT was introduced at Visit 0 (if historical values would not be available), and visits 5 and 9. Collection and evaluation of laboratory parameters is intended to confirm the safety profile of riociguat in the studied pediatric population.

Sections affected by this modification are:

Study flow chart

Section 6.1.1 pre-treatment phase (Visit 0, day -14 to -1)

Section 6.1.2.1 Individual titration phase (Visit 1- Visit 4)

Section 6.1.2.2 Maintenance phase (Visit 5- Visit 9)

Section 7.4.1 Safety analysis

17.1.1.9 Modification 9: Change of calculation formula for glomerular filtration rate

According to original protocol the glomerular filtration rate is calculated based on Cockroft formula. Since Schwartz formula is more appropriate for children in the age group this study is conducted, the calculation is changed to base on Schwartz formula. In addition, the wording is modified for this exclusion criteria.

Section affected by this modification is:

Section 4.3 Exclusion criteria

17.1.1.10 Modification 10: Deleting sentences describing bosentan formulation and preclinical bone findings.

In order to respond to the feedback from French authorities, the sentence describing bosentan galenic formulation and its approval in EU is deleted since galenic formulation is not actually a pediatric formulation.

Section affected by the modification is:

Section 1 Introduction

17.1.1.11 Modification 11: Deleting sentences about bosentan

Since bosentan is not provided by Sponsor, and compound name, dose, quantity and batch numbers are not collected for any concomitant medication, the sentence in Section 5.6 from original protocol is deleted.

Section affected by this change:

Section 5.6 Treatment assignment

17.1.1.12 Modification 12: Changing the growth charts for boys and girls with Down syndrome

Original protocol growth charts for subjects (boys and girls) having Down syndrome are replaced with similar than presented for subjects without Down. New growth charts are having height scales with centimeters and inches, weight scales with kilograms and pounds, and are having easier readability.

Section affected by this change is:

Appendix 18.1 Growth chart

17.1.1.13 Modification 13: Clarifying the wording about dosing pipette

The terminology in original protocol for describing the dosing pipette, which will be used to administer the oral suspension to children, and which is considered a medical device, has been harmonized. Specific information about the manufacturer of the dosing pipette has been added. In addition, the clarification of the wording describing dosing increments is done.

Sections affected by this change are:

Section 5.1.1 Body-weight adjusted individual dose titration regimen

Section 5.4 Formulation and dose

Section 8.1.1 Adverse events

17.1.1.14 Modification 14: Deleting wording from study visits

Wording ***adjust study drug dose according to body weight*** is deleted from visit description of **Main study treatment visit** and **Optional long-term extension phase**. The study drug dose adjustment is based on systolic blood pressure, and the wording is misleading in original protocol.

Sections affected by this change are:

Section 6.1.2.2 Maintenance phase (Visit 5- Visit 9)

Section 6.1.6 Long-term extension phase (until adulthood or approval in the indication and commercial availability)

17.1.1.15 Modification 15: Adjustments for Flow chart

The superscript j is deleted from following Flow Chart points: demographics, medical history, concomitant PAH specific medication, physical examination, vital signs, ECG, Child health questionnaire, and tanner Scale. These procedures are done per protocol at Screening visit (V0).

Section affected by this change:

Study flow chart

17.1.1.16 Minor clarifications

Minor, consistency and logical clarifications were made throughout the document. The changes were made to ensure clear wording and consistency throughout the document. These changes do not affect the overall study concept.

Sections affected by the changes are:

Title page: The Study medical expert is changed.

List of abbreviations: Correction to the phrasing of one abbreviation is done and new abbreviations have been added due to the Amendment 3 modifications.

Flow chart, table for Study visits: Clarification of the wording in column headers and deleting one row of PK sampling. PK sampling was twice in the original protocol.

Section 1.2 Rationale of the study and risk benefit assessment: Clarification of the wording and correcting the numbers describing bone changes.

Section 4.2 Inclusion criteria: Correction of inclusion criteria numbering, as well as clarification for inclusion criteria 6.

Section 4.3 Exclusion criteria: Clarification of wording in exclusion criteria 1. Wording in Synopsis is also changed due to the new sentence structures in Section 4.3.

Section 4.4 Concomitant medication: Word equivalent is added to the sentence describing the starting dose of riociguat.

Section 5.1.1Body weight adjusted dosing: Wording ***of the day*** is added for clarification to the sentence describing individual dosing at titration visits.

Section 6.1.1 Main study treatment period: For clarification that pregnancy test is mandatory at screening visit, the wording ***at the discretion of the investigator*** is deleted.

Section 6.1.2.1 Individual titration phase: For clarification that pregnancy test is mandatory at the visits mentioned, the wording ***at the discretion of the investigator*** is deleted.

Section 6.1.2.2 Maintenance phase: For clarification that pregnancy test is mandatory at the visits mentioned, the wording ***at the discretion of the investigator*** is deleted.

Section 6.1.3 End-of-treatment: For clarification that each subject should have this visit, the following sentence '***All patients will be encouraged to perform this visit.***' is deleted.

Section 6.4 Pharmacokinetics: For clarification, wording ***peak and through*** is replaced by ***pre- and post-dose.***

References: Three new references added.

Appendices: Replacement of the sample of SF-10 health survey with a final copy.

17.1.2 Changes to the protocol text

All affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the original protocol. Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text". Minor editorial changes or corrections are not listed.

17.1.2.1 Title page

Old text:

[…]

Sponsor: **Bayer HealthCare AG, D-51368 Leverkusen, Germany**

Sponsor's medical expert: PPD
Bayer HealthCare Pharmaceuticals
~~Av. Domingos Jorge 1100, 04779-900 São Paulo-SP Brasil~~
~~Phone:~~ PPD PPD

[...]

New text:

[…]

Sponsor: **Bayer HealthCare AG, D-51368 Leverkusen, Germany**

Sponsor's medical expert: PPD
Bayer HealthCare Pharmaceuticals
BPH-GD-P&O
Aprather Weg, Bd 402
42113, Wuppertal, Germany
Phone: PPD

[…]

17.1.2.2 List of abbreviations

Old text:

[…]

BCRP	breast cancer ~~related~~ protein
BP	blood pressure
CCDS	Company Core Data Sheet

[…]

New text:

[…]

BCRP	breast cancer resistance protein
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CCDS	Company Core Data Sheet

[…]

17.1.2.3 Synopsis

Old text:

[…]

Dose(s)	Body-weight adjusted dose equivalent to the exposure of (0.5mg) 1.0 - 2.5 mg-three times a day (TID), individual dose titration (IDT) in adults treated for PAH. The individual optimal (maintenance) dose is to be determined based on patients' monitoring of systolic blood pressure, well-being and clinical status.

[…]

New text:

[…]

Dose(s)	For children with body-weight <50 kg at screening, body-weight adjusted dose equivalent to the exposure of (0.5 mg) 1.0 - 2.5 mg three times a day (TID), individual dose titration (IDT) in adults treated for PAH. Doses of 1.0 to 2.5 mg TID will be applied for children ≥50 kg at screening. The individual optimal (maintenance) dose is to be determined based on patients' monitoring of systolic blood pressure, well-being and clinical status.

[…]

Old text:

[…]

Diagnosis and main criteria for inclusion /exclusion	• Concomitant use of the following medication: phosphodiesterase 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific phosphodiesterase (PDE) inhibitors (theophylline, dipyridamole), nitrates or NO donors ~~(such as amyl nitrite)~~ in any form or pre-treatment ~~within the last 2-weeks before Visit 1 with NO donors (e.g. nitrates).~~

[…]

New text:

[…]

Diagnosis and main criteria for inclusion /exclusion	• Concomitant use of the following medications: phosphodiesterase 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific phosphodiesterase (PDE) inhibitors (theophylline, dipyridamole) in any form or pretreatment are not allowed. Concomitant use of nitrates or NO donors are allowed up to two weeks before Visit 1.

[…]

Old text:

[…]

Methodology	This study is designed to evaluate the safety, tolerability, pharmacodynamics and pharmacokinetics of riociguat ~~at age-, sex- and body-weight-adjusted doses of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg TID in children from ≥6 to less than 18 years with pulmonary arterial hypertension (PAH) group 1.~~ The study consists of two phases: titration phase up to 8 weeks and a maintenance phase up to 16 weeks.

[…]

New text:

[…]

Methodology	This study is designed to evaluate the safety, tolerability, pharmacodynamics and pharmacokinetics of riociguat in children from ≥6 to less than 18 years with pulmonary arterial hypertension (PAH) group 1. For children with body weight < 50 kg at screening, body weight adjusted doses of 1.0 mg, 1.5mg, 2.0 mg, and 2.5 mg TID will be applied. For children with body weight ≥50 kg, doses of 1.0 mg, 1.5 mg, 2.0 mg,

	and 2.5 mg TID will be applied. The study consists of two phases: titration phase up to 8 weeks and a maintenance phase up to 16 weeks.

[…]

17.1.2.4 Study flow chart

Old text:

Table 0-1: Flow chart

		Main study treatment period - 24 weeks												
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Long-term extension phase**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***				
Informed consent/assent	•													
In-/exclusion criteria	•	•												
Demographics	•[j]													
Medical history	•[j]	•												
Concomitant medication		•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant PAH specific medication	•[j]	•	•	•	•	•	•	•	•	•	•	•	•	•
Physical examination [m]	•[j]	•[d]	•	•	•	•	•	•	•	•	•	•	•	•[h]
Obtain lab test[-j]	•													
~~Check lab test~~		▲										▲		
Pregnancy test [a]	•	•		•		•	•	•	•	•		•	•	•
Dispense study medication		•	•	•	•	•	•	•	•	•	(•)			•

Instruct how to take study drug		•	•	•	•	•	•	•	•	•	•			•
Provide booklet		•												
Vital signs [d]	• [j]	•	•	•	•	•	•	•	•	•	•	•	•	•
ECG [d]	• [j]	•								•		•		
Echocardiogram		•								•		•		•
WHO functional class		•								•		•		•
6MWD		•								•		•		•
NT-proBNP		•								•		•		•
Left hand x-ray		• [j]								•				• [e]
Adverse events [n]		•	•	•	•	•	•	•	•	•	•	•	•	•
~~Update eCRF~~		•	•	•	•	•	•	•	•	•	•	•		
Drug accountability			•	•	•	•	•	•	•	•		•		•
PK blood sample [b]		•		•		•								
Child Health Questionnaire (SF-10)	• [j]									•		•		•
Tanner scale [c]	• [j]									•		•		• [e]
Taste assessment questionnaire		•								•		•		

~~Abbreviation: eCRF = electronic case report form~~

a Urine pregnancy test for women of childbearing potential ~~at the discretion of the investigator (mandatory at screening).~~
b A volume of 1.0 mL per sample is needed. Accurate adherence to time points is essential and has to be documented, see Table 0-2
c Scale of physical development in children and adolescents
d Blood pressure, heart rate and ECG pre-dose, 2 and 4 hours after first dose (see Table 0-2)
e Every 12 months until growth velocity is plateauing and growth plates are closed (see section 6.1.6)
f ±2 days for Visits 1 to 4, ±5 days for Visits 5 to 9
g Visit 1 is considered the baseline visit.
h Incl. height, growth velocity and weight
i Obtain blood sample if AST and ~~or~~ ALT are not available within 30 days prior to Visit ~~1~~
j If no historical data (≤30 days) is available
k Home visits (only at week 12 and/or 20 of maintenance phase) at the discretion and responsibility of the investigator
l For subjects dropping off the protocol at any time after V1 and before V9
m Including height and weight
n Including AEs of special interest

New text:

Table 0–1: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
Informed consent/assent	•														
In-/exclusion criteria	•	•													
Demographics	•														
Medical history	•	•													
Concomitant medication		•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant PAH specific medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Physical examination [m]	•	• [d]	•	•	•	•	•	•	•	•	•	•	•	• [h]	•
Obtain lab test	•[i]					•				•		•			
Pregnancy test [a]	•	•		•		•	•	•	•	•		•	•	•	•
Dispense study medication		•	•	•	•	•	•	•	•	•	(•)			•	

Instruct how to take study drug		•	•	•	•	•	•	•	•	•	•			•	
Provide booklet		•													
Vital signs [d]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
ECG [d]	•	•								•		•			
Echocardiogram		•								•		•		•	
WHO functional class		•								•		•		•	
6MWD		•								•		•		•	
NT-proBNP		•								•		•		•	
Left hand x-ray		• [j]								•				• [e]	
Adverse events [n]		•	•	•	•	•	•	•	•	•	•	•	•	•	•
Drug accountability			•	•	•	•	•	•	•	•		•		•	
PK blood sample [b]		•		•		•									
Child Health Questionnaire (SF-10)	•									•		•		•	
Tanner scale [c]	•									•		•		• [e]	
Taste assessment questionnaire		•								•		•			

a Urine pregnancy test for women of childbearing potential
b A volume of 1.0 mL per sample is needed. Accurate adherence to time points is essential and has to be documented, see Table 0-2
c Scale of physical development in children and adolescents
d Blood pressure, heart rate and ECG pre-dose, 2 and 4 hours after first dose (see Table 0-2)
e Every 12 months until growth velocity is plateauing and growth plates are closed (see section 6.1.6)
f ±2 days for Visits 1 to 4, ±5 days for Visits 5 to 9
g Visit 1 is considered the baseline visit.
h Incl. height, growth velocity and weight
i Obtain blood samples if AST and ALT, creatinine, BUN, and CBC are not available within 30 days prior to Visit0

j If no historical data (≤30 days) of x-ray is available
k Home visits (only at week 12 and/or 20 of maintenance phase) at the discretion and responsibility of the investigator
l For subjects dropping off the protocol at any time after V1 and before V9
m Including height and weight
n Including AEs of special interest

Old text:

Table 0–2: Visit details

		Visit 1 (Baseline visit)						**Visit 3 and 5**	
		~~First study medication dose intake~~ ~~Second study medication dose intake~~						**First study medication dose intake**	
Order of procedures	Time interval (h)	pre-dose	0:00	0:30 to 1:30	2:00	2:30 to 4:00	4:00	-1:00 to 0:00	0:00
	Pharmacokinetic blood sample			•		•		•	
	Blood sample for safety laboratory (incl. NT-proBNP)	•							
	Blood pressure, heart rate	•			•		•		
	ECG	•			•		•		
	WHO functional class	•							
	Left hand x-ray	•							
	Administration study drug		•						•
	~~Pharmacokinetic blood sample~~			~~•~~		~~•~~			
	Echocardiogram	•							

Abbreviations: ECG = electrocardiogram, ~~PK = pharmacokinetic~~

New text:

Table 0–2: Visit details

		Visit 1 (Baseline visit)						**Visit 3 and 5**	
		Detailed study activities at pre-dose and after the first study medication dose intake						**Study activities before first study medication dose intake**	
Order of procedures	Time interval (h)	pre-dose	0:00	0:30 to 1:30	2:00	2:30 to 4:00	4:00	-1:00 to 0:00	0:00
↓	Pharmacokinetic blood sample			•		•		•	
	Blood sample for safety laboratory (incl. NT-proBNP)	•							
	Blood pressure, heart rate	•			•		•		
	ECG	•			•		•		
	WHO functional class	•							
	Left hand x-ray	•							
	Administration study drug		•						•
	Echocardiogram	•							

Abbreviations: ECG = electrocardiogram

17.1.2.5 Section 1 Introduction

Old text:

[…]

The only PAH-specific drug approved for children is Revatio (sildenafil), and this approval is restricted to the European Union only. Bosentan is widely used in children with PAH. The medical treatment recommendations of Tracleer (International non-proprietary name [INN]: bosentan) in pediatric populations with PAH in the European Union (EU) are mainly based on extrapolation from experience in adult populations. ~~For bosentan a pediatric galenic formulation is approved in the EU.~~

[…]

New text:

[…]

The only PAH-specific drug approved for children is Revatio (sildenafil), and this approval is restricted to the European Union only. Bosentan is widely used in children with PAH. The medical treatment recommendations of Tracleer (International non-proprietary name [INN]: bosentan) in pediatric populations with PAH in the European Union (EU) are mainly based on extrapolation from experience in adult populations.

[…]

17.1.2.6 Section 1.2 Rationale of the study and risk-benefit assessment

Old text:

[…]

Considering the severity and prognosis of PAH and the fact that the bone findings in rats were ~~only~~ seen at ~~high multiples of exposure (≥ 66-fold~~ of human exposure ~~in adults at the maximum clinical dose of 10 mg)~~ and that the findings were reversible and can be monitored in the clinical setting, the preclinical bone findings are ~~not~~ considered as ~~critical~~ for the initiation of a clinical study in children.

The expected benefit-risk balance of riociguat is considered positive if used in adherence to this clinical trial protocol and in accordance with the recommendations and guidance given in the Investigator's Brochure.

[…]

New text:

[…]

Considering the severity and prognosis of PAH and the fact that the bone findings in rats were seen 3-4 fold of human exposure and that the findings were reversible and can be monitored in the clinical setting, the preclinical findings are considered as not prohibitive for the initiation of a clinical study in children.

The protocol was developed in accordance with ICH Good Clinical Practice, and other ICH/EMA guidelines for conducting clinical trials in pediatric population, in particular the ICH Topic E 11 (Clinical Investigation of Medicinal Products in the Pediatric Population) and

the guideline on Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population.

The necessity of minimizing any possible burden and any potential risk for participating child and adolescent patients was taken into consideration and addressed during the development of this protocol. In order to provide guidance for investigators this protocol describes use of all study procedures, as well as outlines any potential related burden for participating patients, whenever applicable, in the respective chapters. In terms of the IMD administration the titration phase has been implemented (as described in the section 5.1.1. "Body-weight adjusted individual dose titration regimen"), as well as a dosing pipette for administration of oral suspension will be used. Educational material for training on the dosing pipette use and dose administration for study site staff, as well as for the patients and their caregivers, to ensure adequate dosing pipette use and treatment compliance will be distributed.

The study design includes standard procedures for pediatric PAH management, and only a few additional, study specific procedures have been included wherever absolutely necessary to ensure the study conduct, and monitoring of safety of enrolled patients. Study-specific procedures are: ECGs, Echocardiogram, serum or urine pregnancy testing for female patients of childbearing potential, selected blood sampling, and the left-hand X-ray for monitoring of bone growth. The above listed study specific procedures are non-invasive, standard medical care procedures. Laboratory samples will be restricted to the selected laboratory tests at screening (only if historical data is not available), visit 1, 5, and 9. Pharmacokinetic samples and blood sampling for study purposes will be aligned with clinically required blood tests whenever possible in order to avoid additional burden of a painful procedure and blood volume taken (see the subchapter "Laboratory parameters" in Section 6.2). Blood samples for pharmacokinetic analysis will have the blood volume minimized to 1 ml per sample. All blood samples collection will be performed by pediatric specialist staff and will be performed with the use of techniques like distraction and local anesthetic techniques, if applicable, to reduce the burden for patients. The left hand X-ray for monitoring of bone growth will be performed and assessed according to the established method. The rare periodicity of this X-ray examination, as well as the standard precautions will ensure minimal and therefore acceptable exposure to radiation (Section 6.2 Safety outcomes).

Investigators are mandated and trained to report adverse events, and all the respective definitions, criteria for qualifying AEs, and their reporting, as well as a description of pharmacovigilance procedures are included in a separate section of this protocol (Section 8.8). The monitoring of safety of participating patients by investigators and the sponsor is ensured by adherence to pharmacovigilance regulations and implementation of study specific monitoring measures (e.g. observation and evaluation of potential AEs of special interest, patients' growth and bone growth monitoring). Close monitoring and ongoing medical review will be performed by the sponsor. An independent Data Monitoring Committee (DMC, which will be acting according to a DMC Charter) will meet periodically to review the safety data of enrolled patients, as well as the scientific merit of the trial. In addition a Steering Committee (SC) will ensure a scientifically sound and safe conduct of the study. Both, the DMC and the SC, are described in a separate subsection of this protocol (6.6 Study committees).

The expected benefit-risk balance of riociguat is considered positive if used in adherence to this clinical trial protocol and in accordance with the recommendations and guidance given in the Investigator's Brochure.

[…]

17.1.2.7 Section 2 Study objectives

Old text:

[…]

- To evaluate safety, tolerability, and pharmacokinetics~~/pharmacodynamics~~ body-weight adjusted riociguat treatment in children with PAH

[…]

New text:

[…]

- To evaluate safety, tolerability and pharmacokinetics of body-weight adjusted riociguat treatment in children with PAH

[…]

17.1.2.8 Section 3.1 Study description

Old text:

[…]

Primary completion

The primary completion event for this study is when the last visit of the last subject for all centers has occurred.

End of study

The end of the study as a whole will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (EU and non-EU).

[…]

New text:

[…]

Primary completion

The primary completion event for this study is when the last visit of the last subject for all centers has occurred after 24 weeks of treatment.

End of study

In accordance to the EU guideline 2009/c28/01 the end of the study will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (EU and non-EU) after 24 weeks of treatment. A clinical study report (CSR) will be written after the completion of the main study.

The LTE is not considered part of the main study and the results will be reported separately.

[…]

17.1.2.9 Section 4.2 Inclusion criteria

Old text:

[…]

5. WHO functional class ~~I-III~~

[…]

New text:

[…]

5. WHO functional class I, II, and III

[…]

17.1.2.10 Section 4.3 Exclusion criteria

Old text:

[…]

1. Concomitant use of the following medication: phosphodiesterase (PDE) 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific PDE inhibitors (theophylline, dipyridamole), nitrates or NO donors ~~(such as amyl nitrite) in any form, or pre-treatment within the last 2 weeks~~ before Visit 1: NO donors ~~(e.g. nitrates)~~

[…]

14. Renal insufficiency (glomerular filtration rate <30 mL/min e.g. calculated based on ~~Cockroft formula~~)

[…]

New text:

[…]

1. Concomitant use of the following medications: phosphodiesterase (PDE) 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific PDE inhibitors (theophylline, dipyridamole) in any form or pretreatment are not allowed. Concomitant use of nitrates or NO donors are allowed up to two weeks before Visit 1.

[…]

14. Renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73m^2 e.g. calculated based on Schwartz formula)

[…]

17.1.2.11 Section 4.4 Concomitant medication

Old text:

[…]

- Strong cytochrome P450 (CYP) and P-glycoprotein 1(P-gp)/breast cancer related protein (BCRP) inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg TID when initiating riociguat in subjects receiving strong CYP and P-gp/BCRP inhibitors and monitor for signs and symptoms of hypotension. A dose reduction should be considered in subjects who may not tolerate the hypotensive effect of riociguat.

[…]

New text:

[…]

- Strong cytochrome P450 (CYP) and P-glycoprotein 1(P-gp)/breast cancer related protein (BCRP) inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg TID <u>equivalent</u> when initiating riociguat in subjects receiving strong CYP and P-gp/BCRP inhibitors and monitor for signs and symptoms of hypotension. A dose reduction should be considered in subjects who may not tolerate the hypotensive effect of riociguat.

[…]

17.1.2.12 Section 5.1.1 Body-weight adjusted individual dose titration regimen

Old text:

Riociguat will be provided to all subjects using an individual dose titration scheme ~~according to a body weight- adjusted dose of riociguat~~ to achieve a similar exposure as that observed in adults treated for PAH (Figure 5-1). The individual optimal dose will be determined based on subject's monitoring of systolic blood pressure, well-being and clinical status.

In subjects with a body-weight below 50 kg at baseline, riociguat will be administered as oral suspension TID with or without food. Subjects with a body-weight ≥50 kg at baseline will receive riociguat as tablet formulation.

~~Riociguat will be dosed according to the dosing calculations given in Appendix 1 (see section 18.1 Appendix 1).~~ The body weight-adjusted riociguat dosing schedule is provided in Table 5-2.

[…]

Educational material for training on the ~~device~~ and dose administration for study site staff as well as for the subjects to ensure adequate ~~device~~ use and treatment compliance will be distributed.

~~All~~ subjects will start with body-weight adjusted riociguat dose equivalent to the exposure of 1.0 mg TID in adults. During the individual titration period, the dose will be uptitrated every 2 weeks (±2 days) at the discretion of the investigator, based on subject’s peripheral systolic

blood pressure and general tolerability measured at trough before intake of the next higher dose of riociguat.

[…]

At each titration visit, the individual dose will be assigned based on the following algorithm where peripheral systolic blood pressure (SBP) will be measured (by oscillometry with the same calibrated device in each center) at trough before intake of the first dose.

[…]

New text:

Riociguat will be provided to all subjects using an individual dose titration scheme to achieve a similar exposure as that observed in adults treated for PAH (Figure 5-1). For children with <50 kg body weight at baseline, a body weight adjusted dosing will be applied. Children with ≥ 50kg body weight will receive adult doses. The individual optimal dose will be determined based on subject's monitoring of systolic blood pressure, well-being and clinical status.

In subjects with a body-weight below 50 kg at baseline, riociguat will be administered as oral suspension TID with or without food. Subjects with a body-weight ≥50 kg at baseline will receive riociguat as tablet formulation.

The body weight-adjusted riociguat dosing schedule is provided in Table 5-2.

[…]

Educational material for training on the dosing pipette and dose administration for study site staff as well as for the subjects to ensure adequate dosing pipette use and treatment compliance will be distributed.

Subjects with <50 kg body weight will start with body-weight adjusted riociguat dose equivalent to the exposure of 1.0 mg TID in adults. Subjects with ≥ 50kg body weight will start with dose 1.0 mg TID. During the individual titration period, the dose will be up-titrated every 2 weeks (±2 days) at the discretion of the investigator, based on subject's peripheral systolic blood pressure and general tolerability measured at trough before intake of the next higher dose of riociguat.

[…]

At each titration visit, the individual dose will be assigned based on the following algorithm where peripheral systolic blood pressure (SBP) will be measured (by oscillometry with the same calibrated device in each center) at trough before intake of the first dose of the day.

[…]

17.1.2.13 Section 5.3 Duration of study treatment

Old text:

During the individual dose titration period with a maximum duration of 8 weeks, the individual maximum equivalent dose will be established. Subjects will be treated on this body-weight adjusted dose level during the 16-week maintenance period as long as well tolerated. Subjects who have completed 24 weeks of treatment will be offered participation in ~~an extension study~~.

New text:

During the individual dose titration period with a maximum duration of 8 weeks, the individual maximum equivalent dose will be established. Subjects will be treated on this body-weight adjusted dose level during the 16-week maintenance period as long as well tolerated. Subjects who have completed 24 weeks of treatment will be offered participation in the Long Term Extension (LTE) phase.

17.1.2.14 Section 5.4 Formulation and dose

Old text:

Riociguat will be provided by Bayer as film-coated tablets and granules for reconstitution in an oral suspension (0.15 mg/mL), see Table 5-1. The following tablet strength will be available: 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg. For the application of the oral formulation two ~~medical devices~~ (LDD- Liquid Dosing Device) are available and certificated. ~~The devices~~ are ~~able~~ to deliver between 1 mL and 5 mL with 0.25 mL dosing increments as well as 2 mL to 10 mL with 0.5 mL dosing increments. ~~This incrementation was~~ chosen to enable accurate bodyweight-related adjustment of subject dosing.

[…]

Table 5-2: Body weight-adjusted riociguat dosing schedule

Body weight (kg)	0.5 mg equivalent TID (mg)	1.0 mg equivalent TID (mg)	1.5 mg equivalent TID (mg)	2.0 mg equivalent TID (mg)	2.5 mg equivalent TID (mg)
≥14 <16	0.14	0.28	0.42	0.56	0.70
≥16 <18	0.15	0.31	0.46	0.62	0.77
≥18 <20	0.17	0.33	0.50	0.67	0.83
≥20 <25	0.19	0.38	0.57	0.75	0.94
≥25 <30	0.22	0.44	0.66	0.87	1.09
≥30 <35	0.25	0.50	0.74	0.99	1.24
≥35 <40	0.28	0.56	0.84	1.12	1.41
≥40 <50	0.33	0.66	1.00	1.33	1.66
≥ 50	0.50	1.00	1.50	2.00	2.50

Abbreviations: TID = three times daily

New text:

Riociguat will be provided by Bayer as film-coated tablets and granules for reconstitution in an oral suspension (0.15 mg/mL), see Table 5–1. The following tablet strength will be available: 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg. For the application of the oral formulation two sizes of dosing pipettes, manufactured by Raumedic, which are considered medical devices (therefore also called LDD- Liquid Dosing Device) are available and certificated. These dosing pipettes are designed to deliver between 1 mL and 5 mL with 0.25 mL dosing increments as well as 2 mL to 10 mL with 0.5 mL dosing increments. These increments were chosen to enable accurate bodyweight-related adjustment of subject dosing.

[…]

Table 5-2: 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)*
≥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	7.00	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)

17.1.2.15 Section 5.6 Treatment assignment

Old text:

After enrolment, the subject identification number will be recorded on the corresponding electronic case report form (eCRF). The subject identification number will also have to be recorded on the label of the study medication.

~~In case bosentan is provided locally, the compound's name, dose, quantity and batch number, or a copy of the prescription has to be included in the subject's files.~~

New text:

After enrolment, the subject identification number will be recorded on the corresponding electronic case report form (eCRF). The subject identification number will also have to be recorded on the label of the study medication.

17.1.2.16 Section 6.1 Study visits

Old text:

[…]

Subjects who have completed 24 weeks of treatment will be offered participation in an extension ~~study~~. Subjects not entering the LTE phase will perform the safety follow-up visit (see section 6.1.4). Subjects dropping-off the protocol any time after Visit 1 and before Visit 9 will perform an end-of-treatment visit (see section 6.1.3).

[…]

New text:

[…]

Subjects who have completed 24 weeks of treatment will be offered participation in an optional long term extension phase. Subjects not entering the LTE phase will perform the safety follow-up visit (see section 6.1.4). Subjects dropping-off the protocol any time after Visit 1 and before Visit 9 will perform an end-of-treatment visit (see section 6.1.3).

[…]

17.1.2.17 Section 6.1.1 pre-treatment phase (Visit 0, day -14 to -1)

Old text:

[…]

Obtain blood sample if AST ~~and~~ ~~or~~ ALT are not available within 30 days prior to screening visit

[…]

New text:

[…]

- Obtain blood sample if AST, ALT, creatinine, BUN and CBC are not available within 30 days prior to screening visit

[…]

17.1.2.18 Section 6.1.2.1 Individual titration phase (Visit 1- Visit 4)

Old text:

[…]

- Pregnancy test for females of childbearing potential (~~at the discretion of the investigator~~ at Visit 1 and 3)
- ~~Update eCRF~~

[…]

New text:

[…]

- Pregnancy test for females of childbearing potential (at Visit 1 and Visit 3)

[…]

17.1.2.19 Section 6.1.2.2 Maintenance phase (Visit 5- Visit 9)

Old text:

[…]

- Perform physical examination (incl. height, weight, vital signs and at Visit 9 only, pubertal assessment using Tanner scale) ~~– adjust study drug dose according to body weight~~

[…]

- Pregnancy test for females of childbearing potential ~~(at the discretion of the investigator)~~

[…]

- ~~Update eCRF~~

[…]

New text:

[…]

- Perform physical examination (incl. height, weight, vital signs and at Visit 9 only, pubertal assessment using Tanner scale)

[…]

- Pregnancy test for females of childbearing potential

- Obtain laboratory parameters (AST, ALT, BUN, creatinine, and CBC) at Visits 5 and 9 as well as when medically required according to medical practice at the study site at any time

17.1.2.20 Section 6.1.3 End of treatment visit

Old text:

For all subjects dropping-off the protocol at any time after V1 and before V9, an end-of-treatment has to be performed. ~~All patients will be encouraged to perform this visit.~~

The same procedures as at Visit 9 will be performed with the exception of the x-ray of left hand.

New text:

For all subjects dropping-off the protocol at any time after V1 and before V9, an end-of-treatment has to be performed.

The same procedures as at Visit 9 will be performed with the exception of the x-ray of left hand.

17.1.2.21 Section 6.1.4 Safety follow up visit

Old text:

For all subjects stopping study medication either at the end of treatment or prematurely discontinuing the study at any time, a follow-up visit 60 days (±8 days) after last study medication intake has to be performed. For subjects directly proceeding with treatment in the long-term extension phase ~~no~~ safety follow-up visit will be scheduled.

[…]

- Pregnancy test for females of childbearing potential ~~(at the discretion of the investigator)~~

[…]

New text:

For all subjects stopping study medication either at the end of treatment or prematurely discontinuing the study at any time, a follow-up visit 60 days (±8 days) after last study medication intake has to be performed. For subjects directly proceeding with treatment in the long-term extension phase, a safety follow-up visit 60 days (+8 days) will be scheduled either at the end of optional LTE phase, when patient's transition to approved and commercially available riociguat in the respective country is possible, or when prematurely discontinuing LTE phase at any time.

[…]

Pregnancy test for females of childbearing potential

[…]

17.1.2.22 Section 6.1.6 Long-term extension phase (until adulthood or approval in the indication and commercial availability)

Old text:

6.1.6 Long-term extension phase (until adulthood or approval in the indication and commercial availability)

Subjects who require treatment with riociguat for more than 24 weeks will be offered participation in an optional extension ~~study~~. Subjects will receive riociguat until they can be transitioned to approved Adempas.

[…]

- Pregnancy test for females of childbearing potential ~~(at the discretion of the investigator)~~
- Perform physical examination (incl. height, weight and vital signs) ~~– adjust study drug dose according to body weight~~

[…]

New text:

6.1.6 <u>Optional</u> long-term extension phase (until adulthood or approval in the indication and commercial availability)

Subjects who require treatment with riociguat for more than 24 weeks will be offered participation in an optional extension <u>phase</u>. Subjects will receive riociguat until they can be transitioned to approved Adempas.

[…]

- Pregnancy test for females of childbearing potential
- Perform physical examination (incl. height, weight and vital signs)

[…]

17.1.2.23 Section 6.2 Safety outcomes

Old text:

Not applicable.

New text:

Laboratory parameters

Laboratory parameters will be collected at V0 (if no historical data is available), V5 and V9.

Hematology: CBC

General Chemistry: AST,ALT, Creatinine and BUN

Afterwards; any additional collection of laboratory parameters will be obtained in case medically required and according to medical practice at the site at any time point and will be captured in the eCRFs.

17.1.2.24 Section 6.4 Pharmacokinetics

Old text:

Primary PK outcome measure:

~~Peak and trough~~ blood samples for PK characterization of riociguat and its active metabolite BAY 60-4552 will be collected during the titration and the maintenance phase of the study.

New text:

Primary PK outcome measure:

Pre- and post-dose blood samples for PK characterization of riociguat and its active metabolite BAY 60-4552 will be collected during the titration and the maintenance phase of the study.

17.1.2.25 Section 7.4.1 Safety analysis

Old text:

[…]

- Descriptive analysis of ~~continuous~~ laboratory parameters and their corresponding changes from baseline

[…]

New text:

[…]

- Descriptive analysis of laboratory parameters (AST, ALT, BUN, creatinine, and CBC) and their corresponding changes from baseline

[…]

17.1.2.26 Section 7.4.5 Analyses

Old text:

The study results will be reported once all the pediatric subjects have completed their main study treatment period. Thereafter only descriptive summaries of study data from the ongoing subjects will be provided.

New text:

The study results will be reported once all the pediatric subjects have completed their main study treatment period of 24 weeks. Thereafter only descriptive summaries of study data from the ongoing subjects will be provided.

17.1.2.27 Section 8.1.1 Adverse events

Old text:

An AE, including AE in relation to a medical device, is any untoward medical occurrence in a subject administered with a pharmaceutical product and does not necessarily have to have a causal relationship with this treatment.

[…]

New text:

An AE, including AE in relation to a medical device (i.e. Raumedic dosing pipette), is any untoward medical occurrence in a subject administered with a pharmaceutical product and does not necessarily have to have a causal relationship with this treatment.

[…]

17.1.2.28 Appendix 18.1 Body-weight adjusted dosing of riociguat

Old text:

~~18.1 Appendix 1: Body-weight adjusted dosing of riociguat~~

~~Body-weight adjusted dosing of riociguat - Suspension~~

~~BW [kg]~~		~~1mg~~	~~1.5mg~~	~~2mg~~	~~2.5mg~~	~~0.5mg~~
~~Min~~	~~Max~~	~~vol [mL]~~	~~vol [mL]~~	~~vol [mL]~~	~~vol [mL]~~	~~vol [mL]~~
~~≥14~~	~~<16~~	~~1,75~~	~~2,75~~	~~3,75~~	~~4,75~~	~~1,00~~
~~≥16~~	~~<18~~	~~2,00~~	~~3,00~~	~~4,25~~	~~5,00~~	~~1,00~~
~~≥18~~	~~<20~~	~~2,25~~	~~3,25~~	~~4,50~~	~~5,50~~	~~1,00~~
~~≥20~~	~~<25~~	~~2,50~~	~~3,75~~	~~5,00~~	~~6,50~~	~~1,25~~
~~≥25~~	~~<30~~	~~3,00~~	~~4,25~~	~~6,00~~	~~7,50~~	~~1,50~~
~~≥30~~	~~<35~~	~~3,25~~	~~5,00~~	~~6,50~~	~~8,50~~	~~1,75~~
~~≥35~~	~~<40~~	~~3,75~~	~~5,50~~	~~7,50~~	~~9,50~~	~~1,75~~
~~≥40~~	~~<50~~	~~4,50~~	~~6,50~~	~~9,00~~	~~11,00~~	~~2,25~~
~~> 50 *~~		~~5,50~~	~~8,00~~	~~10,00~~	~~13,00~~	~~2,50~~

~~5-10 mL 0.5 mL increments~~
~~1-5 mL 0.25 mL increments~~

~~* only for subjects changing to >50kg weight group during main study phase~~

~~Body-weight adjusted dosing of riociguat - Tablet~~

~~BW [kg]~~		~~1mg~~	~~1.5mg~~	~~2mg~~	~~2.5mg~~	~~0.5mg~~
		~~Tablet dose~~	~~Tablet dose~~	~~Tablet dose~~	~~Tablet dose~~	~~Tablet dose~~
~~Min~~	~~Max~~	~~[mg]~~	~~[mg]~~	~~[mg]~~	~~[mg]~~	~~[mg]~~
~~≥14~~	~~<16~~	~~NA~~	~~0,50~~	~~0,50~~	~~1,00~~	~~NA~~
~~≥16~~	~~<18~~	~~NA~~	~~0,50~~	~~0,50~~	~~1,00~~	~~NA~~
~~≥18~~	~~<20~~	~~0,50~~	~~0,50~~	~~0,50~~	~~1,00~~	~~NA~~
~~≥20~~	~~<25~~	~~0,50~~	~~0,50~~	~~1,00~~	~~1,00~~	~~NA~~
~~≥25~~	~~<30~~	~~0,50~~	~~0,50~~	~~1,00~~	~~1,00~~	~~NA~~
~~≥30~~	~~<35~~	~~0,50~~	~~1,00~~	~~1,00~~	~~1,00~~	~~NA~~
~~≥35~~	~~<40~~	~~0,50~~	~~1,00~~	~~1,00~~	~~1,50~~	~~NA~~
~~≥40~~	~~<50~~	~~0,50~~	~~1,00~~	~~1,00~~	~~1,50~~	~~0,50~~
~~> 50kg~~		~~1,00~~	~~1,50~~	~~2,00~~	~~2,50~~	~~0,50~~

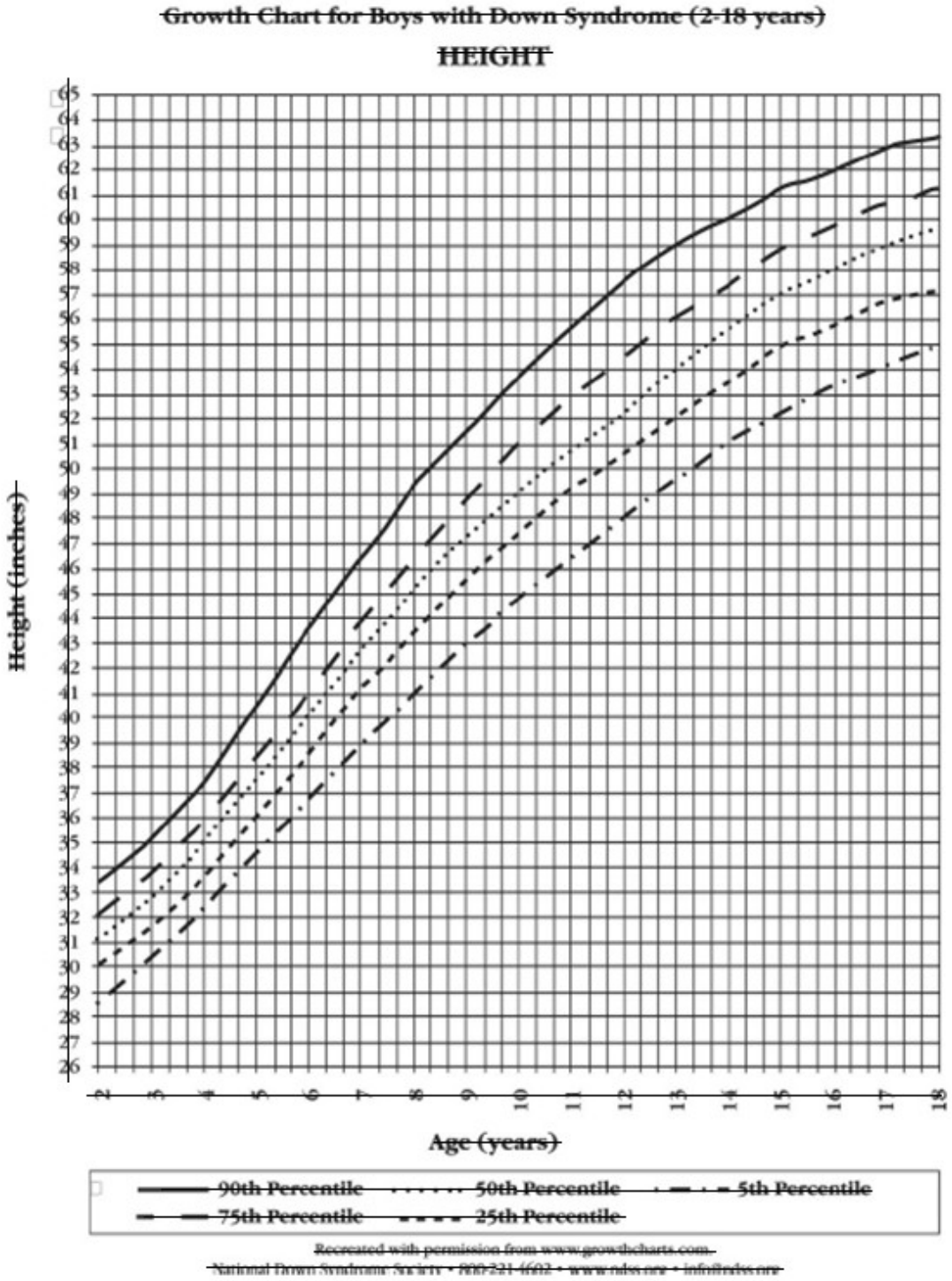
New text:

Not applicable!

Appendix 1 deleted, and the numbering of Appendices is changed accordingly.

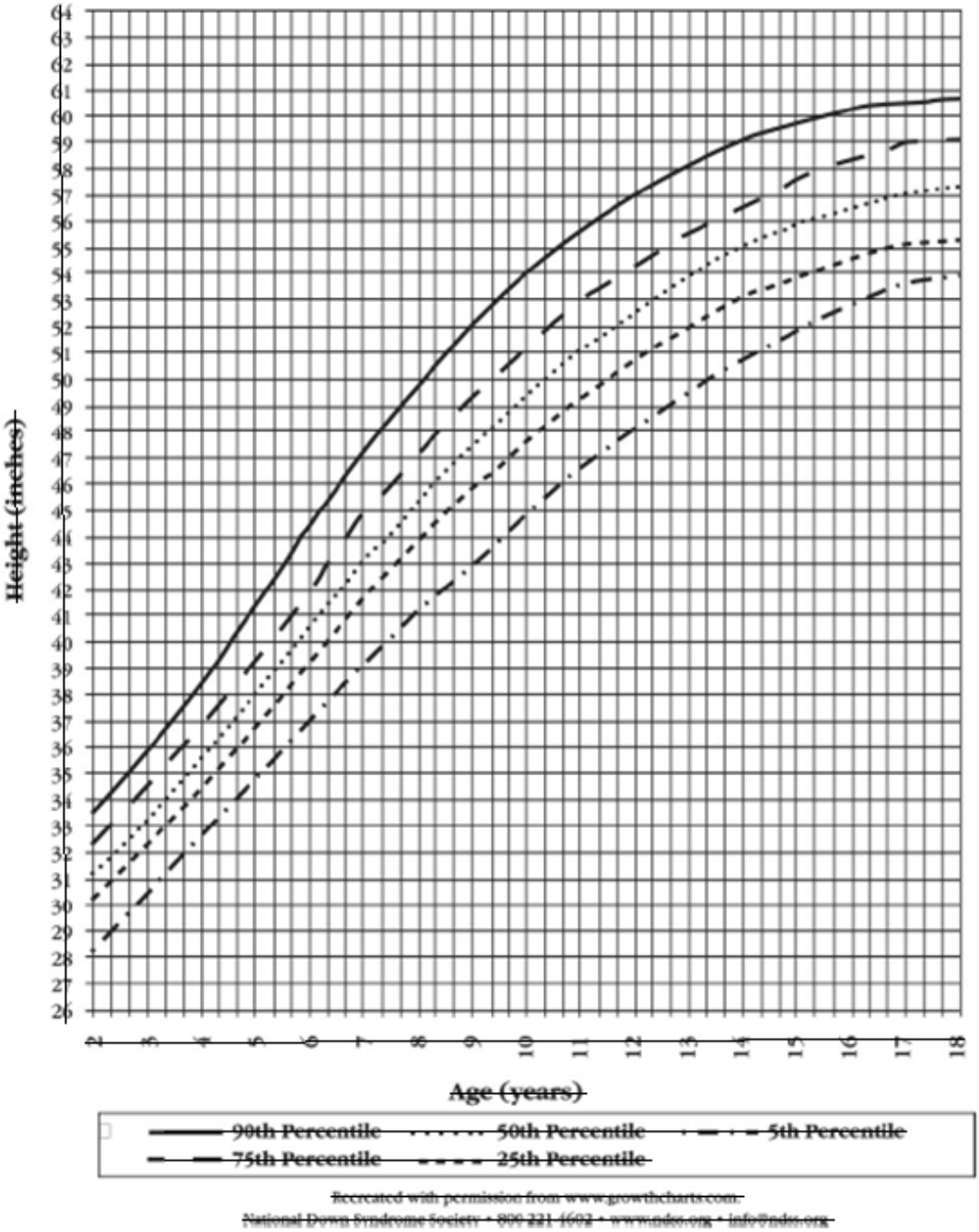
17.1.2.29 Appendix 18.1 Growth charts

Old text:



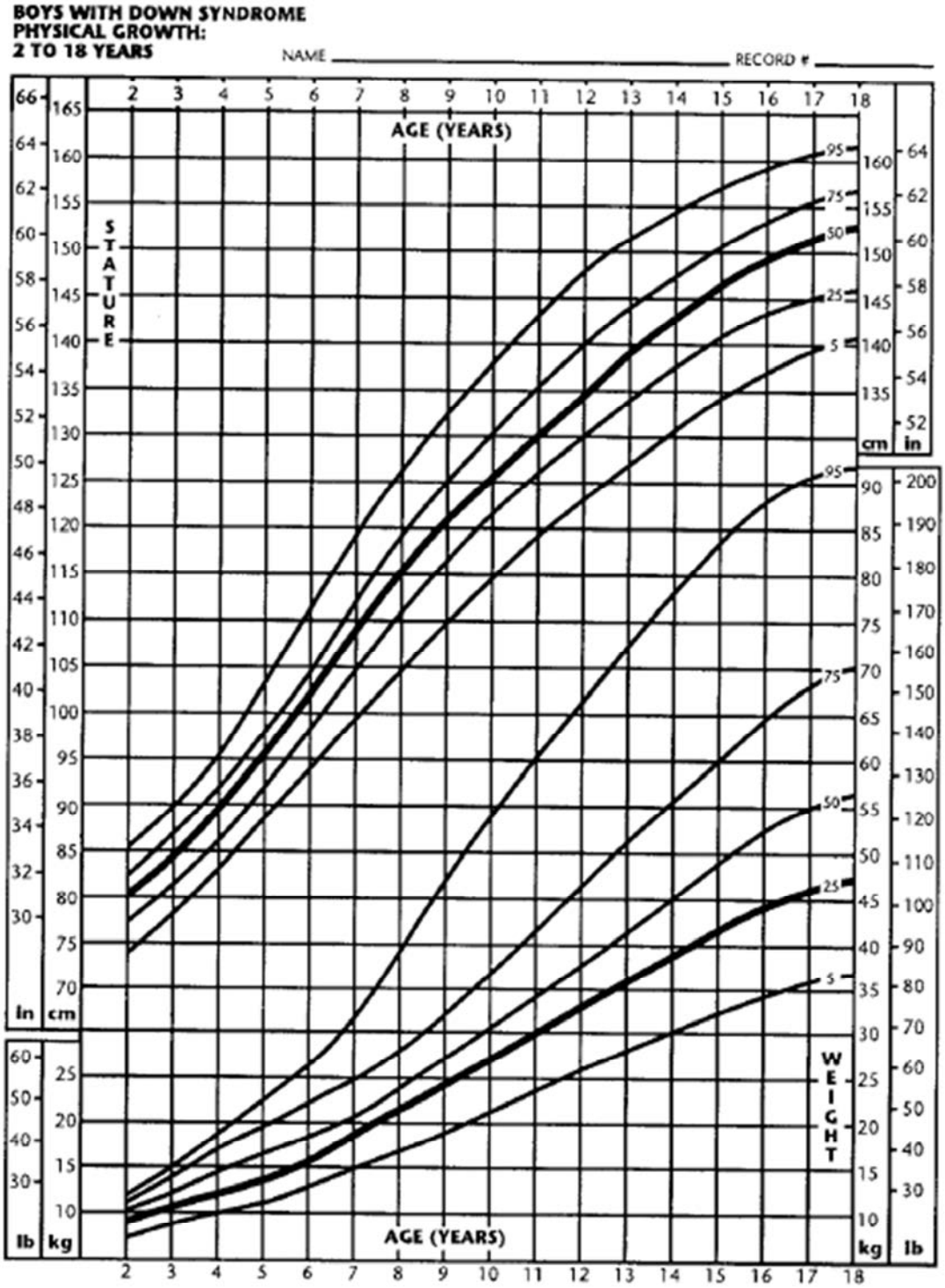
Growth Chart for Girls with Down Syndrome (2-18 years)

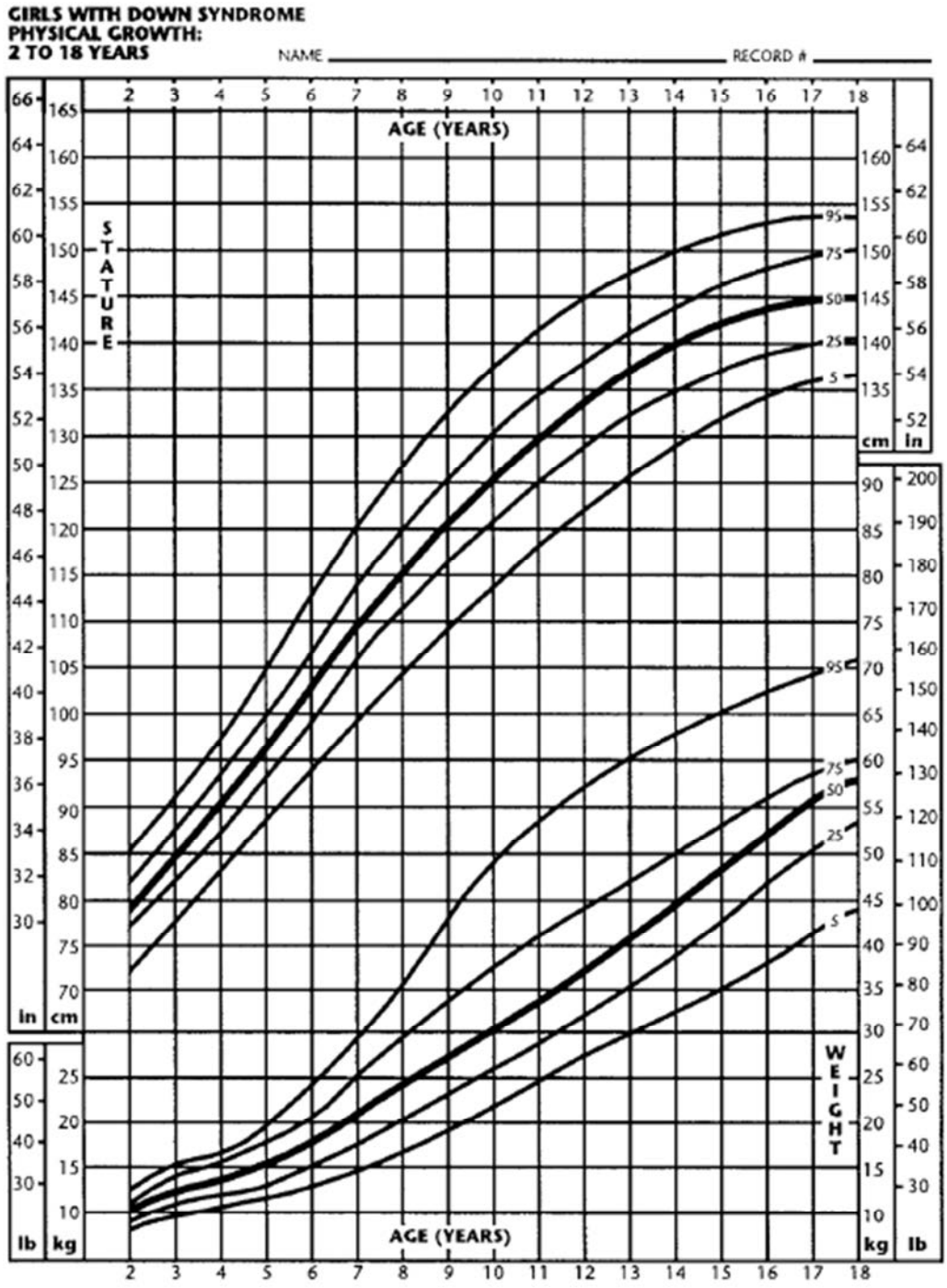
HEIGHT



Recreated with permission from www.growthcharts.com.
National Down Syndrome Society • 800 221 4602 • www.ndss.org • info@ndss.org

New text:

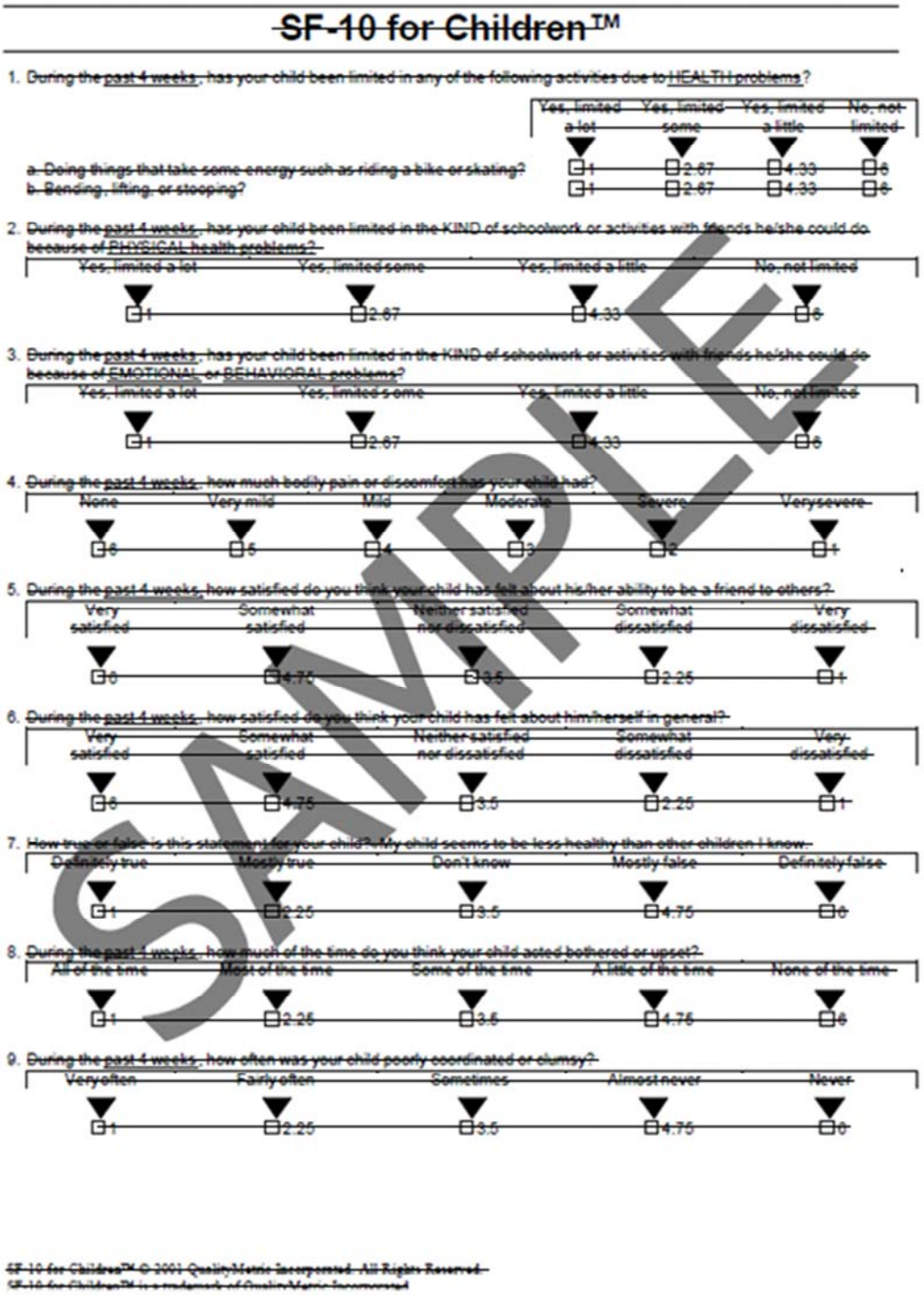

BOYS WITH DOWN SYNDROME
PHYSICAL GROWTH:
2 TO 18 YEARS
NAME
RECORD #
AGE (YEARS)
STATURE
WEIGHT
95
75
50
25
5
in
cm
lb
kg



Growth charts for boys and girls with Down syndrome from (CRONK C., 1988)

17.1.2.30 Appendix 18.3 Child health Questionnaire (SF-10)

Old text:



SF-10 for Children™

1. During the past 4 weeks, has your child been limited in any of the following activities due to HEALTH problems?

	Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
a. Doing things that take some energy such as riding a bike or skating?	1	2.67	4.33	6
b. Bending, lifting, or stooping?	1	2.67	4.33	6

2. During the past 4 weeks, has your child been limited in the KIND of schoolwork or activities with friends he/she could do because of PHYSICAL health problems?

Yes, limited a lot (1) — Yes, limited some (2.67) — Yes, limited a little (4.33) — No, not limited (6)

3. During the past 4 weeks, has your child been limited in the KIND of schoolwork or activities with friends he/she could do because of EMOTIONAL or BEHAVIORAL problems?

Yes, limited a lot (1) — Yes, limited some (2.67) — Yes, limited a little (4.33) — No, not limited (6)

4. During the past 4 weeks, how much bodily pain or discomfort has your child had?

None (6) — Very mild (5) — Mild (4) — Moderate (3) — Severe (2) — Very severe (1)

5. During the past 4 weeks, how satisfied do you think your child has felt about his/her ability to be a friend to others?

Very satisfied (6) — Somewhat satisfied (4.75) — Neither satisfied nor dissatisfied (3.5) — Somewhat dissatisfied (2.25) — Very dissatisfied (1)

6. During the past 4 weeks, how satisfied do you think your child has felt about him/herself in general?

Very satisfied (6) — Somewhat satisfied (4.75) — Neither satisfied nor dissatisfied (3.5) — Somewhat dissatisfied (2.25) — Very dissatisfied (1)

7. How true or false is this statement for your child? My child seems to be less healthy than other children I know.

Definitely true (1) — Mostly true (2.25) — Don't know (3.5) — Mostly false (4.75) — Definitely false (6)

8. During the past 4 weeks, how much of the time do you think your child acted bothered or upset?

All of the time (1) — Most of the time (2.25) — Some of the time (3.5) — A little of the time (4.75) — None of the time (6)

9. During the past 4 weeks, how often was your child poorly coordinated or clumsy?

Very often (1) — Fairly often (2.25) — Sometimes (3.5) — Almost never (4.75) — Never (6)

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New text:

SF-10™ Health Survey for Children

1. **In general, would you say your child's health is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **During the past 4 weeks, has your child been limited in any of the following activities due to HEALTH problems?**

	Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
a. Doing things that take some energy such as riding a bike or skating?	☐1	☐2	☐3	☐4
b. Bending, lifting, or stooping?	☐1	☐2	☐3	☐4

3. **During the past 4 weeks, has your child been limited in the KIND of schoolwork or activities with friends he/she could do because of PHYSICAL health problems?**

Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
☐1	☐2	☐3	☐4

4. **During the past 4 weeks, has your child been limited in the KIND of schoolwork or activities with friends he/she could do because of EMOTIONAL or BEHAVIORAL problems?**

Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
☐1	☐2	☐3	☐4

5. **During the past 4 weeks, how much bodily pain or discomfort has your child had?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐1	☐2	☐3	☐4	☐5	☐6

6. **During the past 4 weeks, how satisfied do you think your child has felt about his/her friendships?**

Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
☐1	☐2	☐3	☐4	☐5

7. **During the past 4 weeks, how satisfied do you think your child has felt about his/her life overall?**

Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
☐1	☐2	☐3	☐4	☐5

United States (English) Version

SF-10™ Health Survey for Children

8. **During the <u>past 4 weeks</u>, how much of the time do you think your child acted bothered or upset?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

9. **Compared to other children your child's age, in general would you say his/her behavior is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

United States (English) Version

17.2 Amendment 5

Amendment 5 is the second global amendment dated 31 MAY 2016.

17.2.1 Overview of changes

17.2.1.1 Modification 1: An addition of following laboratory parameters: GGT, UA, T-Bil, Alb, Na, K, Ca, and P

There is no signal for drug-induced laboratory parameter changes attributable to riociguat in the adult studies. However, considering that riociguat was never administered in this patient population and the fact that patients will be in use of Bosentan, the sponsor decided to add the collection of the following parameters: GGT, UA, T-Bil, Alb, Na, K, Ca, and P at visit 0, 5 and 9 for safety reasons. Furthermore, all laboratory parameters are recorded to electronic case report form (eCRF) when obtained as medically required according to a local package insert of bosentan or medical practice at any time. The protocol sections affected by this modification are:

Study flow chart - amended

6.1.1 Pre-treatment phase (Visit 0, Day -14 to -1) - amended

6.1.2.1 Individual titration phase (Visit 1 – Visit 4) - amended

6.1.2.2 Maintenance phase (Visit 5 - Visit 9) - amended

6.1.4 Safety follow-up visit - amended

6.1.5 Unscheduled visit - amended

6.1.6 Optional long-term extension phase (until adulthood or approval in the indication and commercial availability) - amended

6.2 Safety outcomes - amended

7.4.1 Safety analysis - amended

17.2.1.2 Modification 2: An addition of collection of right heart catheterization parameters to eCRF

The collection of RHC parameters in the eCRF was included in order to have access to hemodynamics data at baseline and at any time during the study, in case a RHC will be performed. This will allow us the possibility of analyzing hemodynamics response to riociguat (in case patient has more than one RHC).

The protocol sections affected by this modification are:

Study flow chart - amended

6.1.1 Pre-treatment phase (Visit 0, Day -14 to -1) - amended

6.1.2.1 Individual titration phase (Visit 1 – Visit 4) - amended

6.1.2.2 Maintenance phase (Visit 5 - Visit 9) - amended

6.1.3 End-of-treatment visit - amended

6.1.4 Safety follow-up visit - amended

6.1.5 Unscheduled visit - amended

6.1.6 Optional long-term extension phase (until adulthood or approval in the indication and commercial availability) - amended

6.3 Efficacy/Pharmacodynamic/Other outcomes - amended

7.4.2 Efficacy analysis - amended

17.2.1.3 Modification 3: Addition of right heart dimensions Echo parameters: right atrial and right ventricular dimensions

It has been demonstrated that right atrial and right ventricular dimensions correlate with disease severity and outcome in children with pulmonary arterial hypertension (PAH) and a recent study in adults has shown that long term treatment with riociguat significantly reduced right heart size and improved right ventricular function in PAH. Taking these facts in consideration, the echocardiography parameter of right heart dimensions was introduced in the study. Furthermore, all Echo parameters were listed as secondary main variables.

The protocol sections affected by this modification are:

Synopsis - amended

6.3 Efficacy/Pharmacodynamic/Other outcomes - amended

17.2.1.4 Modification 4: Echocardiography central reading

Echocardiographic parameters are one of our main secondary variables which will be analyzed in our study. Considering that it is an open label study, with a low number of patients, and the fact that echocardiogram is an operator dependent exam, the sponsor decided to include central reading in order to have a more reliable data.

The protocol section affected by this modification is:

6.2 Safety outcomes - amended

17.2.1.5 Modification 5: Modification of the wording which describes approved drugs for children with PAH, as well as modification regarding to the expert guidelines was done in Introduction.

Since both drugs Revatio (sildenafil) and bosentan are approved to be used in children with PAH in EU, the sentences describing the Revatio and bosentan in Introduction were not accurate and were modified. Furthermore, according to recent expert guidelines not only endothelin receptor antagonists (ERA) but also phosphodiesterase 5(PDE5) inhibitors are suggested to be used, and for accuracy the wording for expert guidelines was modified.

The protocol section affected by these modifications is:

1. Introduction - amended

17.2.1.6 Modification 6: Addition Appendix 6; calculation instructions for eGFR by Schwartz formula

Since there are two Schwartz formulas which are based on the creatinine assessment method used, the calculation instructions for estimated glomerular filtration rate (eGFR) calculation by Schwartz formula was added to ensure the sites have easy access to correct calculation formula.

The protocol sections affected by this modification are:

4.3 Exclusion criteria - amended

18.6 Appendix 6.

17.2.1.7 Modification 7: Changes regarding to taste and texture questionnaire

Taste and texture of the pediatric formulation will be assessed by use of a questionnaire at the beginning and at the end of the study. The questionnaire is not considered to be a main secondary variable nor affect to the pharmacodynamic profile of riociguat, and the protocol is modified to clarify the use of taste and texture questionnaire.

The protocol sections affected by this modification are:

Synopsis - amended

2. Study objectives - amended

6.3 Efficacy/Pharmacodynamic/Other outcomes - amended

17.2.1.8 Modification 8: Minor clarifications

Minor, consistency and logical clarifications were made throughout the document. The changes were made to ensure clear wording and consistency throughout the document. These changes do not affect the overall study concept.

Sections affected by the changes are:

- **Title page:** Sponsor name and medical expert contact details were updated.
- **List of Abbreviations:** New abbreviations were added due to the Amendment 5 modifications. Additionally, the abbreviation DSMB was deleted since not found from the document.
- **Study flow chart, table 0-2**: For better readability the line describing blood sampling for NT-proBNP and safety laboratory was divided to two individual lines, and a missing dot for safety laboratory was added.
- **Section1. Introduction:** The symbol > was corrected as ≥ in the sentence describing the guidelines for definition of the pulmonary hypertension (the mean pulmonary artery pressure should be ≥ 25 mmHg instead of > 25mmHg).
- **Section 5.1.1 Body-weight adjusted individual dose titration regimen**: For clarity the word *device* has been replaced with wording *oscillometry unit* in the paragraph describing individual dose assignment.
- **Section 8.12 Device malfunction failure and medical device related events reporting:** Correction of wording regarding to reporting of dosing device malfunction or device related events was done. Furthermore, to ensure clarity the wording under Incident and Investigators notification of the sponsor was modified to highlight that word device means suspension dosing device.

17.2.2 Changes to the protocol text

All affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the “old text” refers to the original

protocol. Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text". Minor editorial changes or corrections are not listed.

17.2.2.1 Title page

Old text:

Sponsor: ~~**Bayer HealthCare AG, D-51368 Leverkusen, Germany**~~

Sponsor's medical expert: PPD

~~Bayer HealthCare Pharmaceuticals~~

BPH-GD-P&O

Aprather Weg, Bd 402

42113, Wuppertal, Germany

Phone: PPD

New text:

Sponsor: **Bayer AG, D-51368 Leverkusen, Germany**

Sponsor's medical expert: PPD

Bayer Pharma AG

BPH-GD-P&O

Aprather Weg, Bd 402

42113, Wuppertal, Germany

Phone: PPD

17.2.2.2 Abbreviations - amended:

Old text:

~~DSMB~~ ~~data safety monitoring board~~

New text:

[…]

Alb	albumin
Ca	calcium
eGFR	estimated glomerular filtration rate
GGT	gamma-glutamyltransferase
IDMS	isotope dilution mass spectrometry
K	potassium
Na	sodium
P	phosphate
SCr	serum creatinine

T-Bil	total bilirubin
UA	uric acid

[…]

17.2.2.3 Synopsis - amended

Old text:

Main secondary variable(s)	[…] • Echocardiographic parameters including o pulmonary arterial systolic pressure (PASP), o tricuspid annular plane systolic excursion (TAPSE), o pericardial effusion, o left ventricular eccentricity index, o estimated inferior vena cava pressure. […] • ~~Taste and texture of the pediatric formulation(s) must be assessed by use of a questionnaire.~~

New text:

Main secondary variable(s)	[…] • Echocardiographic parameters including o pulmonary arterial systolic pressure (PASP), o tricuspid annular plane systolic excursion (TAPSE), o pericardial effusion, o left ventricular eccentricity index, o estimated inferior vena cava pressure. o <u>right ventricular pressure by tricuspid regurgitant jet velocity</u> o <u>acceleration time of pulmonary flow and</u> o <u>right heart dimensions</u> […] Not applicable.

17.2.2.4 Study flow chart - amended

Old text:

Table 0-1: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
[…]															
Obtain lab test [i]	•[i]					•				•		•			
[…]															

i. Obtain blood samples if AST ~~and~~ ALT, creatinine, BUN and CBC are not available within 30 days prior to Visit 0

New text:

Table 0-1: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
[…]															
Obtain lab test [i]	•[i]					•				•		•			
[…]															
RHC data [o]	•[o]														
[…]															

i. Obtain blood samples if AST, ALT, creatinine, BUN, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC are not available within 30 days prior to Visit 0. Record the same laboratory parameters to eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time.

o. In case RHC has been performed for a study subject before enrollment, record most recent RHC parameters to the eCRF on V0 (timing of RHC not limited to the period of Day -14 to -1). Additionally, if RHC is conducted on medical reasons during the study, the RHC data should be recorded to the eCRF.

Old text:

Table 0–2: Visit details - amended

		Visit 1 (Baseline visit)						**Visit 3 and 5**	
		Detailed study activities at pre-dose and after the first study medication dose intake						**Study activities before first study medication dose intake**	
Order of procedures	Time interval (h)	pre-dose	0:00	0:30 to 1:30	2:00	2:30 to 4:00	4:00	-1:00 to 0:00	0:00
↓	Pharmacokinetic blood sample			•		•		•	
	Blood sample for ~~safety laboratory (incl~~. NT-proBNP~~)~~	•							
	Blood pressure, heart rate	•			•		•		
	ECG	•			•		•		
	WHO functional class	•							
	Left hand x-ray	•							
	Administration study drug		•						•
	Echocardiogram	•							

Abbreviations: ECG = electrocardiogram

New text:

Table 0–2: Visit details - amended

		Visit 1 (Baseline visit)						**Visit 3 and 5**	
		Detailed study activities at pre-dose and after the first study medication dose intake						**Study activities before first study medication dose intake**	
Order of procedures	Time interval (h)	pre-dose	0:00	0:30 to 1:30	2:00	2:30 to 4:00	4:00	-1:00 to 0:00	0:00
↓	Pharmacokinetic blood sample			•		•		•	
	Blood sample for NT-proBNP	•							
	Blood sample for safety laboratory							• [a]	
	Blood pressure, heart rate	•			•		•		
	ECG	•			•		•		
	WHO functional class	•							
	Left hand x-ray	•							
	Administration study drug		•						•
	Echocardiogram	•							

a. Obtain blood sample for safety parameters on Visit 5 only.

Abbreviations: ECG = electrocardiogram

17.2.2.5 1. Introduction - amended

Old text:

[…]

Pulmonary Hypertension (PH) according to the current European Society of Cardiology (ESC) guidelines (Galie et al., 2009) is defined by a mean pulmonary artery pressure (PAP) ~~>~~25 mmHg at rest, which is still consistent with the definition of the 5th World Symposium on Pulmonary Hypertension, which took place in Nice, 2013 (Simonneau et al., 2013).

[…]

~~The only PAH-specific drug approved for children is Revatio (sildenafil), and this approval is restricted to the European Union only. Bosentan is widely used in children with PAH.~~ The medical treatment recommendations of Tracleer (International non-proprietary name [INN]: bosentan) in pediatric populations with PAH in the European Union (EU) are mainly based on extrapolation from experience in adult populations (EMA, 2012b). Data from clinical studies in pediatric patients are derived from retrospective cohort studies (without control-group) in mono-therapy and combination therapy, (Hislop et al., 2011, Ivy et al., 2010, Maiya et al., 2006, Rosenzweig et al., 2005), from clinical studies in pediatric patients with PAH and focus on pharmacokinetics (without control group) (Beghetti, 2009, Barst et al., 2003), from a European non-interventional post-marketing surveillance database (Beghetti et al., 2008), and from a double-blind placebo controlled study in patients > 12 years of age with Eisenmenger's syndrome (Galie et al., 2006). These studies showed encouraging results for the benefit of the pediatric population but still indicate that improvement in medical treatment is needed. Recent expert guidelines suggest the use of endothelin receptor antagonists (ERA) and, when children deteriorate on ~~this~~ medication, additional agents may be considered, either in an up-front approach or sequential add-on (Ivy et al., 2013).

[…]

New text:

[…]

Pulmonary Hypertension (PH) according to the current European Society of Cardiology (ESC) guidelines (Galie et al., 2009) is defined by a mean pulmonary artery pressure (PAP) ≥25 mmHg at rest, which is still consistent with the definition of the 5th World Symposium on Pulmonary Hypertension, which took place in Nice, 2013 (Simonneau et al., 2013).

[…]

Revatio (sildenafil) and bosentan are PAH-specific drugs approved for children in European Union. The medical treatment recommendations of Tracleer (International non-proprietary name [INN]: bosentan) in pediatric populations with PAH in the European Union (EU) are mainly based on extrapolation from experience in adult populations (EMA, 2012b). Data from clinical studies in pediatric patients are derived from retrospective cohort studies (without control-group) in mono-therapy and combination therapy, (Hislop et al., 2011, Ivy et al., 2010, Maiya et al., 2006, Rosenzweig et al., 2005), from clinical studies in pediatric patients with PAH and focus on pharmacokinetics (without control group) (Beghetti, 2009, Barst et al., 2003), from a European non-interventional post-marketing surveillance database (Beghetti et al., 2008), and from a double-blind placebo controlled study in patients > 12 years of age

with Eisenmenger's syndrome (Galie et al., 2006). These studies showed encouraging results for the benefit of the pediatric population but still indicate that improvement in medical treatment is needed. Recent expert guidelines suggest the use of endothelin receptor antagonists (ERA) or phosphodiesterase 5 (PDE5) inhibitor and, when children deteriorate on use of any of these medications, additional agents may be considered, either in an up-front approach or sequential add-on (Ivy et al., 2013).

[…]

17.2.2.6 2. Study objectives - amended

Old text:

[…]

Secondary exploratory objectives are:

- To characterize the pharmacodynamic profile of riociguat comprising the following exploratory parameters: time to clinical worsening (TTCW), exercise capacity (6MWD test), functional capacity (measured by WHO FC), laboratory biomarkers (NT-proBNP), QoL measurements (SF-10), echocardiographic variables ~~and taste assessment (questionnaire)~~.

New text:

[…]

Secondary exploratory objectives are:

- To characterize the pharmacodynamic profile of riociguat comprising the following exploratory parameters: time to clinical worsening (TTCW), exercise capacity (6MWD test), functional capacity (measured by WHO FC), laboratory biomarkers (NT-proBNP), QoL measurements (SF-10), echocardiographic variables

Other objective is:

- To assess taste and texture of the pediatric formulation(s) by use of a questionnaire

17.2.2.7 4.3 Exclusion criteria - amended

Old text:

[…]

14. Renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73m^2 e.g. calculated based on Schwartz formula)

[…]

New text:

[…]

14. Renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73m^2 e.g. calculated based on Schwartz formula, for detailed calculation instructions, see 18.6)

[…]

17.2.2.8 5.1.1 Body weight adjusted individual dose titration regimen - amended

Old text:

[…]

At each titration visit, the individual dose will be assigned based on the following algorithm where peripheral systolic blood pressure (SBP) will be measured (by oscillometry with the same calibrated ~~device~~ in each center) at trough before intake of the first dose of the day.

[…]

New text:

[…]

At each titration visit, the individual dose will be assigned based on the following algorithm where peripheral systolic blood pressure (SBP) will be measured (by oscillometry with the same calibrated oscillometry unit in each center) at trough before intake of the first dose of the day.

[…]

17.2.2.9 6.1.1 Pre-treatment phase (Visit 0, Day -14 to -1) - amended

Old text:

[…]

- Obtain blood sample if AST, ALT, creatinine, BUN, and CBC are not available within 30 days prior to screening visit

[…]

- Not applicable.

[…]

New text:

[…]

- Obtain blood sample if AST, ALT, creatinine, BUN, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC are not available within 30 days prior to screening visit

[…]

- In a case RHC has been performed for a study subject before enrollment, record the most recent RHC parameters to the eCRF (timing of RHC not limited to the period of Day -14 to -1).

[…]

17.2.2.10 6.1.2.1 Individual titration phase (Visit 1 – Visit 4) - amended

Old text:

Not applicable.

New text:

[…]

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time
- In a case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF

17.2.2.11 6.1.2.2 Maintenance phase (Visit 5 - Visit 9) - amended

Old text:

[…]

- Obtain laboratory parameters (AST, ALT, BUN, creatinine, and CBC) at Visits 5 and 9 as well as when medically required according to medical practice at the study site at any time

New text:

[…]

- Obtain laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) at Visits 5 and 9 as well as record the same parameters when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time
- In a case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF

17.2.2.12 6.1.3 End-of-treatment visit - amended

Old text:

Not applicable.

New text:

[…]

In a case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF.

17.2.2.13 6.1.4 Safety follow-up visit - amended

Old text:

Not applicable.

New text:

[…]

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time
- In a case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF

17.2.2.14 6.1.5 Unscheduled visit - amended

Old text:

Not applicable.

New text:

[…]

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time
- In a case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF

17.2.2.15 6.1.6 Optional long-term extension phase (until adulthood or approval in the indication and commercial availability) - amended

Old text:

Not applicable.

New text:

[…]

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time
- In a case RHC is conducted based on medical reasons during the study, record RHC parameters to eCRF

[…]

17.2.2.16 6.2 Safety outcomes - amended

Old text:

Laboratory parameters

Laboratory parameters will be collected at V0 (if no historical data is available), V5 and V9.

- Hematology: CBC
- General Chemistry: AST,ALT, Creatinine and BUN

Afterwards; any additional collection of laboratory parameters will be obtained in case medically required ~~and~~ according to medical practice at the site at any time point and will be captured in the eCRFs.

New text:

Laboratory parameters

Laboratory parameters will be collected at V0 (if no historical data is available), V5 and V9.

- Hematology: CBC
- General Chemistry: AST,ALT, Creatinine, BUN, GGT, UA, T-Bil, Alb, Na, K, Ca and P

Afterwards; any additional collection of laboratory parameters will be obtained in case medically required according to a local package insert of bosentan or medical practice at the site at any time point and will be captured in the eCRFs.

Echocardiograph

Echocardiographic parameters will be evaluated centrally by a specialist during the main study phase and optional long term extension. Details are specified in the respective Imaging documents.

17.2.2.17 6.3 Efficacy/Pharmacodynamic/Other outcomes - amended

Old text:

6.3 Efficacy/Pharmacodynamic outcomes

Secondary pharmacodynamic outcomes (descriptive analysis) are the change from baseline (Day 0) to end of treatment (week 24) of:

[…]

- 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 inferior vena cava pressure, acceleration time of the pulmonary flow

[…]

Not applicable.

New text:

6.3 Efficacy/Pharmacodynamic/Other outcomes

Secondary efficacy, pharmacodynamic, and other outcomes (descriptive analysis) are the change from baseline (Day 0) to end of treatment (week 24) of:

[…]

- 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 inferior vena cava pressure, acceleration time of the pulmonary flow and right heart dimensions

[…]

Right heart catheterization

A change in RHC parameters (if available) obtained from RHC performed before study enrollment and during the study conduct.

17.2.2.18 7.4.1 Safety analysis - amended

Old text:

[…]

- Descriptive analysis of laboratory parameters (AST, ALT, BUN, creatinine, and CBC) and their corresponding changes from baseline

[…]

New text:

[…]

- Descriptive analysis of laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) and their corresponding changes from baseline

[…]

17.2.2.19 7.4.2 Efficacy analysis - amended

Old text:

Not applicable.

New text:

[…]

RHC parameters (if available) will be analyzed descriptively by summary tables.

[…]

17.2.2.20 8.12 Device malfunction or failure and medical device related events reporting - amended

Old text:

Any device malfunction or failure including use errors or inadequacy in the labeling will be recorded by the clinical/investigational site, including all relevant device information, using the Product Technical Compliant (PTC) form, ~~medical clinical investigations device complaint form and the eCRF for device related events~~, and forwarded within 24 hours to the Sponsor or Sponsor's designee for evaluation and investigation.

[…]

Any event which meets all three basic reporting criteria (a-c) is considered an incident and must be reported to the relevant National Competent Authority. The criteria are that:

a) An event has occurred

b) The device is suspected to be a contributory cause of the Incident.

[…]

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for incidents and serious public health threats related to the ~~investigational~~ device.

[…]

New text:

Any device malfunction or failure including use errors or inadequacy in the labeling will be recorded by the clinical/investigational site, including all relevant device information, using the Product Technical Compliant (PTC) form, and forwarded within 24 hours to the Sponsor or Sponsor's designee for evaluation and investigation.

[…]

Any event which meets all three basic reporting criteria (a-c) is considered an incident and must be reported to the relevant National Competent Authority. The criteria are that:

a) An event has occurred

b) The <u>suspension dosing</u> device is suspected to be a contributory cause of the Incident

[…]

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for incidents and serious public health threats related to the <u>suspension</u> dosing device.

[…]

17.2.2.21 18.6 Appendix 6. Glomerular filtration rate: Calculation instructions by Schwartz formula

Old text:

Not applicable, the Appendix 6 was applied in Amendment 5.

New text:

18.6 Appendix 6: Glomerular filtration rate: Calculation instructions by Schwartz formula

If serum creatinine (SCr) is measured with routine methods that have not been recalibrated to be traceable to isotope dilution mass spectrometry (IDMS) (e.g. the traditional Jaffé reaction), the eGFR should be obtained from the original Schwartz formula:

eGFR (mL/min/1.73 m^2) = k * height (cm) / SCr (mg/dL)

Where k is proportionality constant:

k = 0.55 in children up to 13 years of age

k = 0.70 in boys >13 years and <18 years of age (not in girls; because of the presumed increase in male muscle mass, the constant remains 0.55 for girls)

If SCr is measured by an enzymatic creatinine method that has been calibrated to be traceable to IDMS, the updated Schwartz formula should be used to obtain the eGFR:

eGFR (mL/min/1.73 m^2) = 0.413 * height (cm) / SCr (mg/dL)

Note: To express SCr in micromoles per liter, the value should be multiplied by 88.4 (1 mg/dL = 88.4 µmol/L).

17.3 Amendment 6

Amendment 6 is the third global amendment dated 9 JAN 2017.

17.3.1 Overview of changes

17.3.1.1 Modification 1: An exclusion criterion related to patients with pulmonary hypertension associated with idiopathic interstitial pneumonia was added

A new exclusion criterion “patients with pulmonary hypertension associated with idiopathic interstitial pneumonia (PH-IIP)" was added to the protocol as according to the new updated CCDS, riociguat is now contraindicated in patients with PH-IIP.

Study RISE-IIP was recently terminated early on the recommendation of DMC. RISE-IIP study was a randomized, double-blind, placebo-controlled, multicenter phase II study to investigate the efficacy and safety of riociguat in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP). An evaluation of the interim results by European Medicinal Agency concluded that the benefit risk balance of riociguat in patients with PH-IIP is negative and thus patients with PH-IIP should not be treated with riociguat. The protocol section affected by this modification is:

4.3 Exclusion criteria

8.9 Premature discontinuation of study medication

17.3.1.2 Modification 2: Broadening of the study population and wording adaptation to keep compliance with pediatric investigation plan (PIP)

The agreed study population was broadened to include patients treated with PAH medications including endothelin receptor antagonists (ERA) (besides bosentan), prostacycling analogues (PCAs) or combination of these. The protocol was modified according to positive opinion of the Paediatric Committee, EMEA. Furthermore, several wording adaptations were made to keep consistency and compliance with the PIP.

The protocol sections affected by this modification are:

Synopsis

Study Flow chart

2. Study objectives

3. Study design

3.1 Study description

4.1 Planned number of subjects

4.2 Inclusion criteria

4.3 Exclusion criteria

5.1.1 Body-weight adjusted individual dose titration regimen

6.1 Study visits

6.1.1 Pre-treatment phase (Visit 0, Day -14 to -1)

6.1.2.1 Individual titration phase (Visit 1- Visit 4)

6.1.2.2 Maintenance phase (Visit 5 - Visit 9)

6.1.4 Safety follow-up visit

6.1.5 Unscheduled visit

6.1.6 Optional long-term extension phase (until adulthood or approval in the indication and commercial availability)

6.2 Safety outcomes

6.3 Efficacy/Pharmacodynamic/Other outcomes

6.4 Pharmacokinetics/Pharmacodynamics analyses

7.4 Analyses

7.4.1 Safety analysis

7.4.2 Efficacy analysis

7.5 Determination of sample size

8.9 Premature discontinuation of study medication

17.3.1.3 Modification 3: New Quality of Life questionnaire

The quality of life questionnaire currently used in the protocol is a parent questionnaire. Studies have shown that there is a discrepancy between parents and patients perceptions of psychosocial quality of life scores, indicating that parents and patients questionnaires should be applied in order to have more accurate results.

The protocol sections affected by this modification are:

Study Flow chart

6.1.1 Pre-treatment phase (Visit 0, Day -14 to -1)

6.1.2.2 Maintenance phase (Visit 5 - Visit 9)

6.1.6 Optional long-term extension phase (until adulthood or approval in the indication and commercial availability)

6.3 Efficacy/Pharmacodynamic/Other outcomes

7.4.2 Efficacy analysis

17.3.1.4 Modification 4: Pretreatment with PDE5 inhibitors

Patients are not expected to be withdrawn from treatment with PDE5i for the purpose of entering into this trial.

Guidelines for management of PAH in pediatric patients recommend use of PDE5 inhibitors. In fact, most pediatric patients are being treated with PDE5i as monotherapy or as a

component of a combination therapy, including with PCAs or ERAs. Furthermore, some patients may have a degree of intolerance to PDE5i and could require a treatment change in the future. The inclusion of patients previously treated with PDE5i takes into consideration these elements. However, pretreatment with PDE5i is now allowed but up to 3 three days prior to start of riociguat treatment (Visit 1), considered as washout period. Acknowledgement of treatment practice of PDE5i use, before entering into the trial, is also relevant as sequential modification of treatment is a potential management approach in real life. This criterion is consistent with study participation criteria in trials of riociguat in adults with PAH. In these trials riociguat showed consistent efficacy across multiple endpoints, with an acceptable safety profile. Finally, addressing the NO pathway with an alternative to PDE5i, such as riociguat, can provide benefits to the pediatric population as it did in adults. During the treatment period, the contraindication of co-treatment with PDE5i will stay.

Section affected by this modification:

4.3 Exclusion criteria

17.3.1.5 Modification 5: Exclusion criterion 1 divided to two criteria

Exclusion criterion 1 converted into two criteria to assure that the wording “last 2 weeks period” applies to NO donors only.

Note: The overall criteria numbering in Section 4.3 was changed due to this modification.

Sections affected by this change are:

Synopsis

4.3 Exclusion criteria

17.3.1.6 Modification 6: Brain natriuretic peptide added as an alternative for N-terminal natriuretic peptide

Both biomarkers provide prognostic information in various cardiovascular diseases and there is no meaningful clinical difference between them (Weber and Hamm, 2006). This is a global clinical trial with sites in different continents, therefore each laboratory may have different capabilities in relation to which one of biomarkers can be collected. As a percentage change from baseline for NT pro-BNP and BNP can be done separately, brain natriuretic peptide was added as an alternative for the NT-proBNP collection.

Sections affected by this change are:

Synopsis

Study Flow chart

2. Study objectives

6.1.2.1 Individual titration phase (Visit 1- Visit 4)

6.1.2.2 Maintenance phase (Visit 5 - Visit 9)

6.1.6 Optional long-term extension phase (until adulthood or approval in the indication and commercial availability)

6.3 Efficacy/Pharmacodynamic/Other outcomes

7.4.2 Efficacy analysis

17.3.1.7 Modification 7: Visit window for Visit 5 adjusted

The time window between visit 4 and visit 5 was adapted due to the number of tablets in the bottle supplied to the patients. Bottles supplied to patients have a total of 54 tablets, which allows up to a maximum of 18 days of time window between the visits 4 and 5.

Sections affected by this change are:

Study Flow chart

17.3.1.8 Modification 8: Urine or Serum pregnancy test

Pregnancy test is done in almost every visit. As in some of the visits patient has blood sampling done, an option of serum pregnancy test was added in order to facilitate the process of having the test performed.

Sections affected by this change are:

Study Flow chart

1.2 Rationale of the study and risk-benefit assessment

17.3.1.9 Modification 9: Wording related to bosentan reinserted

The respective wording referent to bosentan was reinserted due to a request from Health Authority in Germany in order to improve clarity of the text. As PAH specific medications also include other ERAs and PCA, these two classes of medications were also added in the sentence.

Section affected by this change:

5.6 Treatment assignment

17.3.1.10 Modification 10: Minor clarifications

Minor, consistency and logical clarifications were made throughout the document. The changes were made to ensure clear wording and consistency throughout the document. These changes do not affect the overall study concept.

Sections affected by the changes are:

- **Title page:** Sponsor information for USA was added
- **Introduction:** The wording clarification and a reference added to point describing European Respiratory Society meeting and AMBITION study
- **Reference list:** A reference for Amendment 6, Modification 6 was added.
- **Appendix 4:** The logo in the Taste and texture assessment was changed

17.3.2 Changes to the protocol text

All affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the original protocol. Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text". Minor editorial changes or corrections are not listed.

17.3.2.1 Title page

Old text:

[…]

Sponsor: **Bayer AG, D-51368 Leverkusen, Germany**

[…]

New text:

[…]

Sponsor: **Bayer AG, D-51368 Leverkusen, Germany**

US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ

07981-0915, USA

[…]

17.3.2.2 Synopsis

Old text:

[…]

Background treatment	Patients must be ~~treated with~~ standard of care ~~comprising background therapy and stable dose of bosentan (> 12 weeks with stable doses).~~

[…]

Diagnosis and main criteria for inclusion /exclusion	Children from 6 years to less than 18 years of age with pulmonary arterial hypertension (PAH). Main inclusion criteria: • Pulmonary arterial hypertension (PAH), diagnosed by right heart catheterization (RHC) (for patients with closed shunts – RHC no less than 4 months after surgery). • Patients must be ~~treated with~~ standard of care ~~comprising background therapy and stable dose of bosentan (at least 12 weeks with stable doses).~~ • Two groups of patients will be included: Prevalent: Patients currently on ~~monotherapy with bosentan~~ who need additional treatment (discretion of the investigator) Incident: Treatment naïve patients initiated on ~~bosentan~~ then riociguat added once ~~bosentan dose is stable for at least 12 weeks.~~ • WHO functional class I-III. Main exclusion criteria: • Concomitant use of the following medications: phosphodiesterase 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific phosphodiesterase (PDE) inhibitors (theophylline, dipyridamole) in any form or pretreatment ~~are not allowed. Concomitant use of nitrates or NO donors are allowed up to two weeks before Visit 1.~~ • […]

[…]

Number of subjects	At least 20 children must be enrolled.
Main secondary variable(s)	Change from baseline to end of treatment (week 24) of: • 6-Minute Walking Distance (6MWD). • WHO functional class. • N-terminal prohormone brain-type natriuretic peptide […]

[…]

New text:

[…]

Background treatment	Patients must be on standard of care PAH medications, allowing Endothelin Receptor Antagonists (ERA) and/or Prostacyclin Analogues (PCA), for at least 12 weeks prior to baseline visit

[…]

Diagnosis and main criteria for inclusion /exclusion	Children from 6 years to less than 18 years of age with pulmonary arterial hypertension (PAH). Main inclusion criteria: • Pulmonary arterial hypertension (PAH), diagnosed by right heart catheterization (RHC) (for patients with closed shunts – RHC no less than 4 months after surgery). • Patients must be on standard of care PAH medications, allowing Endothelin Receptor Antagonists (ERA) and/or Prostacyclin Analogues (PCA), for at least 12 weeks prior to baseline visit • Two groups of patients will be included: Prevalent: Patients currently on PAH medication (allowing ERA and/or PCA) who need additional treatment (discretion of the investigator) Incident: Treatment naïve patients initiated on PAH medication (allowing ERA and/or PCA) and then riociguat added once patients are stable on standard of care. • WHO functional class I-III. Main exclusion criteria: • Concomitant use of the following medications: phosphodiesterase 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific phosphodiesterase (PDE) inhibitors (theophylline, dipyridamole), nitrates or NO donors (such as amyl nitrite) in any form • Pretreatment with NO donors (e.g. nitrates) within the last 2-weeks before visit1 […]

[…]

Number of subjects	Children on treatment with ERAs and/or PCAs can be enrolled. At least 20 children on treatment with bosentan or other Endothelin Receptor Antagonists (ERA) must be enrolled.

[…]

Main secondary variable(s)	Change from baseline to end of treatment (week 24) of: • 6-Minute Walking Distance (6MWD). • WHO functional class. • N-terminal prohormone brain-type natriuretic peptide or brain-type natriuretic peptide. When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit. […]

[…]

17.3.2.3 Study Flow chart

Old text:

[…]

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
[…]															
NT-proBNP		•								•		•		•	
[…]															
Child Health Questionnaire (SF-10)	•									•		•		•	
[…]															

[…]

a Urine pregnancy test for women of childbearing potential
b A volume of 1.0 mL per sample is needed. Accurate adherence to time points is essential and has to be documented, see Table 0-2
[…]
f ±2 days for Visits 1 to 4, ±5 days for Visits 5 to 9
[…]

i Obtain blood samples if AST and ALT, creatinine, BUN, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC are not available within 30 days prior to Visit 0. Record the same laboratory parameters to eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time.

[…]

Table 0–2: Visit details - amended

		Visit 1 (Baseline visit)						**Visit 3 and 5**	
		Detailed study activities at pre-dose and after the first study medication dose intake						**Study activities before first study medication dose intake**	
Order of procedures	Time interval (h)	pre-dose	0:00	0:30 to 1:30	2:00	2:30 to 4:00	4:00	-1:00 to 0:00	0:00
↓	[…]								
	Blood sample for NT-proBNP	•							
	[…]								

New text:

[…]

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
[…]															
NT-proBNP or BNP[p]		•								•		•		•	
[…]															
Child Health Questionnaire (SF-10 and PedsQL)	•									•		•		•	
[…]															

[…]

a Urine or serum pregnancy test for women of childbearing potential
b A minimum volume of 1.0 mL per sample is needed. Accurate adherence to time points is essential and has to be documented, see Table 0-2
[…]
f ±2 days for Visits 1 to 4, ±4 days for Visit 5, ±5 days for Visits 6 to 9
[…]

i Obtain blood samples if AST and ALT, creatinine, BUN, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC are not available within 30 days prior to Visit 0. Record the same laboratory parameters to eCRF when obtained as medically required according to a local package insert of bosentan or other ERAs, or medical practice at the study site at any time.

[…]

p When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit

[…]

Table 0–2: Visit details - amended

		Visit 1 (Baseline visit)						**Visit 3 and 5**	
		Detailed study activities at pre-dose and after the first study medication dose intake						**Study activities before first study medication dose intake**	
Order of procedures	Time interval (h)	pre-dose	0:00	0:30 to 1:30	2:00	2:30 to 4:00	4:00	-1:00 to 0:00	0:00
	[…]								
	Blood sample for NT-proBNP or BNP[b]	•							
	[…]								

[…]

b When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit

17.3.2.4 1. Introduction

Old text:

[…]

At the ~~recent~~ European Society ~~of Respirology~~, the results of the randomized, double-blind AMBITION study were presented.

[…]

New text:

[…]

At the international European Respiratory Society meeting 2014, the results of the randomized, double-blind AMBITION study were presented (Galie et al., 2014).

[…]

17.3.2.5 1.2 Rationale of the study and risk-benefit assessment

Old text:

[…]

Study-specific procedures are: ECGs, Echocardiogram, urine pregnancy testing for female patients of childbearing potential, selected blood sampling, and the left-hand X-ray for monitoring of bone growth.

[…]

New text:

[…]

Study-specific procedures are: ECGs, Echocardiogram, urine or serum pregnancy testing for female patients of childbearing potential, selected blood sampling, and the left-hand X-ray for monitoring of bone growth.

[…]

17.3.2.6 2. Study objectives

Old text:

The primary objective ~~is~~:

- To evaluate safety, tolerability and pharmacokinetics of ~~body-weight adjusted riociguat treatment in children with PAH~~

Secondary ~~exploratory~~ objectives ~~are~~:

- To characterize the pharmacodynamic profile of riociguat comprising the following exploratory parameters: time to clinical worsening (TTCW), exercise capacity (6MWD test), functional capacity (measured by WHO FC), laboratory biomarkers (NT-proBNP), QoL measurements (SF-10), echocardiographic variables

[…]

New text:

The primary objectives:

- To evaluate safety, tolerability and pharmacokinetics of oral riociguat treatment

Secondary objectives:

- Exploratory efficacy. To characterize the pharmacodynamic profile of riociguat comprising the following exploratory parameters: time to clinical worsening (TTCW), exercise capacity (6MWD test), functional capacity (measured by WHO FC), laboratory biomarkers (NT-proBNP or BNP), QoL measurements (SF-10, PedsQL), echocardiographic variables

[…]

17.3.2.7 3. Study design

Old text:

This is an international, multicenter, single-arm, open-label study to evaluate the safety, tolerability and pharmacokinetics of a body-weight adjusted riociguat regimen in subjects aged between ≥6 years old and <18 years old who have been diagnosed with idiopathic PAH, hereditable PAH, or PAH associated with connective tissue disease or congenital heart disease with shunt closure. These subjects must be on stable treatment with ~~bosentan~~ prior to receiving the first dose of riociguat.

New text:

This is an international, multicenter, single-arm, open-label study to evaluate the safety, tolerability and pharmacokinetics of a body-weight adjusted riociguat regimen in subjects aged between ≥6 years old and <18 years old who have been diagnosed with idiopathic PAH, hereditable PAH, or PAH associated with connective tissue disease or congenital heart disease with shunt closure. These subjects must be on stable treatment with PAH medications (ERA and/or PCA) prior to receiving the first dose of riociguat.

17.3.2.8 3.1 Study description

Old text:

After providing written informed consent and assent (if applicable), subjects will undergo a screening evaluation, to determine their eligibility. Eligible subjects – once on stable background treatment with ~~bosentan~~ - will start body-weight adjusted individual dose titration (IDT) regimen as described in section 5.1.1.

[…]

~~Subjects~~ who ~~completed the 24-week main study treatment phase and~~ require ~~further~~ treatment with riociguat will be offered ~~to participate~~ in ~~a long-term~~ extension ~~phase~~ and ~~continue~~ until market approval of riociguat for the pediatric population or until they are ≥18 years of age (whatever comes first). Subjects reaching adulthood can be transitioned to commercially-available Adempas.

New text:

After providing written informed consent and assent (if applicable) subjects will undergo a screening evaluation to determine their eligibility. Eligible subjects – once on stable background treatment with PAH medications (ERA and/or PCA) - will start body-weight adjusted individual dose titration (IDT) regimen as described in section 5.1.1.

[…]

Children who require treatment with riociguat for more than 24 weeks will be offered participation in an extension study and continuation until market approval of riociguat for the pediatric population or until they are ≥18 years of age (whatever comes first). Subjects reaching adulthood can be transitioned to commercially-available Adempas.

[…]

17.3.2.9 4.1 Planned number of subjects

Old text:

At least 20 ~~subjects~~ must be enrolled in the study.

[…]

After 5 patients in the ≥12 to <18 years old group have reached their optimal dose, have been treated on their maintenance dose and obtained the control x-ray of left hand at week 24, their data will be evaluated by DMC. ~~After agreement of the DMC, the enrolment of patients in the age group ≥6 to <12 years will start.~~

[…]

New text:

Children on treatment with ERAs and/or PCAs can be enrolled. At least 20 children on treatment with bosentan or other Endothelin Receptor Antagonists (ERA) must be enrolled in the study.

[…]

After 5 patients in the ≥12 to <18 years old group have reached their optimal dose, have been treated on their maintenance dose and obtained the control x-ray of left hand at week 24, their data will be evaluated by DMC. Only after obtaining positive safety and efficacy data in the first 5 patients, enrolment in the group from 6 to less than 12 years of age will be started.

[…]

17.3.2.10 4.2 Inclusion criteria

Old text:

[…]

1. Children ~~aged ≥6 to <18 years~~

[…]

3. ~~Diagnosis of~~ PAH ~~confirmed~~ by right heart catheterization (RHC) at any time prior to enrolment (for patients with closed shunts – RHC no less than 4 months after surgery)

[…]

5. Patients must be ~~treated with~~ standard of care ~~comprising background therapy and stable dose of bosentan (at least 12 weeks with stable doses).~~

Two groups of patients will be included:

- Prevalent: Patients currently on ~~monotherapy with bosentan~~ who need additional treatment (discretion of the investigator)
- Incident: Treatment naïve patients initiated on ~~bosentan~~ then riociguat added once ~~bosentan dose is stable for at least 12 weeks~~.

6. WHO functional class I~~, II, and~~ -III

[…]

New text:

[…]

1. Children <u>from 6 years to less than 18 years of age with pulmonary arterial hypertension (PAH)</u>

[…]

3. <u>Pulmonary arterial hypertension (</u>PAH<u>), diagnosed</u> by right heart catheterization (RHC) at any time prior to enrolment (for patients with closed shunts – RHC no less than 4 months after surgery)

[…]

5. Patients must be <u>on</u> standard of care <u>PAH medications, allowing Endothelin Receptor Antagonists (ERA) and/or Prostacyclin Analogues (PCA), for at least 12 weeks prior to baseline visit</u>.

Two groups of patients will be included:

- Prevalent: Patients currently on <u>PAH medication (allowing ERA and/or PCA)</u> who need additional treatment (discretion of the investigator)
- Incident: Treatment naïve patients initiated on <u>PAH medication (allowing ERA and/or PCA) and</u> then riociguat added once patients are stable on standard of care.

6. WHO functional class I-III

[…]

17.3.2.11 4.3 Exclusion criteria

Old text:

1. Concomitant use of the following medications: phosphodiesterase (PDE) 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific PDE inhibitors (theophylline, dipyridamole) in any form or pretreatment ~~are not allowed. Concomitant use of nitrates or NO donors are allowed up to two weeks before Visit 1.~~

[…]

New text:

Please note that criteria numbering was changed in this section due to the modification

1. Concomitant use of the following medications: phosphodiesterase (PDE) 5 inhibitors (such as sildenafil, tadalafil, vardenafil) and non-specific phosphodiesterase (PDE) inhibitors (theophylline, dipyridamole), nitrates or NO donors (such as amyl nitrite) in any form [a]
2. Pretreatment with NO donors (e.g. nitrates) within the last 2-weeks before visit 1

[a] Pretreatment with phosphodiesterase (PDE) 5 inhibitors is allowed up to 3 three days prior to start of riociguat treatment (Visit 1). Patients are not expected to be withdrawn from treatment with PDE5i for the purpose of entering into this trial. During the 3 days period without PDE5i, patients who received treatment with PDE5i are expected to be on stable clinical condition and receiving standard of care treatment with ERA and/or PCAs.

[…]

22. PH associated with idiopathic interstitial pneumonia (PH-IIP)

17.3.2.12 5.1.1 Body-weight adjusted individual dose titration regimen

Old text:

Riociguat ~~will~~ be provided to all ~~subjects~~ using an individual dose titration scheme to achieve a similar exposure as that observed in adults treated for PAH (Figure 5-1). For children with <50 kg body weight at baseline, a body weight adjusted dosing will be applied. Children with ≥ 50kg body weight will receive adult doses. The individual optimal dose ~~will~~ be determined based on ~~subject's~~ monitoring of systolic blood pressure, well-being and clinical status.

[…]

New text:

Riociguat must be provided to all patients using an individual dose titration scheme according to a body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for PAH (Figure 5-1). The individual optimal (maintenance) dose is to be determined based on patient's monitoring of systolic blood pressure, well-being and clinical status. For children with <50 kg body weight at baseline, a body weight adjusted dosing will be applied. Children with ≥ 50kg body weight will receive adult doses.

[…]

17.3.2.13 5.6 Treatment assignment

Old text:

After enrolment, the subject identification number will be recorded on the corresponding electronic case report form (eCRF). The subject identification number will also have to be recorded on the label of the study medication.

New text:

After enrolment, the subject identification number will be recorded on the corresponding electronic case report form (eCRF). The subject identification number will also have to be recorded on the label of the study medication.

In case bosentan or other ERA and/or PCA is/are provided locally, the compound's name, dose, quantity and batch number, or a copy of the prescription has to be included in the subject's files

17.3.2.14 6.1 Study visits

Old text:

The main study comprises 3 ~~phases~~:

- Pre-treatment ~~phase:~~ this ~~phase~~ is to identify potential eligibility of subjects who have been diagnosed with PAH. This visit will take place up to 2 weeks before Visit 1 (baseline visit).
- ~~Main study~~ treatment period ~~is divided into 2 periods~~:
  - The individual titration phase ~~compromises~~ 4 visits 2 weeks (±2 days) apart.
  - The maintenance phase ~~compromises~~ 5 visits 4 weeks (±5 days) apart.
- ~~Safety~~ follow-up ~~phase (60±8days)~~

Subjects who have completed 24 weeks of treatment will be offered participation in an optional long term extension phase. Subjects not entering the LTE phase will perform the safety follow-up visit (see section 6.1.4). Subjects dropping-off the protocol any time after Visit 1 and before Visit 9 will perform an end-of-treatment visit (see section 6.1.3).

[…]

New text:

The main study comprises 3 periods:

- Pre-treatment period: up to 2 weeks. This period is to identify potential eligibility of subjects who have been diagnosed with PAH. This visit will take place up to 2 weeks before Visit 1 (baseline visit).
- Active treatment period: 24 weeks (titration phase: 8 weeks, maintenance phase: 16 weeks.) (Main study treatment period):
  - The individual titration phase comprises 4 visits 2 weeks (±2 days) apart.
  - The maintenance phase comprises 5 visits 4 weeks (±5 days) apart.
- Follow-up period: at least 60 days for serious adverse events (SAEs). (Only for patients who do not enter the long term extension study or who stop the study medication prematurely.)

Subjects who have completed 24 weeks of treatment will be offered participation in an optional long term extension phase. Subjects not entering the LTE will perform the safety follow-up visit (see section 6.1.4). Subjects completing the optional LTE will also perform the

safety follow up visit after 60 ± 8 days after LTE. Subjects dropping-off the protocol any time after Visit 1 and before Visit 9 will perform an end-of-treatment visit (see section 6.1.3).

[…]

17.3.2.15 6.1.1 Pre-treatment phase (Visit 0, Day -14 to -1)

Old text:

[…]

- Pregnancy test for females of childbearing potential
- Child Health Questionnaire (SF-10) (section 18.2)

[…]

New text:

[…]

- Pregnancy test for females of childbearing potential
- Child Health Questionnaire (SF-10 and PedsQL Generic Core Scales self-report) (section 18.2 and 18.7)

[…]

17.3.2.16 6.1.2.1 Individual titration phase (Visit 1- Visit 4)

Old text:

[…]

- Collect NT-proBNP (Visit 1 only)

[…]

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time.

[…]

New text:

[…]

- Collect NT-proBNP or BNP (Visit 1 only; when both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit)

[…]

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or other ERA, or medical practice at the study site at any time.

[…]

17.3.2.17 6.1.2.2 Maintenance phase (Visit 5 - Visit 9)

Old text:

[…]

- Collect NT-proBNP (Visit 9 only)

[…]

- Child Health Questionnaire (SF-10) (Visit 9 only)

[…]

- Obtain laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) at Visits 5 and 9 as well as record the same parameters when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time

[…]

New text:

[…]

- Collect NT-proBNP or BNP (Visit 9 only; when both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit)

[…]

- Child Health Questionnaire (SF-10 and PedsQL Generic Core Scales self-report) (Visit 9 only)

[…]

- Obtain laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) at Visits 5 and 9 as well as record the same parameters when obtained as medically required according to a local package insert of bosentan or other ERA, or medical practice at the study site at any time

[…]

17.3.2.18 6.1.4 Safety follow-up visit

Old text:

[…]

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time.

[…]

New text:

[…]

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or other ERA, or medical practice at the study site at any time.

[…]

17.3.2.19 6.1.5 Unscheduled visit

Old text:

[…]

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time.

[…]

New text:

[…]

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or other ERA, or medical practice at the study site at any time.

[…]

17.3.2.20 6.1.6 Optional long-term extension phase (until adulthood or approval in the indication and commercial availability)

Old text:

~~Subjects~~ who require treatment with riociguat for more than 24 weeks will be offered participation in an ~~optional~~ extension phase. Subjects will receive riociguat until they can be transitioned to approved Adempas.

The following procedures will be performed:

Every 3 (± 14 days) months

[…]

- Exploratory efficacy (6MWD test, WHO FC, NT-proBNP, QoL [SF-10], echocardiography, TTCW)

- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at the study site at any time

[…]

~~Bone-age x-ray of the left hand and~~ pubertal assessment using Tanner scale will be performed every 12 months ~~until growth velocity is plateauing and growth plates are closed and at the discretion of the investigator in case of clinical suspicion for bone and/or growth anomalies.~~

New text:

Children who require treatment with riociguat for more than 24 weeks will be offered participation in an extension study (optional extension phase). Subjects will receive riociguat until they can be transitioned to approved Adempas.

The following procedures will be performed:

Every 3 (± 14 days) months

[…]

- Exploratory efficacy (6MWD test, WHO FC, NT-proBNP or BNP [when both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit], QoL [SF-10 and PedsQL Generic Core Scales self-report], echocardiography, TTCW)
- Record laboratory parameters (AST, ALT, BUN, creatinine, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC) to eCRF when obtained as medically required according to a local package insert of bosentan or other ERA, or medical practice at the study site at any time

[…]

- X-ray of the left hand will be performed every 12 months until growth plates are closed
- Pubertal assessment using Tanner scale will be performed every 12 months

[…]

17.3.2.21 6.2 Safety outcomes

Old text:

[…]

Bone age and also bone morphology will be determined centrally by a specialist. Every 12 months until growth velocity is plateauing and growth plates are closed, the subject's overall development will also be assessed by physical examination, growth chart evaluation and pubertal development using Tanner scale.

[…]

Afterwards; any additional collection of laboratory parameters will be obtained in case medically required according to a local package insert of bosentan or medical practice at the site at any time point and will be captured in the eCRFs.

New text:

[…]

Bone age and also bone morphology will be determined centrally by a specialist. Every 12 months until growth velocity is plateauing and growth plates are closed, the subject's overall development will also be assessed by physical examination, growth chart evaluation and pubertal development using Tanner scale, and at the discretion of the investigator in case of clinical suspicion for bone and/or growth anomalies.

[…]

Afterwards; any additional collection of laboratory parameters will be obtained in case medically required according to a local package insert of bosentan, or other ERA, or medical practice at the site at any time point and will be captured in the eCRFs.

[…]

17.3.2.22 6.3 Efficacy/Pharmacodynamic/Other outcomes

Old text:

~~Secondary efficacy, pharmacodynamic, and other outcomes (descriptive analysis) are the~~ change from baseline to end of treatment (week 24) of:

- ~~Functional capacity measured by a 6MWD test~~
- ~~Functional status measured by WHO FC assessment~~
- ~~Laboratory biomarker: NT-proBNP~~
- Quality of life: Child Health-related Questionnaire (SF-10)

[…]

- Taste and texture of the pediatric formulation(s) by use of a questionnaire at the beginning and at the end of the study.

[…]

New text:

Main secondary endpoints will be assessed as: Change from baseline to end of treatment (week 24) of:

- 6-Minute Walking Distance (6MWD)
- WHO functional class
- Lab N-terminal prohormone brain-type natriuretic peptide or brain-type natriuretic peptide (when both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit)
- Quality of Life scores (parent questionnaire and in children able to understand questions): Child Health-related Questionnaire (SF-10) and PedsQL Generic Core scales self-report

[…]

- Taste and texture of the pediatric formulation(s) must be assessed by use of a questionnaire at the beginning and at the end of the study.

[…]

17.3.2.23 6.4 Pharmacokinetics/Pharmacodynamics analyses

Old text:

6.4 Pharmacokinetics - amended

Primary PK outcome measure:

[…]

New text:

6.4 Pharmacokinetics/Pharmacodynamics analyses

Blood samples will be taken for pharmacokinetic and pharmacodynamic measurements from all participants treated with riociguat. The number of blood samples to be taken has been optimized using physiologically based pharmacokinetic (PBPK) modelling predictions in conjunction with clinical trials simulations (CTS) in order to only collect the minimum amount of blood needed for adequate analysis (sparse sampling).

Based on these evaluations the following measures to minimize pain and distress have been included: the number of blood samples in children from 6 to less than 18 years of age for PK analysis must not exceed four, and the minimum amount of blood needed for adequate analysis of each sample is 1.0mL of blood.

Primary PK outcome measure:

[…]

17.3.2.24 7.4 Analyses

Old text:

Not applicable.

New text:

A descriptive analysis of the safety and efficacy parameters will be performed.

17.3.2.25 7.4.1 Safety analysis

Old text:

The primary objective is to evaluate the safety and tolerability of riociguat in children with PAH. ~~Safety and tolerability will be assessed by adverse event recording, vital signs, left hand x-ray~~ and laboratory panel.

[…]

New text:

The primary objective is to evaluate the safety and tolerability of riociguat in children with PAH. Primary endpoint of the study is: Change from baseline to end of treatment (week 24) of safety and tolerability assessed by incidence of adverse events and serious adverse events, recording of vital signs and left-hand X-ray and laboratory panel.

[…]

17.3.2.26 7.4.2 Efficacy analysis

Old text:

Other objectives are to characterize the pharmacodynamic profile of riociguat using the following parameters: time to clinical worsening (TTCW), exercise capacity (6MWD test), functional capacity (measured by WHO FC), laboratory biomarkers (NT-proBNP), echocardiographic parameters and QoL measurements (SF-10).

Continuous efficacy parameters~~, and their corresponding changes from baseline to the end of treatment (week 24),~~ will be analyzed descriptively by sample summary statistics.

[…]

New text:

Other objectives are to characterize the pharmacodynamic profile of riociguat using the following parameters: time to clinical worsening (TTCW), exercise capacity (6MWD test), functional capacity (measured by WHO FC), laboratory biomarkers (NT-proBNP or BNP [when both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit]), echocardiographic parameters and QoL measurements (SF-10 and PedsQL Generic Core Scales self-report).

Continuous efficacy parameters will be analyzed descriptively by sample summary statistics. Time points of efficacy assessment: Exploratory efficacy at baseline and week 24 and every 3 to 4 months in the extension phase.

[…]

17.3.2.27 7.5 Determination of sample size

Old text:

At least 20 subjects ~~will~~ be enrolled in the study.

[…]

New text:

Children on treatment with ERAs and/or PCAs can be enrolled. At least 20 subjects on treatment with bosentan or other Endothelin Receptor Antagonists (ERA) must be enrolled in the study.

[…]

17.3.2.28 8.9 Premature discontinuation of study medication

Old text:

[…]

- Subject does not tolerate the lowest possible riociguat dose (0.5 mg TID)

Discontinuation of bosentan treatment (i.e. due to elevated liver enzymes) during the course of the study does not mandate withdrawal of the subject from the study. The final decision of withdrawal will be the responsibility of the investigator.

[…]

New text:

[…]

- Subject does not tolerate the lowest possible riociguat dose (0.5 mg TID)
- Patient with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP)

Discontinuation of bosentan or other ERA treatment (i.e. due to elevated liver enzymes) during the course of the study does not mandate withdrawal of the subject from the study. Also, discontinuation PCA treatment, during the course of the study, does not mandate withdrawal of the subject from the study. The final decision of withdrawal will be the responsibility of the investigator.

[…]

17.3.2.29 16. Reference list

Old text:

Not applicable

New text:

Weber M, Hamm C. Role of B-Type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart 2006; 92 (6):843-849

17.3.2.30 18.4 Appendix 4: Taste assessment

Old text:

Taste and Texture Questionnaire
Riociguat liquid formulation

Bayer HealthCare

Study Title:	**Open label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 years to less than 18 years of age with pulmonary arterial hypertension (PAH)**
Study No.:	Study number 15681 EudraCT no.: 2014-003952-29
Date	|__|__| |__|__|__| |__|__|__|__|
Subject number	|__|__|__|__|__|__|__|__|__|__|
Trial unit number	|__|__|__|__|__|__|

The questionnaire will be completed at visit 1, visit 9 and at the end of treatment visit

Instruction for the interviewer prior to the interview:

- ➔ **This questionnaire will be used to determine the preference for oral suspension in the pediatric subjects aged from 6 to 18 years if they have been allocated to riociguat.**
- ➔ **If possible, please give the child a glass of water prior to starting the questionnaire (i.e. before study drug administration) to neutralize taste**
- ➔ **Please give the "3-point-explanation scale" with the smiles to the child and explain the meaning of the faces:**

  - ☺ **The happy face means you like it**
  - 😐 **The neutral face means you don't know if you like or don't like it**
  - ☹ **The sad face means you don't like this**

Please make sure that the child understands the meaning of the smiley faces with an example:
Do you like your dress/ toys, or: Do you like pancakes, lemonade, apple juice?
Have the child point out to you the smiley face on the "3-point explanation scale".

[…]

New text:

Taste and Texture Questionnaire
Riociguat liquid formulation

Study Title:	**Open label, multicenter, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 years to less than 18 years of age with pulmonary arterial hypertension (PAH)**
Study No.:	Study number 15681 EudraCT no.: 2014-003952-29
Date	_____
Subject number	_____
Trial unit number	_____

The questionnaire will be completed at visit 1, visit 9 and at the end of treatment visit

Instruction for the interviewer prior to the interview:

- **This questionnaire will be used to determine the preference for oral suspension in the pediatric subjects aged from 6 to 18 years if they have been allocated to riociguat.**
- **If possible, please give the child a glass of water prior to starting the questionnaire (i.e. before study drug administration) to neutralize taste**
- **Please give the "3-point-explanation scale" with the smiles to the child and explain the meaning of the faces:**
  - **The happy face means you like it**
  - **The neutral face means you don't know if you like or don't like it**
  - **The sad face means you don't like this**

Please make sure that the child understands the meaning of the smiley faces with an example:
Do you like your dress/ toys, or: Do you like pancakes, lemonade, apple juice?
Have the child point out to you the smiley face on the "3-point explanation scale".

[…]

17.3.2.31 18.7 Appendix 7: PedsQL Generic Core Scales

Old text:

Not applicable.

New text:

New Pediatric Quality of Life questionnaire: PedsQL Generic Core Scales self-report was added as Appendix 7

17.4 Amendment 9

Amendment 9 is the fourth global amendment dated 13 MAR 2018.

17.4.1 Overview of changes

17.4.1.1 Modification 1: Change to allow the inclusion of patients with ostium secundum atrial septal defect ≤ 1 cm without hemodynamic alterations

In the current protocol, inclusion criterion 2 states that children from 6 to < 18 years with PAH associated with congenital heart disease (CHD) should only be enrolled if the CHD is associated with shunt closure more than 6 months ago. Taking into account: (i) the high prevalence of atrial septal defects (ASD), which account for approximately 6%–10% of all congenital heart diseases; (ii) the fact that ostium secundum ASD (OS-ASD) is the most common form of ASD (75% of cases); (iii) that OS-ASD generally presents as an isolated defect; and (iv) that OS-ASD ≤ 1 cm of effective diameter assessed by echocardiogram usually remains asymptomatic and itself does not account for the development of PAH; the inclusion of such patients into the study was discussed with the Steering Committee and was allowed.

The protocol sections affected by this modification are:

4.2 Inclusion criteria

17.4.1.2 Modification 2: Change to allow the inclusion of patients with patent foramen ovale ≤ 1 cm

In the current protocol, inclusion criterion 2 states that children from 6 to < 18 years with PAH associated with CHD should only be enrolled if the CHD is associated with shunt closure more than 6 months ago. Taking into account: (i) the fact that PFO is considered a physiological connection rather than a congenital heart disease; (ii) the high prevalence (25 to 30% of the general population) of PFO; (iii) that PFO ≤ 1 cm is not associated with significant shunt through the defect and itself does not account for the development of PAH, the inclusion of such patients into the study was discussed with the Steering Committee and was allowed.

The protocol sections affected by this modification are:

4.2 Inclusion criteria

17.4.1.3 Modification 3: Change of text in the inclusion criterion of pediatric female patients of child bearing potential not agreeing to use effective contraception

The inclusion criterion 7 was adjusted according to applicable guidelines on contraception during clinical trials to clarify that all adolescent females of childbearing potential must agree to use an "effective" contraception method to be allowed to be enrolled in the study. The inclusion criterion text was adjusted to include the definition of "effective" methods, covering combination of methods, some of which to be applied when sexually active, and to receive sexual counseling as applicable.

The protocol sections affected by this modification are:

4.2 Inclusion criteria

17.4.1.4 Modification 4: Change of the washout period for Sildenafil (24h instead of 3 days), to align with current label and ongoing studies

As the concomitant use of PDE5i and riociguat is contraindicated, a washout period needs to be considered when switching between these classes.

The Adempas label has been updated to provide guidance on the required time before stopping sildenafil and starting riociguat therapy. Patients switching to riociguat from sildenafil should discontinue sildenafil treatment at least 24 hours prior to riociguat administration.

Since the elimination half-life of sildenafil is short, about 4 hours, sildenafil concentration in the bloodstream after 24 hours is negligible. Differing from nitrates, riociguat has not been found to act synergistically with PDE5i, although similarities in the mode of action suggest this as a possibility. Considering the lack of synergistic hypotension, and a 24-hour washout period that is effective in reducing the interaction with nitrates, initiating riociguat 24 hours after discontinuation of sildenafil is recommended.

The washout time of 24 hours is consistent with ongoing randomized riociguat study REPLACE (*A prospective, randomized, international, multicenter, double-arm, controlled, open-label study of Riociguat in patients with pulmonary arterial hypertension (PAH) who are on a stable dose of phosphodiesterase-5 inhibitors (PDE-5i) with or without endothelin receptor antagonist (ERA), but not at treatment goal*).

The protocol sections affected by this modification are:

4.3 Exclusion criteria

17.4.1.5 Modification 5: Change to allow dose to be taken at midday during the visits without PK sampling

Since, as per in the protocol, PK samples are not required to be taken at Visit 2 and 4, subjects were allowed to take the morning dose of the study drug until midday.

After Visit 1, PK blood sampling occurs at Visits 3 and 5, for which patients are required to come to the hospital without having taken the riociguat morning dose.

It has been noticed that the same requirement is kept in the study protocol at Visits 2 and 4 although no PK sampling takes place. In the amendment this requirement only applies to Visits 3 and 5, where in the visits without PK sampling it is allowed to take the morning dose until midday.

The protocol sections affected by this modification are:

6.1.2.1 Individual titration phase (Visit 1 – Visit 4)

17.4.1.6 Modification 6: Change to allow up-titration during the LTE phase at the discretion of the investigator

According to the protocol: "At the end of the individual titration period, the subjects should have reached their individually adjusted dose. The established individual equivalent dose will then be taken as optimal dose to be administered during the 16 week maintenance period… and a subsequent re-increase is not possible…".

Taking into consideration the feedback received so far from some investigators requesting up-

titration of the dose of riociguat during LTE phase and preliminary PK data available to the DMC, the study protocol is amended to allow up-titration in the LTE phase at the discretion of the investigator.

The protocol sections affected by this modification are:

5.1.1 Body-weight adjusted individual dose titration regimen

17.4.1.7 Modification 7: Addition of computing cardiac output to the echocardiographic assessment

There is a direct relationship between riociguat plasma concentration and hemodynamic parameters such as systemic vascular resistance, systolic blood pressure, pulmonary vascular resistance (PVR), and cardiac output (IB BAY 63-2521).

The current study protocol includes exploratory echocardiographic assessments; and by means of the amendment it will be included the computing of cardiac output as part of the exploratory efficacy measurements.

The protocol sections affected by this modification are:

Synopsis

6.3 Efficacy/Pharmacodynamic/Other outcomes

17.4.1.8 Modification 8: Change to specify that collection of AEs starts after informed consent is signed

To clarify the procedure during the pre-treatment phase, it is specified that the collection period for AEs will begin after informed consent is obtained consistent with safety reporting rules in clinical trials.

The protocol sections affected by this modification are:

Study Flow chart

6.1.1 Pre-treatment phase (Visit 0, Day -14 to -1)

17.4.1.9 Modification 9: Clarification of the planned number of patients

For clarity and compliance with the PIP, this statement regarding the number of patients, which does not fall under the PIP commitment, was removed: "At least 20 subjects are planned to be enrolled into this study. Every effort is made to enroll equal numbers (i.e. approximately 10 subjects each) in both age cohorts."

"…In case of inadequate availability of patients in the age group ≥6 to <12 years total enrolment will be stopped only if at least 5 patients of this younger age group have completed their 24-week initial treatment period.", was modified to "if at least 5 patients of this younger age group have been enrolled".

Sections affected by this change are:

4.1 Planned number of subjects

5.1.1 Body-weight adjusted individual dose titration regimen

17.4.1.10 Modification 10: Clarification of the study algorithm for dose titration, for completeness

The symbol equal was missing. Therefore, the ≥ symbol was added as applicable in the following bullet points:

- If SBP is ≥ 5 mmHg but less than 10 mmHg lower than the age-, sex- and height-adapted level of the 50th blood pressure (BP) percentile, maintain dose of riociguat.
- If SBP is ≥10 mmHg lower than the age-, sex- and height-adapted level of the 50th BP percentile, reduce riociguat dose (- 0.5 mg dose-equivalent TID)
- If any SBP is ≥ 5 mmHg lower than the age-, sex- and height-adapted level of the 50th BP percentile, with clinical symptoms of hypotension such as dizziness or presyncope, stop study treatment; restart after 24 hours with reduced dose - 0.5 mg dose-equivalent TID).

The protocol sections affected by this modification are:

5.1.1 Body-weight adjusted individual dose titration regimen

17.4.1.11 Modification 11: Change to exclusion criteria to cover any condition that is not recommended with riociguat

Rewording of exclusion criteria 18 was updated to cover any conditions that are not recommended with riociguat according to the reference safety information

The protocol sections affected by this modification are:

4.3 Exclusion criteria

17.4.1.12 Modification 12: Adjustments to the Flow chart and visit detail table

For clarification, the collection of AEs was added at screening. The term study booklet was replaced with study guidelines. Medical history at Visit 1 was removed. The footnote "i" was removed from the position after 'Obtain lab test'. Under instruct how to take study drug, brackets were added at the unscheduled visit. Footnote "d" positioned directly after Vital signs and in ECG was shifted to Visit 1.

In the visit detail table (Table 0-2), "At pre-dose, blood sample safety laboratory" was shaded out. In the order of procedures, the administration study drug was placed at the end.

The protocol sections affected by this modification are:

Study Flow chart

17.4.1.13 Modification 13: Minor editing corrections

Minor, consistency and logical clarifications were made throughout the document. The changes were made to ensure clear wording and consistency throughout the document. These changes do not affect the overall study concept.

Sections affected by the changes are:

- **Title page:** The Study medical expert was changed.
- **Signature of the sponsor's medically responsible person:** The Global Clinical Lead was changed.
- **List of Abbreviations:** New abbreviations were added due to the Amendment 9, Modifications 1 and 2. The spelling of calcium was corrected. Additional abbreviations were added.
- **Synopsis:** Under primary variables, the paragraph describing pharmacokinetics/pharmacodynamics analyses was split into two separate lines, and PK was specified to the number of blood samples. Under main secondary variables: inferior vena cava pressure was replaced with right atrial pressure, the word *both* was removed from the definition of worsening of PAH symptoms, and the spelling of *tricuspide* to *tricuspid was corrected*.
- **Section 6.1.2.2 Maintenance phase (Visit 5 - Visit 9):** For clarification Visit 5 was added to the sentence. The bullet points were reordered according to the procedures to be performed starting at Visit 5 to 9.
- **Section 6.1.3 End-of-treatment visit:** For completeness the word Visit was added.
- **Section 6.1.1 Optional long-term extension phase (until adulthood or approval in the indication and commercial availability):** In the LTE phase the physical examination includes monitoring of growth velocity was included for consistency with the flow chart.
- **Section 6.3 Efficacy/Pharmacodynamic/Other outcomes:** Inferior vena cava pressure was replaced with right atrial pressure. Under the bullet point "Worsening of PAH symptoms, the word both was removed from the definition of worsening of PAH

symptoms and the bullet point at the position of "need for additional PAH therapy" was removed.

- **Section 6.4 Pharmacokinetics/Pharmacodynamics analyses:** For correctness, the word PK was added. Section 7.4.3 paragraph describing blood sampling at each visit was moved to Section 6.4. For clarity, "For all visits in the main study phase, the exact time of three riociguat dosing (current and the previous two doses) and time of PK/PD blood sampling will be documented in the eCRF", was added.
- **6.5 Study guidelines for parents and children:** For correctness the term *study guidelines* was added to replace study booklet.
- **Section 7.4.3 Pharmacokinetic analysis:** For completeness the sentence *For investigation of exposure behavior, plasma concentrations of BAY63-2521 and its metabolite (M1) will be analyzed descriptively*, the cross-reference to Section 6.4, and term PK/PD evaluations were added.
- **Section 7.5 Determination of sample size:** For clarity and compliance with the PIP, *(i.e. 10 subjects each)* was removed, and the word *patient* was added.

17.4.2 Changes to the protocol text

All affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the original protocol. Deletions are ~~crossed out~~ in the "old text". Additions are <u>underlined</u> in the "new text". Minor editorial changes or corrections are not listed.

17.4.2.1 Title page

Old text:

[…]

Sponsor's medical expert:

(*Note: Study medical expert was changed according to Amendment 3, see section 17.1.1.16. The contact details were updated according to Amendment 5, see Section 17.2.1.8.)*

PPD

~~Bayer Pharma AG~~

~~BPH GD P&O~~

~~Aprather Weg, Bd 402~~

~~42113, Wuppertal, Germany~~

~~Phone:~~ PPD

[…]

New text:

[…]

Sponsor's medical expert:

(*Note: Study medical expert was changed according to Amendment 3, see section 17.1.1.16. The contact details were updated according to Amendment 5, see Section 17.2.1.8.)*

PPD

Study Medical Expert - TA Cardiology & Coagulation
Global Development-Portfolio & Operations
Bayer SA
Rua Cancioneiro de Évora 255 - Prédio E1 - 1º andar
04708-010 São Paulo - SP Brasil
Tel: PPD

17.4.2.2 Signature of the sponsor's medically responsible person

Old text:

[…]

Name: PPD Role: GCL (Global Clinical Lead)

Date: Signature:

[…]

New text:

[…]

Name: PPD Role: GCL (Global Clinical Lead)

Date: Signature:

17.4.2.3 Synopsis

Old text:

[…]

Primary variable(s)	• Change from baseline to end of treatment (week 24) of safety and tolerability assessed by incidence of adverse events and serious adverse events, recording of vital signs and left-hand x-ray. • Pharmacokinetics/Pharmacodynamics analyses. Blood samples will be taken for pharmacokinetic and pharmacodynamic measurements from all participants treated with riociguat. The number of blood samples to be taken will be determined using physiologically based pharmacokinetic (PBPK) modelling predictions. It is intended to collect the minimum amount of blood needed for adequate analysis (sparse sampling).

New text:

[…]

Primary variable(s)	• Change from baseline to end of treatment (week 24) of safety and tolerability assessed by incidence of adverse events and serious adverse events, recording of vital signs and left-hand x-ray. • Pharmacokinetics/Pharmacodynamics analyses. Blood samples will be taken for pharmacokinetic and pharmacodynamic measurements from all participants treated with riociguat. The number of pharmacokinetic (PK) blood samples to be taken will be determined using physiologically based pharmacokinetic (PBPK) modelling predictions. It is intended to collect the minimum amount of blood needed for adequate analysis (sparse sampling).

Old text:

Main secondary variable(s) *(Note: this part was modified according to Amendment 5, see Sections 17.2.1.3 and 17.2.1.7. This part was modified according to Amendment 6, see Section 17.3.1.6.)*	Change from baseline to end of treatment (week 24) of: • 6-Minute Walking Distance (6MWD). • WHO functional class. • N-terminal prohormone brain-type natriuretic peptide or brain-type natriuretic peptide. When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit. • Quality of Life scores (parent questionnaire and in children able to understand questions). • Echocardiographic parameters including o pulmonary arterial systolic pressure (PASP), o tricuspid annular plane systolic excursion (TAPSE), o pericardial effusion, o left ventricular eccentricity index, o estimated ~~inferior vena cava~~ pressure, o right ventricular pressure by tricuspid~~e~~ regurgitant jet velocity, o acceleration time of pulmonary flow, and o right heart dimensions. • Time to clinical worsening defined as o hospitalization for right heart failure, o death, o lung transplantation, o Pott's anastomosis and atrioseptostomy, o worsening of PAH symptoms, which must include either ▪ an increase in WHO functional class, OR ▪ ~~both~~ appearance/worsening symptoms of right heart failure AND ▪ need for additional PAH therapy.

New text:

Main secondary variable(s) *(Note: this part was modified according to Amendment 5, see Sections 17.2.1.3 and 17.2.1.7. This part was modified according to Amendment 6, see Section 17.3.1.6 This part was modified according to Amendment 9, see Section 17.4.1.7 and 17.4.1.13.)*	Change from baseline to end of treatment (week 24) of: • 6-Minute Walking Distance (6MWD). • WHO functional class. • N-terminal prohormone brain-type natriuretic peptide or brain-type natriuretic peptide. When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit. • Quality of Life scores (parent questionnaire and in children able to understand questions). • Echocardiographic assessment of the following: o pulmonary arterial systolic pressure (PASP), o tricuspid annular plane systolic excursion (TAPSE), o pericardial effusion, o left ventricular eccentricity index, o estimated right atrial pressure, o right ventricular pressure by tricuspid regurgitant jet velocity, o acceleration time of pulmonary flow o right heart dimensions, and o cardiac output Time to clinical worsening defined as: o hospitalization for right heart failure, o death, o lung transplantation, o Pott's anastomosis and atrioseptostomy, o worsening of PAH symptoms, which must include either ▪ an increase in WHO functional class, OR ▪ appearance/worsening symptoms of right heart failure AND need for additional PAH therapy.

17.4.2.4 Study Flow chart

Old text:

[…]

Table 17–1: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
Informed consent/assent	•														
In-/exclusion criteria	•	•													
Demographics	•														
Medical history	•	•													
Concomitant medication		•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant PAH specific medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Physical examination [m]	•	• [d]	•	•	•	•	•	•	•	•	•	•	•	• [h]	•
Obtain lab test [i]	•[i]					•				•		•			
Pregnancy test [a]	•	•		•		•	•	•	•	•		•	•	•	•

Table 17–1: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
Dispense study medication		•	•	•	•	•	•	•	•	•	(•)			•	
Instruct how to take study drug		•	•	•	•	•	•	•	•	•	•			•	
Provide ~~booklet~~		•													
Vital signs [d]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
ECG [d]	•	•								•		•			
Echocardiogram		•								•		•		•	
RHC data [o]	•[o]														
WHO functional class		•								•		•		•	
6MWD		•								•		•		•	
NT-proBNP or BNP[p]		•								•		•		•	
Left hand x-ray		•[j]								•				•[e]	
Adverse events [n]		•	•	•	•	•	•	•	•	•	•	•	•	•	•
Drug accountability			•	•	•	•	•	•	•	•		•		•	
PK blood sample[b]		•		•		•									

Table 17–1: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
Child Health Questionnaire (SF-10 and PedsQL)	•									•		•		•	
Tanner scale [c]	•									•		•		• [e]	
Taste assessment questionnaire		•								•		•			

Table 17-1: Flow chart - amended

a Urine or serum pregnancy test for women of childbearing potential
b A minimum volume of 1.0 mL per sample is needed. Accurate adherence to time points is essential and has to be documented, see Table 0–2
c Scale of physical development in children and adolescents
d Blood pressure, heart rate and ECG pre-dose, 2 and 4 hours after first dose (see Table 0–2)
e Every 12 months until growth velocity is plateauing and growth plates are closed (see section 6.1.6)
f ±2 days for Visits 1 to 4, ±4 days for Visit 5, ±5 days for Visits 6 to 9
g Visit 1 is considered the baseline visit
h Incl. height, growth velocity and weight
i Obtain blood samples if AST and ALT, creatinine, BUN, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC are not available within 30 days prior to Visit 0. Record the same laboratory parameters to eCRF when obtained as medically required according to a local package insert of bosentan or other ERAs, or medical practice at the study site at any time.

j If no historical data (~~≤30 days~~) of x-ray is available
k Home visits (only at week 12 and/or 20 of maintenance phase) at the discretion and responsibility of the investigator
l For subjects dropping off the protocol at any time after V1 and before V9
m Including height and weight
n Including AEs of special interest
o In case RHC has been performed for a study subject before enrollment, record most recent RHC parameters to the eCRF on V0 (timing of RHC not limited to the period of Day -14 to -1). Additionally, if RHC is conducted on medical reasons during the study, the RHC data should be recorded to the eCRF.
p When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit

New text:

[…]

Table 17–2: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
Informed consent/assent	•														
In-/exclusion criteria	•	•													
Demographics	•														
Medical history	•														

Table 17–2: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
Concomitant medication		•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant PAH specific medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Physical examination [m]	•	• [d]	•	•	•	•	•	•	•	•	•	•	•	•[h]	•
Obtain lab test	•[i]					•				•		•			
Pregnancy test [a]	•	•		•		•	•	•	•	•		•	•	•	•
Dispense study medication		•	•	•	•	•	•	•	•	•	(•)			•	
Instruct how to take study drug		•	•	•	•	•	•	•	•	•	(•)			•	
Provide study guidelines		•													
Vital signs	•	•[d]	•	•	•	•	•	•	•	•	•	•	•	•	•
ECG	•	•[d]								•		•			
Echocardiogram		•								•		•		•	
RHC data [o]	•[o]														
WHO functional class		•								•		•		•	

Table 17–2: Flow chart - amended

		Main study treatment period - 24 weeks													
	Screening	**Individual titration phase (8 weeks)**				**Maintenance phase (16 weeks)**					**Unscheduled visit**	**End of treatment visit [l]**	**Safety follow-up 60 ± 8 days**	**Optional Long-term extension phase**	**Safety follow up visit 60 +8 days after optional LTE**
Visit	***V0***	***V1 [g]***	***V2***	***V3***	***V4***	***V5***	***V6[k]***	***V7***	***V8[k]***	***V9***				***Every 3 months (± 14 days)***	
Week [f]	***Day -14 to -1***	***0***	***2***	***4***	***6***	***8***	***12***	***16***	***20***	***24***					
6MWD		•								•		•		•	
NT-proBNP or BNP[p]		•								•		•		•	
Left hand x-ray		• [j]								•				• [e]	
Adverse events [n]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Drug accountability			•	•	•	•	•	•	•	•		•		•	
PK blood sample[b]		•		•		•									
Child Health Questionnaire (SF-10 and PedsQL)	•									•		•		•	
Tanner scale [c]	•									•		•		• [e]	
Taste assessment questionnaire		•								•		•			

Table 0-1: Flow chart - amended

a Urine or serum pregnancy test for women of childbearing potential

b A minimum volume of 1.0 mL per sample is needed. Accurate adherence to time points is essential and has to be documented, see Table 0–2

c Scale of physical development in children and adolescents

d At Visit 1 blood pressure, heart rate and ECG pre-dose, 2 and 4 hours after first dose (see Table 0–2)
e Every 12 months until growth velocity is plateauing and growth plates are closed (see section 6.1.6)
f ±2 days for Visits 1 to 4, ±4 days for Visit 5, ±5 days for Visits 6 to 9
g Visit 1 is considered the baseline visit
h Including monitoring of growth velocity.
i Obtain blood samples if AST and ALT, creatinine, BUN, GGT, UA, T-Bil, Alb, Na, K, Ca, P, and CBC are not available within 30 days prior to Visit 0. Record the same laboratory parameters to eCRF when obtained as medically required according to a local package insert of bosentan or other ERAs, or medical practice at the study site at any time.
j If no historical data (not older than 30 days) of x-ray is available
k Home visits (only at week 12 and/or 20 of maintenance phase) at the discretion and responsibility of the investigator
l For subjects dropping off the protocol at any time after V1 and before V9
m Including height and weight
n Including AEs of special interest
o In case RHC has been performed for a study subject before enrollment, record most recent RHC parameters to the eCRF on V0 (timing of RHC not limited to the period of Day -14 to -1). Additionally, if RHC is conducted on medical reasons during the study, the RHC data should be recorded to the eCRF.
p When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit

Old text:

Table 17–3: Visit details - amended

		Visit 1 (Baseline visit)						**Visit 3 and 5**	
		Detailed study activities at pre-dose and after the first study medication dose intake						**Study activities before first study medication dose intake**	
Order of procedures	Time interval (h)	pre-dose	0:00	0:30 to 1:30	2:00	2:30 to 4:00	4:00	-1:00 to 0:00	0:00
↓	Pharmacokinetic blood sample			•		•		•	
	Blood sample for NT-proBNP or BNP[b]	•							
	Blood sample for safety laboratory							• [a]	
	Blood pressure, heart rate	•			•		•		
	ECG	•			•		•		
	WHO functional class	•							
	Left hand x-ray	•							
	Administration study drug		•						•
	Echocardiogram	•							

1. Obtain blood sample for safety parameters on Visit 5 only.
2. When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit

Abbreviations: ECG = electrocardiogram

(Note: Visit details were modified according to Amendment 3, see Section 17.1.1.16.The table for visit details was modified according to Amendment 5, see Section 17.2.1.8. The table for details was modified according to Amendment 6, see Section 17.3.1.6.)

New text:

Table 17–4: Visit details - amended

		Visit 1 (Baseline visit)						Visit 3 and 5	
		Detailed study activities at pre-dose and after the first study medication dose intake						Study activities before first study medication dose intake	
Order of procedures	Time interval (h)	pre-dose	0:00	0:30 to 1:30	2:00	2:30 to 4:00	4:00	-1:00 to 0:00	0:00
↓	Pharmacokinetic blood sample			•		•		•	
	Blood sample for NT-proBNP or BNP[b]	•							
	Blood sample for safety laboratory							• [a]	
	Blood pressure, heart rate	•			•		•		
	ECG	•			•		•		
	WHO functional class	•							
	Left hand x-ray	•							
	Echocardiogram	•							
	Administration study drug		•						•

a. Obtain blood sample for safety parameters on Visit 5 only.
b. When both tests are available, NT-proBNP should be chosen over BNP and the same test should be performed at every required visit

Abbreviations: ECG = electrocardiogram

(Note: Visit details were modified according to Amendment 3, see Section 17.1.1.16.The table for visit details was modified according to Amendment 5, see Section 17.2.1.8. The table for details was modified according to Amendment 6, see Section 17.3.1.6.)

17.4.2.5 4.1 Planned number of subjects

[…]

Old text:

[…]

The sponsor will make every effort to facilitate an equal distribution between the two age cohorts with a minimum of 5 patients in each age cohort. In case of inadequate availability of patients in the age group ≥6 to <12 years total enrolment will be stopped only if at least 5 patients of this younger age group have been enrolled ~~have completed their 24-week initial treatment period~~.

[…]

New text:

[…]

The sponsor will make every effort to facilitate an equal distribution between the two age cohorts with a minimum of 5 patients in each age cohort. In case of inadequate availability of patients in the age group ≥6 to <12 years total enrolment will be stopped only if at least 5 patients of this younger age group have been enrolled.

17.4.2.6 4.2 Inclusion criteria

Old text:

[…]

2. Diagnosed with PAH :

- Idiopathic (IPAH)
- Hereditable (HPAH)
- PAH associated with (APAH)
    - Connective tissue disease
    - Congenital heart disease with shunt closure more than 6 months ago (no open shunts, confirmed by RHC no less than 4 months after surgery)

[…]

New text:

[…]

- PAH associated with (APAH)
    - Connective tissue disease
    - Congenital heart disease with shunt closure more than 6 months ago (no open shunts, confirmed by RHC no less than 4 months after surgery)

Regardless of the type of PAH, the following findings are not exclusionary:

- Patent foramen ovale (PFO) ≤ 1 cm (confirmed by echocardiogram) is not exclusionary
- Asymptomatic, isolated, ostium secundum atrial septal defect (OS-ASD) ≤ 1 cm (confirmed by echocardiogram) and not associated with hemodynamic alterations indicative of significant shunt, e.g. Qp/Qs ratio less <1.5:1 is not exclusionary

[…]

Old text:

[…]

10. Adolescent females of childbearing potential can only be included in the study if a pregnancy test is negative. Adolescent females of childbearing potential must agree to use adequate contraception when sexually active. ~~'Adequate~~ contraception' is defined as any ~~combination of at least 2 effective methods of birth control, of which at least one is a physical barrier~~ (e.g. condoms with hormonal contraception ~~or implants or combined oral contraceptives, certain intrauterine devices). Adequate~~ contraception is required from the signing of the informed consent form up until ~~6~~ weeks after the last study drug administration.

New text:

[…]

10. Adolescent females of childbearing potential can only be included in the study if a pregnancy test is negative. Adolescent females of childbearing potential must agree to use adequate contraception when sexually active. 'Effective contraception' is defined as progestogen-only hormonal contraception associated with inhibition of ovulation (implant), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), or combination of adequate methods of birth control (e.g. condoms with hormonal contraception). Agreement to use effective contraception is required from the signing of the informed consent form up until 4 weeks after the last study drug administration.

17.4.2.7 4.3 Exclusion criteria

Old text:

[a] Pretreatment with phosphodiesterase (PDE) 5 inhibitor~~s~~ is allowed up to ~~3 three days prior to start of riociguat treatment (Visit 1)~~. Patients are not expected to be withdrawn from treatment with PDE5i for the purpose of entering into this trial. During the ~~3 days~~ period without PDE5i, patients who received treatment with PDE5i are expected to be on stable clinical condition and receiving standard of care treatment with ERA and/or PCAs.

New text:

[a] Pretreatment with the phosphodiesterase (PDE) 5 inhibitor Sildenafil is allowed up to 24 h prior to start of riociguat treatment (Visit 1). Pretreatment with the phosphodiesterase (PDE) 5 inhibitor tadalafil is allowed up to 3 days prior to start of riociguat treatment (Visit 1). Patients are not expected to be withdrawn from treatment with PDE5i for the purpose of entering into this trial. During the period without PDE5i, patients who received treatment with PDE5i are expected to be on stable clinical condition and receiving standard of care treatment with ERA and/or PCAs.

Old text:

[…]

18. Subjects ~~with known HIV infection (evaluated by medical history)~~

New text:

[…]

18. Subjects with <u>any other condition that is not recommended with riociguat</u>

17.4.2.8 5.1.1 Body-weight adjusted individual dose titration regimen

Old text:

[…]

At the end of the individual titration period (Visit 4), the subjects should have reached their individually adjusted dose (maximum equivalent dose of 2.5 mg riociguat TID). The established individual equivalent dose will then be taken as optimal dose to be administered during the 16-week maintenance period. Dose reductions for safety reasons are allowed in the maintenance phase, but a subsequent re-increase is not possible.

[…]

New text:

[…]

At the end of the individual titration period (Visit 4), the subjects should have reached their individually adjusted dose (maximum equivalent dose of 2.5 mg riociguat TID). The established individual equivalent dose will then be taken as optimal dose to be administered during the 16-week maintenance period. Dose reductions for safety reasons are allowed in the maintenance phase, but a subsequent re-increase is not possible. <u>During the LTE phase the dose may be up-titrated at the investigator's discretion.</u>

[…]

Old text:

[…]

In case an interruption takes place after completion of the titration period and lasts longer than 14 consecutive days, it is not allowed to restart the study medication again. In case of shorter interruptions, study medication can be restarted at the discretion of the investigator. Dose interruptions will be communicated to the DMC and/or SC.

~~At least 20 subjects are planned to be enrolled into this study. Every effort is made to enroll equal numbers (i.e. approximately 10 subjects each) in both age cohorts.~~

New text:

[…]

In case an interruption takes place after completion of the titration period and lasts longer than 14 consecutive days, it is not allowed to restart the study medication again. In case of shorter interruptions, study medication can be restarted at the discretion of the investigator. Dose interruptions will be communicated to the DMC and/or SC.

Old text:

[…]

Dose titration algorithm

- If systolic blood pressure (SBP) is less than 5 mmHg lower than the age-, sex- and height-adapted level of the 50th SBP percentile (NHBPEP, 2004) (see appendix 18.5), increase riociguat dose (+0.5 mg dose-equivalent TID)
- If SBP is ~~more than~~ 5 mmHg but less than 10 mmHg lower than the age-, sex- and height-adapted level of the 50th blood pressure (BP) percentile, maintain dose of riociguat.
- If SBP is ~~more than~~ 10 mmHg lower than the age-, sex- and height-adapted level of the 50th BP percentile, reduce riociguat dose (- 0.5 mg dose-equivalent TID)
- If any SBP is ~~more than~~ 5 mmHg lower than the age-, sex- and height-adapted level of the 50th BP percentile, with clinical symptoms of hypotension such as dizziness or presyncope, stop study treatment; restart after 24 hours with reduced dose - 0.5 mg dose-equivalent TID).

New text:

[…]

Dose titration algorithm

- If systolic blood pressure (SBP) is less than 5 mmHg lower than the age-, sex- and height-adapted level of the 50th SBP percentile (NHBPEP, 2004) (see appendix 18.5), increase riociguat dose (+0.5 mg dose-equivalent TID)
- If SBP is ≥ 5 mmHg but less than 10 mmHg lower than the age-, sex- and height-adapted level of the 50th blood pressure (BP) percentile, maintain dose of riociguat.
- If SBP is ≥ 10 mmHg lower than the age-, sex- and height-adapted level of the 50th BP percentile, reduce riociguat dose (- 0.5 mg dose-equivalent TID)
- If any SBP is ≥ 5 mmHg lower than the age-, sex- and height-adapted level of the 50th BP percentile, with clinical symptoms of hypotension such as dizziness or presyncope, stop study treatment; restart after 24 hours with reduced dose - 0.5 mg dose-equivalent TID).

17.4.2.9 6.1.1 Pre-treatment phase (Visit 0, Day -14 to -1)

Old text:

The parents/legal guardians and children will be given an explanation about the study and will be given sufficient time to consider their participation in the study and to ask any questions. Afterwards, informed consent and, if applicable, assent will be obtained (see section 11.2).
[…]

New text:

The parents/legal guardians and children will be given an explanation about the study and will be given sufficient time to consider their participation in the study and to ask any questions. Afterwards, informed consent and, if applicable, assent will be obtained (see section 11.2).
Collection of AEs starts after informed consent is signed.

[…]

17.4.2.10 6.1.2.1 Individual titration phase (Visit 1 – Visit 4)

Old text:

~~At Visit 2 - 4, subjects should come to the hospital without having taken the riociguat morning dose.~~ The following procedures will be performed during the titration period:

- Re-confirm in-/exclusion criteria (Visit 1 only, prior to study drug intake)
- ~~Obtain medical history (Visit 1 only)~~
- Record concomitant medication incl. concomitant PAH specific medication
- Perform physical examination (incl. height, weight and vital signs)
- Pregnancy test for females of childbearing potential (at Visit 1 and Visit 3)
- Decide on the next dose based on the titration algorithm and dispense study medication
    - Instruct how to take study drug
    - Provide ~~booklet/~~guidelines for dosing/suspension (Visit 1 only)
- Determine WHO functional class (Visit 1 only)
- Perform echocardiogram (Visit 1 only)
- Perform electrocardiogram (Visit 1 only)
- X-ray of left hand for determination of bone age (Visit 1 only ~~[~~if no historical data (≤30 days) are available])

[…]

New text:

<u>At Visit 1, subjects should come to the hospital for the riociguat morning dose. At Visits 2 and 4, subjects are allowed to take the riociguat morning dose up to midday. The following procedures will be performed during the titration period.</u> The following procedures will be performed during the titration period:

- Procedures and assessments for the baseline visit (Visit 1) should be completed within the span of one day
- Re-confirm in-/exclusion criteria (Visit 1 only, prior to study drug intake)
- Record concomitant medication incl. concomitant PAH specific medication
- Perform physical examination (incl. height, weight and vital signs)
- Pregnancy test for females of childbearing potential (at Visit 1 and Visit 3)
- Decide on the next dose based on the titration algorithm and dispense study medication
    - Instruct how to take study drug

- Provide study guidelines for dosing/suspension (Visit 1 only)

- Determine WHO functional class (Visit 1 only)
- Perform echocardiogram (Visit 1 only)
- Perform electrocardiogram (Visit 1 only)
- X-ray of left hand for determination of bone age (Visit 1 only: if no historical data [not older than 30 days] are available)

[…]

17.4.2.11 6.1.6 Optional long-term extension phase (until adulthood or approval in the indication and commercial availability)

Old text:

[…]

Every 3 (± 14 days) months

- Record concomitant medication incl. concomitant PAH specific medication
- Pregnancy test for females of childbearing potential
- Perform physical examination (~~incl. height, weight and vital signs~~)

New text:

Every 3 (± 14 days) months

- Record concomitant medication incl. concomitant PAH specific medication
- Pregnancy test for females of childbearing potential
- Perform physical examination (In the long term extension phase the physical examination includes monitoring of growth velocity in addition to the. height, weight and vital signs)

17.4.2.12 6.1.2.2 Maintenance phase (Visit 5 - Visit 9)

Old text:

Subjects should come to the hospital without having taken the riociguat morning dose. The following procedures will be performed during the maintenance period:

[…]

New text:

Subject should take the riociguat morning dose at home as usual, except of Visit 5, where the morning dose will be taken at the hospital. The following procedures will be performed during the maintenance period:

[…]

17.4.2.13 6.1.3 End-of-treatment visit

Old text:

For all subjects dropping-off the protocol at any time after V1 and before V9, an end-of-treatment has to be performed.

[…]

New text:

For all subjects dropping-off the protocol at any time after V1 and before V9, an end-of-treatment visit has to be performed.

[…]

17.4.2.14 6.3 Efficacy/Pharmacodynamic/Other outcomes

Old text:

[…]

- 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 inferior vena cava pressure, acceleration time of the pulmonary flow and right heart dimensions.
- Time to clinical worsening
  - 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

    - ~~both~~ appearance/worsening symptoms of right heart failure

    AND

    - need for additional PAH therapy

[…]

New text:

[…]

- 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 and right heart dimensions, and computing of cardiac output.

- Time to clinical worsening
  - 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

[…]

17.4.2.15 6.4 Pharmacokinetics/Pharmacodynamics analyses

Old text:

[…]

Blood samples will be taken for pharmacokinetic and pharmacodynamic measurements from all participants treated with riociguat. The number of blood samples to be taken has been optimized using physiologically based pharmacokinetic (PBPK) modelling predictions in conjunction with clinical trials simulations (CTS) in order to only collect the minimum amount of blood needed for adequate analysis (sparse sampling).

Based on these evaluations the following measures to minimize pain and distress have been included: the number of blood samples in children from 6 to less than 18 years of age for PK analysis must not exceed four, and the minimum amount of blood needed for adequate analysis of each sample is 1.0mL of blood.

Primary PK outcome measure:

Pre- and post-dose blood samples for PK characterization of riociguat and its active metabolite BAY 60-4552 will be collected during the titration and the maintenance phase of the study. For details, see section 7.4.3.

New text:

[…]

Blood samples will be taken for pharmacokinetic and pharmacodynamic measurements from all participants treated with riociguat.

The number of PK blood samples to be taken has been optimized using physiologically based pharmacokinetic (PBPK) modelling predictions in conjunction with clinical trials simulations

(CTS) in order to only collect the minimum amount of blood needed for adequate analysis (sparse sampling).

Based on these evaluations the following measures to minimize pain and distress have been included: the number of blood samples in children from 6 to less than 18 years of age for PK analysis must not exceed four, and the minimum amount of blood needed for adequate analysis of each sample is 1.0mL of blood.

The following blood samples will be taken:

Visit 1: 2 PK samples will be taken: the first at 0.5 to 1.5 h and the second at 2.5 to 4 h post-dose (Preferred proposal is to have both peak samples at the first visit. (To ensure having PK samples in case of drop-outs, both "peak" samples should be collected at the first visit. If this is not feasible, the second peak sample can be taken at any visit.)

Visit 3 and Visit 5: Trough samples should be collected -1 to 0 hours before the morning dose at both visit 3 and visit 5

For all visits in the main study phase, the exact time of three riociguat dosing (current and the previous two doses) and time of PK/PD blood sampling will be documented in the eCRF.

If, for any reason, PK samples are taken outside of the pre-specified time window, the exact time of the sample was taken should be recorded and not the pre-defined time window. If riociguat was temporarily stopped prior to a PK sample collection visit, sampling of blood for PK analysis according to this visit's schedule should be postponed until riociguat treatment has been restarted and sustained for 3 days.

Primary PK outcome measure:

Pre- and post-dose blood samples for PK characterization of riociguat and its active metabolite BAY 60-4552 will be collected during the titration and the maintenance phase of the study. For details, see section 7.4.3.

17.4.2.16 6.5 Study booklet (Study guidelines for parents and children)

Old text:

Study ~~booklet~~ (Study guidelines for parents and children~~)~~

Parents/children will receive ~~a booklet~~, specifying:

- The local medical contact person and local emergency telephone number
- The dates of hospital visits and telephone calls, if applicable
- Instructions to return empty medication packages and unused study medication
- Instructions on signs and symptoms of hypotension.
- How to take riociguat tablets or suspension
- Calendar to track the date, time of study drug intake

New text:

Study guidelines for parents and children

Parents/children will receive study guidelines, specifying:

- The local medical contact person and local emergency telephone number
- The dates of hospital visits and telephone calls, if applicable
- Instructions to return empty medication packages and unused study medication
- Instructions on signs and symptoms of hypotension.
- How to take riociguat tablets or suspension
- Calendar to track the date, time of study drug intake

17.4.2.17 7.4.3 Pharmacokinetic analysis

Old text:

[…]

The number of blood samples to be taken for the assessment of pharmacokinetic parameters was determined using clinical trial simulation (CTS) based on the physiology based PK (PBPK) modeling predictions. In order to minimize pain and distress for the patient population, the number of PK samples was kept to the minimum. The minimum amount of blood needed for adequate analysis for each sample 1.0 mL of blood.

New text:

[…]

The number of blood samples to be taken for the assessment of pharmacokinetic parameters was determined using clinical trial simulation (CTS) based on the physiology based PK (PBPK) modeling predictions. In order to minimize pain and distress for the patient population, the number of PK samples was kept to the minimum. The minimum amount of blood needed for adequate analysis for each sample 1.0 mL of blood.

For investigation of exposure behavior, plasma concentrations of BAY63-2521 and its active metabolite M1 (BAY 60-4552) will be analyzed descriptively.

17.4.2.18 7.5 Determination of sample size

Old text:

[…]

Children on treatment with ERAs and/or PCAs can be enrolled. At least 20 subjects on treatment with bosentan or other Endothelin Receptor Antagonists (ERA) must be enrolled in the study. The sample size does not originate from a formal sample size calculation, but is based on an evidence-based feasibility assessment. Based on the results of the evidence-based feasibility survey (Davie, 2014) and the proposed PK evaluation (see section 7.4.3), 20 patients will permit an accurate PK evaluation and feasibility of the study in a reasonable time frame. Every effort will be made to enroll equal numbers ~~(i.e. 10 subjects each)~~ in both age cohorts (see section 4.1).

New text:

[…]

Children on treatment with ERAs and/or PCAs can be enrolled. At least 20 subjects on treatment with bosentan or other Endothelin Receptor Antagonists (ERA) must be enrolled in the study. The sample size does not originate from a formal sample size calculation, but is based on an evidence-based feasibility assessment. Based on the results of the evidence-based feasibility survey (Davie, 2014) and the proposed PK evaluation (see section 7.4.3), 20 patients will permit an accurate PK evaluation and feasibility of the study in a reasonable time frame. Every effort will be made to enroll equal number of patients in both age cohorts (see section 4.1).

17.5 Amendment 12

Amendment 12 is the fifth global amendment dated 23 AUG 2019.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

The protocol amendment 12 was prepared to clarify several details for the long-term extension (LTE) phase of the study (i.e. 4-weekly intervals for pregnancy testing, the conditions for transitioning into the optional LTE phase and that 6MWD test and echocardiography can be performed at every second visit in LTE at the discretion of the investigator).

17.5.1 Overview of changes

The most relevant changes and the rationale for changes in Amendment 12 and the affected sections are provided as follows. A separate file with tracked changes against the last integrated protocol version is available upon request.

Section number and name	Description of (wording) change	Brief rationale
4.2 Inclusion criteria	Wording for criterion #2 (regarding PFO ≤ 1 cm confirmed by echocardiogram) was changed	To address redundancy.
4.3 Exclusion criteria 4.4 Concomitant medication	Specification that the use of any drug including NO acutely for testing during catheterization is not an exclusion criterion.	Further specification that this common medical practice is allowed.
4.3 Exclusion criteria	A specification was added prohibiting the smoking of marijuana during the study.	Clarification that smoking marijuana is not permitted.
4.4 Concomitant medication	The reverse-transcriptase inhibitor abacavir may increase the riociguat	A recently conducted DDI study with riociguat in HIV patients revealed an

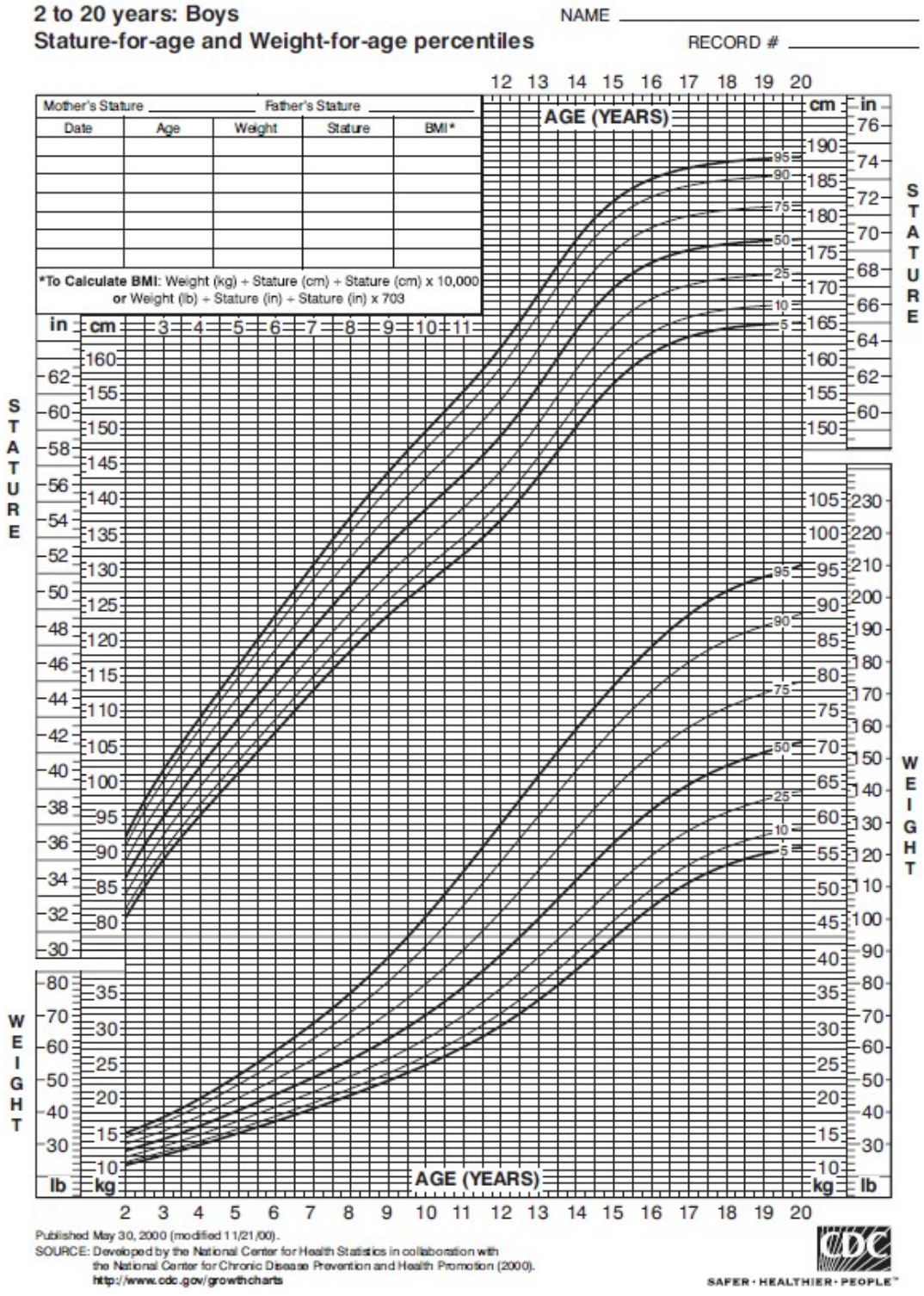
	exposure, and should be used with caution.	increase in exposure when riociguat was administered on top of Triumeq®. In vitro investigations identified abacavir as CYP1A1 inhibitor reducing riociguat clearance.
5.4 Formulation and dose Table 5-2	To correct the volume of 7.0 mL to 7.5 mL for the body weight category of ≥35 <40 kg on 2.0 mg equivalent dose	The correct volume of suspension to administer 1.12 mg is 7.5 mL.
5.4 Formulation and dose Table 5-2	Dosing recommendation for patients with body weight ≥12 <14 kg added	Dosing recommendation required for children with body weight <14 kg. According to in-/exclusion criteria patients with <14 kg may be enrolled. With the minimum age criteria of 6 years BW < 12 kg otherwise matching all other eligibility criteria is not expected. With the given formulations and dosing devices dosing of patients <12 kg is not feasible.
6.1.6 Optional long-term extension phase	Pregnancy testing is to be performed in 4-weekly intervals starting at Visit 1 until 4 weeks after the patient stops intake of study drug	Frequency of pregnancy tests requested by HA
6.1.6 Optional long-term extension phase	To clarify the conditions for transitioning into the optional LTE phase.	Transition must have time frame - especially for subject who becomes 18 years old in main study phase in order to allow them to enter the LTE
6.1.6 Optional long-term extension phase	Clarified that 6MWD test and echocardiography can be performed at every second visit in LTE at the discretion of the investigator	Clarification
6.1.6 Optional long-term extension phase	Child Health-related Questionnaire (SF-10) and PedsQ: The age version used must match with subject´s actual age at time of completing the questionnaire.	Clarification
6.4 Pharmacokinetics – amended	Name of the peak sample is changed to post-dose sample	Samples are taken after dosing and not exactly at peak plasma concentrations, therefore the name of PK sampling was clarified
6.5 Study guidelines for parents and children	To explicitly describe one investigator task at visits: to check the patient´s home SBP monitoring form.	For completeness

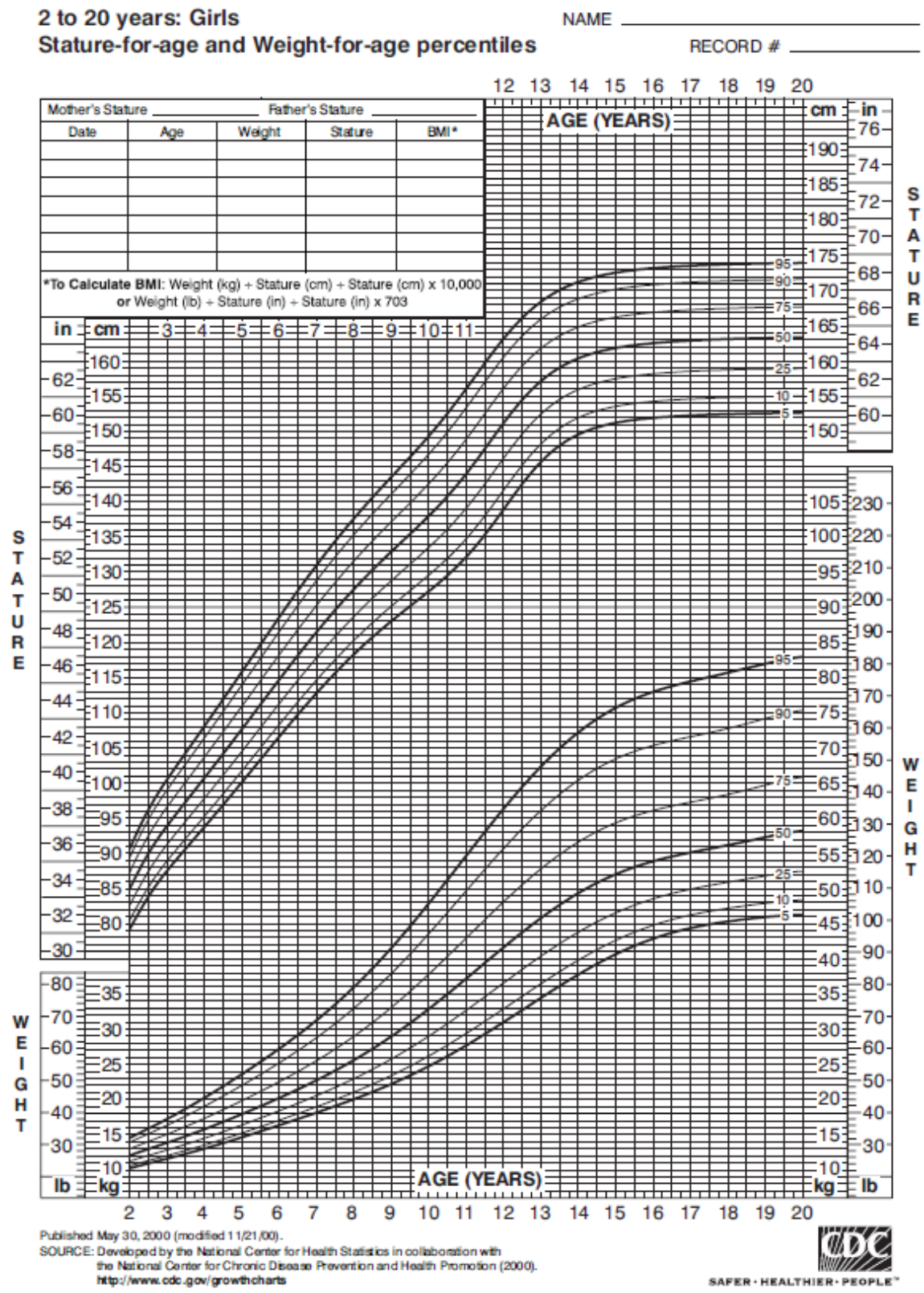
17.6 Amendment 14

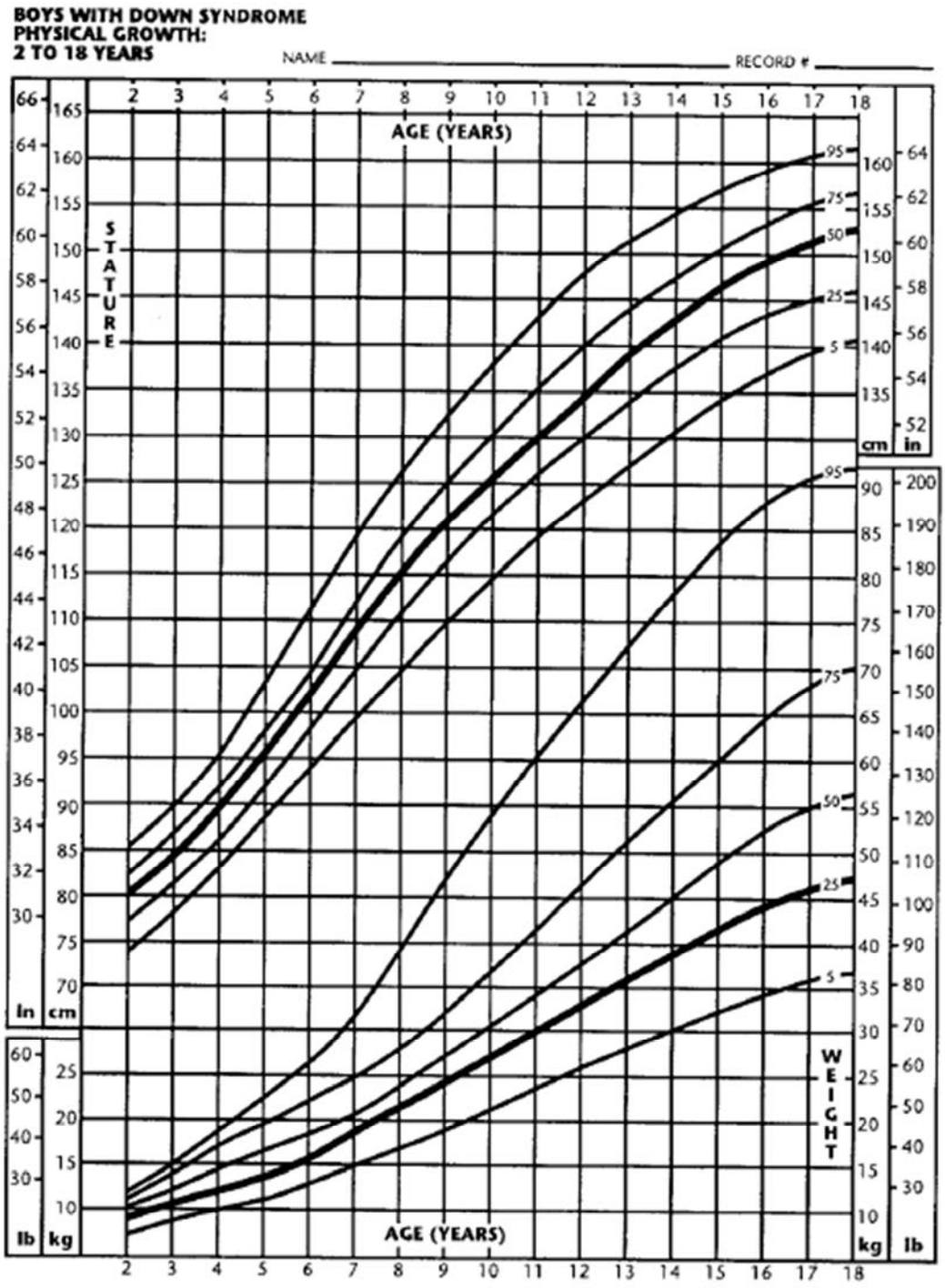
Amendment 14 is the sixth global amendment dated 20 JUL 2020. The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents. A separate file with tracked changes against the last integrated protocol version is available upon request.

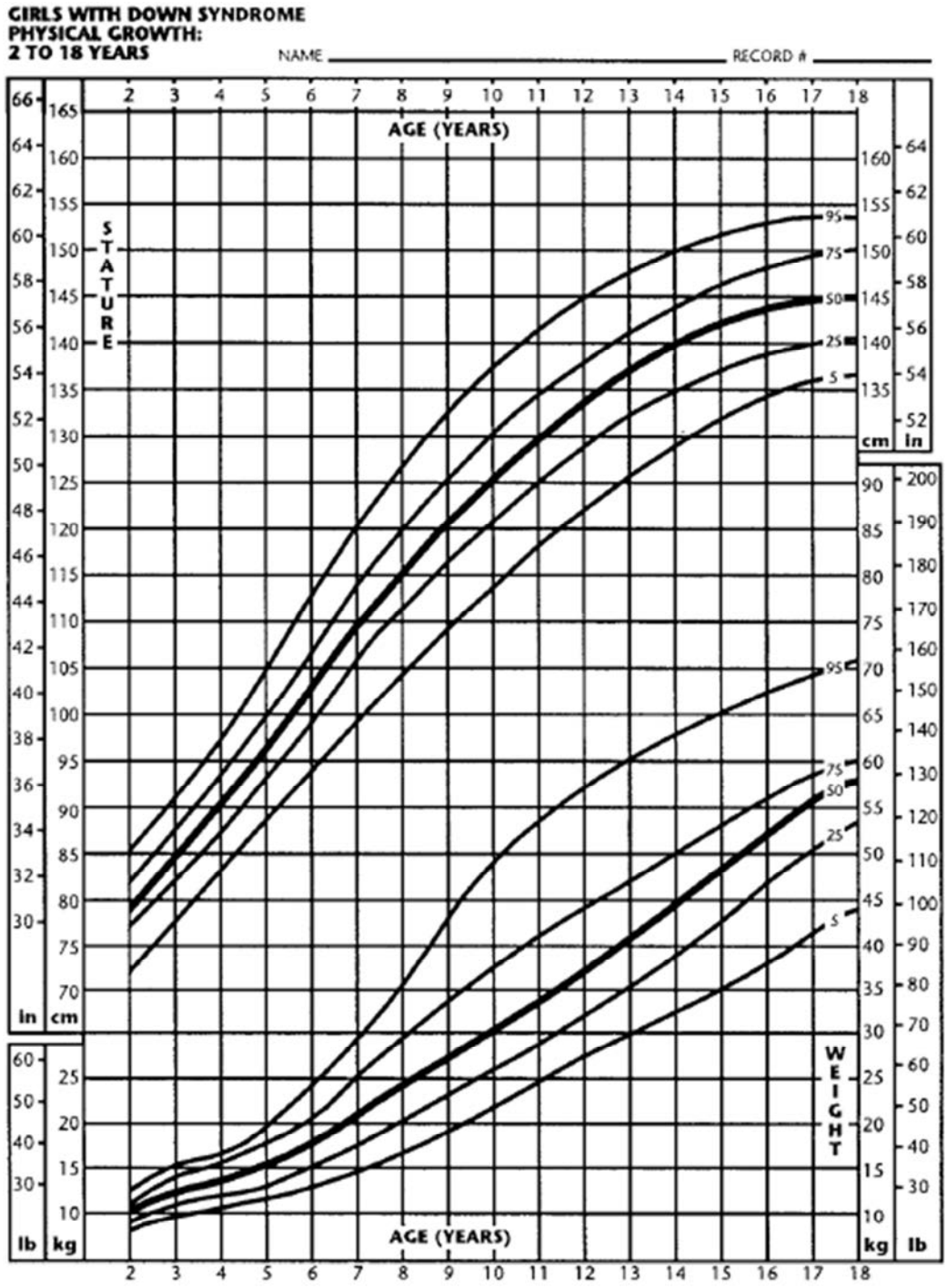
18. Appendices - amended

18.1 Appendix 1: Growth charts - amended




2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
SAFER · HEALTHIER · PEOPLE™


BOYS WITH DOWN SYNDROME
PHYSICAL GROWTH:
2 TO 18 YEARS
NAME
RECORD #
AGE (YEARS)
STATURE
WEIGHT
95
75
50
25
5
in
cm
lb
kg



Growth charts for boys and girls with Down syndrome from: (CRONK C., 1988)

(Note: This section was modified according to Amendment 3, see Section 17.1.1.12.)

18.2 Appendix 2: Child Health Questionnaire (SF-10) - amended

The SF-10, a parent-completed health survey for children will be performed during study visits as specified in Table 0–1.

SF-10™ Health Survey for Children

1. **In general, would you say your child's health is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **During the past 4 weeks, has your child been limited in any of the following activities due to HEALTH problems?**

	Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
a. Doing things that take some energy such as riding a bike or skating?	☐1	☐2	☐3	☐4
b. Bending, lifting, or stooping?	☐1	☐2	☐3	☐4

3. **During the past 4 weeks, has your child been limited in the KIND of schoolwork or activities with friends he/she could do because of PHYSICAL health problems?**

Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
☐1	☐2	☐3	☐4

4. **During the past 4 weeks, has your child been limited in the KIND of schoolwork or activities with friends he/she could do because of EMOTIONAL or BEHAVIORAL problems?**

Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
☐1	☐2	☐3	☐4

5. **During the past 4 weeks, how much bodily pain or discomfort has your child had?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐1	☐2	☐3	☐4	☐5	☐6

6. **During the past 4 weeks, how satisfied do you think your child has felt about his/her friendships?**

Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
☐1	☐2	☐3	☐4	☐5

7. **During the past 4 weeks, how satisfied do you think your child has felt about his/her life overall?**

Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
☐1	☐2	☐3	☐4	☐5

United States (English) Version

SF-10™ Health Survey for Children

8. During the past 4 weeks, how much of the time do you think your child acted bothered or upset?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

9. Compared to other children your child's age, in general would you say his/her behavior is:

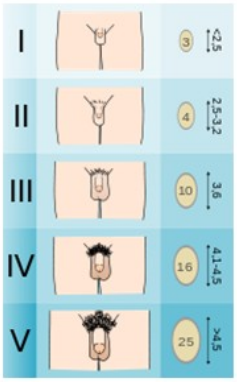
Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

United States (English) Version

(Note: This section was modified according to Amendment 3, see Sections 17.1.1.12 and 17.1.1.16.)

18.3 Appendix 3: Tanner scale

Genitals (male)



Tanner I : prepubertal (testicular volume less than 1.5 ml; small penis of 3 cm or less) [typically age 9 and younger]

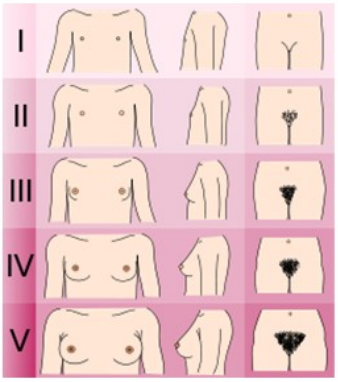
Tanner II : testicular volume between 1.6 and 6 ml; skin on scrotum thins, reddens and enlarges; penis length unchanged [9-11]

Tanner III : testicular volume between 6 and 12 ml; scrotum enlarges further; penis begins to lengthen to about 6 cm [11-12.5]

Tanner IV : testicular volume between 12 and 20 ml; scrotum enlarges further and darkens; penis increases in length to 10 cm and circumference [12.5-14]

Tanner V : testicular volume greater than 20 ml; adult scrotum and penis of 15 cm in length [14+]

Breasts (female)



Tanner I : no glandular tissue: areola follows the skin contours of the chest (prepubertal) [typically age 10 and younger]

Tanner II : breast bud forms, with small area of surrounding glandular tissue; areola begins to widen [10-11.5]

Tanner III : breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast [11.5-13]

Tanner IV : increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast [13-15]

Tanner V : breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla. [15+]

Tanner scale	Pubic hair (both male and female)
I	no pubic hair at all (prepuberal state) [typically age 10 and younger]
II	small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females) [10–11.5]
III	hair becomes more coarse and curly, and begins to extend laterally [11.5–13]
IV	adult-like hair quality, extending across pubis but sparing medial thighs [13–15]
V	hair extends to medial surface of the thighs [15+]

18.4 Appendix 4: Taste assessment - amended

Taste and Texture Questionnaire
Riociguat liquid formulation

Study Title:	**Open label, multicenter, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 years to less than 18 years of age with pulmonary arterial hypertension (PAH)**
Study No.:	Study number 15681 EudraCT no.: 2014-003952-29
Date	__| __| __| __| __| __| __| __|
Subject number	__| __| __| __| __| __| __| __| __| __|
Trial unit number	__| __| __| __| __|

The questionnaire will be completed at visit 1, visit 9 and at the end of treatment visit

Instruction for the interviewer prior to the interview:

- **This questionnaire will be used to determine the preference for oral suspension in the pediatric subjects aged from 6 to 18 years if they have been allocated to riociguat.**
- **If possible, please give the child a glass of water prior to starting the questionnaire (i.e. before study drug administration) to neutralize taste**
- **Please give the "3-point-explanation scale" with the smiles to the child and explain the meaning of the faces:**

  - **The happy face means you like it**
  - **The neutral face means you don't know if you like or don't like it**
  - **The sad face means you don't like this**

Please make sure that the child understands the meaning of the smiley faces with an example:
Do you like your dress/ toys, or: Do you like pancakes, lemonade, apple juice?
Have the child point out to you the smiley face on the "3-point explanation scale".

Questions Q.1. and Q.2. should be answered before the child receives the drink (suspension)!

APPEARANCE AND SMELL

Please ask for APPEARANCE first

Show the medication (suspension) to the child. Responders should only look at the medication (suspension)!

Capture spontaneous expressions of the child concerning the appearance of the medication.

- Comfortable ☐
- Indifferent ☐
- Displeased ☐

Q.1. Do you like the look of the medication (suspension)?

Show and describe the list (3-point-Scale)

- YES ☐
- NO ☐
- I DON'T KNOW / UNSURE ☐

SMELL:

Simply smelling at the medication (suspension)! Let the child smell from the bottle of the medication (suspension).

Capture spontaneous expressions of the child concerning the smell of the medication (suspension).

- Comfortable ☐
- Indifferent ☐
- Displeased ☐

Q.2. Do you like the smell of the medication (suspension)?

Show and describe the list (3-point-Scale)

- YES ☐
- NO ☐
- I DON'T KNOW / UNSURE ☐

Questions Q.3. and Q.4. should be answered right after the child received the medication (suspension)!

TASTE:

Capture spontaneous expressions of the child concerning the taste of the medication (suspension) (just right after having the study medication dose).

- Comfortable ☐
- Indifferent ☐
- Displeased ☐

Q.3. Did you like the medication (suspension)?

Show and describe the list (3-point-Scale)

- YES ☐
- NO ☐
- I DON'T KNOW / UNSURE ☐

Q.4. Would you like to drink this medication (suspension) again?

Show and describe the list (3-point-Scale)

- YES ☐
- NO ☐
- I DON'T KNOW / UNSURE ☐

Please proceed with questions Q.5. to Q.7., IF:

- **Questions Q.3. or Q.4. were answered with "NO"!**

Q.5. Now I would like to ask you a little bit more about the medication. I will read out loud a few statements to you concerning the taste of the medication (suspension). Please tell me for every statement if it applies or not.

- Show and describe the list (3-point-Scale); only one answer is possible per statement.
- Please change the order of the statements for each child (randomization) e.g. for the first child start with the item sweet; for the second child start with the item bitter and so on.
- If the child doesn't understand the description of the taste, please provide examples (e.g. "like sugar" for sweet, "like lemon" for sour), if possible. If the child still doesn't understand the description of the taste, please tick "not understood."

The medication (suspension) tastes	Yes 	No 	I don't know/ Unsure 	Not under-stood
Sweet	☐	☐	☐	☐
Sour	☐	☐	☐	☐
Bitter	☐	☐	☐	☐
Salty	☐	☐	☐	☐
Disgusting	☐	☐	☐	☐
Fruity	☐	☐	☐	☐

Other: if applicable, capture other expressions regarding the taste

.....

.....

.....

Q.6. Now I would like to know how the medication (suspension) feels in your mouth. Please tell me for every statement if it applies or not.

- Show and describe the list (3-point-Scale); only one answer possible per statement.
- Please change the order of the statements for each child (randomization) e.g. for the first child start with the item like sand; for the second child start with the item slimy and so on.
- If the child doesn't understand the description of the mouth feeling, please provide examples (e.g. "like chewing gum" for gooey, "like candy" for sticky), if possible. If the child still doesn't understand the description of the mouth feeling, please tick "not understood."

The medication (suspension) feels in the mouth	Yes 	No 	I don't know/ Unsure 	Not under-stood
Like sand	☐	☐	☐	☐
Sticky	☐	☐	☐	☐
Gooey	☐	☐	☐	☐
Slimy	☐	☐	☐	☐
Creamy	☐	☐	☐	☐

Other: if applicable, capture other expressions regarding the taste

.....

.....

.....

Q.7. Did you like the taste in your mouth now after you swallowed the medication (suspension)?

Show and describe the list (3-point-Scale)

YES	☐
NO	☐
I DON'T KNOW / UNSURE	☐

3-point-Explanation scale

(Note: The new logo was updated to the Taste and Texture Questionnaire front page according to Amendment 6, see Section 17.3.1.10.)

18.5 Appendix 5: Blood pressure levels for children and adolescents by gender, age and height percentile according to the National High Blood Pressure Education Program Working Group

TABLE 3. BP Levels for Boys by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	96	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

TABLE 4. BP Levels for Girls by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

Source: (NHBPEP, 2004)

18.6 Appendix 6: Glomerular filtration rate: Calculation instructions by Schwartz formula - amended

If serum creatinine (SCr) is measured with routine methods that have not been recalibrated to be traceable to isotope dilution mass spectrometry (IDMS) (e.g. the traditional Jaffé reaction), the eGFR should be obtained from the original Schwartz formula:

eGFR (mL/min/1.73 m^2) = k * height (cm) / SCr (mg/dL)

Where k is proportionality constant:

k = 0.55 in children up to 13 years of age

k = 0.70 in boys >13 years and <18 years of age (not in girls; because of the presumed increase in male muscle mass, the constant remains 0.55 for girls)

If SCr is measured by an enzymatic creatinine method that has been calibrated to be traceable to IDMS, the updated Schwartz formula should be used to obtain the eGFR:

eGFR (mL/min/1.73 m^2) = 0.413 * height (cm) / SCr (mg/dL)

Note: To express SCr in micromoles per liter, the value should be multiplied by 88.4 (1 mg/dL = 88.4 µmol/L).

(*Note: The Appendix 6 was applied to Amendment 5, see Section 17.2.1.6.*)

18.7 Appendix 7: PedsQL Generic Core Scales

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YOUNG CHILD REPORT (ages 5-7)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

PedsQL 2

Think about how you have been doing for the last few weeks. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PHYSICAL FUNCTIONING *(problems with…)*	Not at all	Some-times	A lot
1. Is it hard for you to walk	0	2	4
2. Is it hard for you to run	0	2	4
3. Is it hard for you to play sports or exercise	0	2	4
4. Is it hard for you to pick up big things	0	2	4
5. Is it hard for you to take a bath or shower	0	2	4
6. Is it hard for you to do chores (like pick up your toys)	0	2	4
7. Do you have hurts or aches (***Where?_____***)	0	2	4
8. Do you ever feel too tired to play	0	2	4

Remember, tell me how much of a problem this has been for you for the last few weeks.

EMOTIONAL FUNCTIONING *(problems with…)*	Not at all	Some-times	A lot
1. Do you feel scared	0	2	4
2. Do you feel sad	0	2	4
3. Do you feel mad	0	2	4
4. Do you have trouble sleeping	0	2	4
5. Do you worry about what will happen to you	0	2	4

SOCIAL FUNCTIONING *(problems with…)*	Not at all	Some-times	A lot
1. Is it hard for you to get along with other kids	0	2	4
2. Do other kids say they do not want to play with you	0	2	4
3. Do other kids tease you	0	2	4
4. Can other kids do things that you cannot do	0	2	4
5. Is it hard for you to keep up when you play with other kids	0	2	4

SCHOOL FUNCTIONING *(problems with…)*	Not at all	Some-times	A lot
1. Is it hard for you to pay attention in school	0	2	4
2. Do you forget things	0	2	4
3. Is it hard to keep up with schoolwork	0	2	4
4. Do you miss school because of not feeling good	0	2	4
5. Do you miss school because you have to go to the doctor's or hospital	0	2	4

How much of a problem is this for you?

Not at all	Sometimes	A lot
		

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CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you ...*

ABOUT MY HEALTH AND ACTIVITIES *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

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TEEN REPORT (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you ...*

ABOUT MY HEALTH AND ACTIVITIES *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT SCHOOL *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4