

**Clinical trial results:**

**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)**

**Summary**

EudraCT number	2014-003952-29
Trial protocol	HU IT GB DE FR ES PL Outside EU/EEA BE RO
Global end of trial date	

**Results information**

Result version number	v1 (current)
This version publication date	19 September 2020
First version publication date	19 September 2020

**Trial information****Trial identification**

Sponsor protocol code	15681
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02562235
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000718-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

## Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	07 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2020
Global end of trial reached?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to evaluate safety, tolerability and pharmacokinetics of oral riociguat treatment

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects or their legally authorized representative. Subjects or legal representatives signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Subjects 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.

Evidence for comparator: -

Actual start date of recruitment	29 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	11 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Poland: 2
Worldwide total number of subjects	24
EEA total number of subjects	12

Notes:

**Subjects enrolled per age group**

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	6
Adolescents (12-17 years)	18
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at multiple centers in 9 countries or regions between 29-Oct-2015 (first subject first visit) and 07-Mar-2020 (last subject last visit of main study part).

### Pre-assignment

Screening details:

A total of 26 subjects were screened. Of them, 2 subjects were screening failures and 24 subjects received study treatment.

### Period 1

Period 1 title	Baseline and main treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Riociguat $\geq 6$ to $< 18$ years
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Arm description:

Subjects with age  $\geq 6$  to  $< 18$  years received riociguat up to 2.5 mg three times a day (titration between 0.5 mg and 2.5 mg) for up to 8 weeks during the individual dose titration (IDT) phase, and followed with the last dose administered in the IDT phase for up to 16 weeks during the maintenance phase. Down-titration of the dose for safety reasons was allowed at any time.

Arm type	Experimental
Investigational medicinal product name	Riociguat
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Granules for oral suspension, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

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, IDT in adults treated for PAH; oral suspension. For children  $\geq 50$  kg at screening, 1.0 to 2.5 mg three times a day; oral tablet.

<b>Number of subjects in period 1</b>	Riociguat $\geq 6$ to $< 18$ years
Started	24
Completed	21
Not completed	3
Adverse event	3

## Baseline characteristics

### Reporting groups

Reporting group title	Riociguat $\geq 6$ to $< 18$ years
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Reporting group description:

Subjects with age  $\geq 6$  to  $< 18$  years received riociguat up to 2.5 mg three times a day (titration between 0.5 mg and 2.5 mg) for up to 8 weeks during the individual dose titration (IDT) phase, and followed with the last dose administered in the IDT phase for up to 16 weeks during the maintenance phase. Down-titration of the dose for safety reasons was allowed at any time.

Reporting group values	Riociguat $\geq 6$ to $< 18$ years	Total	
Number of subjects	24	24	
Age Categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	12.8		
standard deviation	$\pm 2.8$	-	
Gender Categorical			
Units: Subjects			
Female	11	11	
Male	13	13	

Bone age compared to chronological age

X-ray of left hand was performed for each subject and bone age was determined centrally by a specialist. For each subject, bone age was compared to chronological age and assessed as "delayed, in accordance or advanced".

Units: Subjects			
Delayed	1	1	
In accordance	12	12	
Advanced	10	10	
Missing	1	1	

WHO functional class

The World Health Organization (WHO) functional class describes how severe a patient's pulmonary hypertension (PH) symptoms are. There are four different classes – I is the mildest and IV the most severe form of PH.

Units: Subjects			
Class I	1	1	
Class II	18	18	
Class III	5	5	
Class IV	0	0	

Heart rate

Units: Beats per minute (BPM)

arithmetic mean	84.5		
standard deviation	$\pm 19.0$	-	

Diastolic blood pressure

Units: millimetre of mercury (mmHg)

arithmetic mean	63.8		
standard deviation	$\pm 7.9$	-	

Systolic blood pressure

Units: millimetre of mercury (mmHg)			
arithmetic mean	112.9		
standard deviation	± 10.9	-	
Respiratory Rate			
Number of subjects with respiration rate data at baseline: n=21			
Units: Breath per minute			
arithmetic mean	19.6		
standard deviation	± 4.4	-	
6-minute walking distance			
6-minute walking distance (6MWD) is a exercise test used to assess aerobic capacity and endurance. The distance covered over a time of 6 minutes is used as the outcome by which to compare changes in performance capacity. An increase in the distance walked indicates improvement in basic mobility. Number of subjects with 6MWD data at baseline: n=23			
Units: Meter			
arithmetic mean	442.12		
standard deviation	± 109.67	-	
N-terminal prohormone brain-type natriuretic peptide			
Laboratory biomarkers N-terminal prohormone brain-type natriuretic peptide (NT-proBNP) or brain-type natriuretic peptide (BNP) were tested for the subjects. When both tests were available, NT-proBNP was chosen over BNP and the same test was performed at every required visit. Number of subjects with NT-proBNP data at baseline: n=15			
Units: Picograms per milliliter (pg/mL)			
arithmetic mean	982.68		
standard deviation	± 1595.77	-	
Brain-type natriuretic peptide			
Laboratory biomarkers N-terminal prohormone brain-type natriuretic peptide (NT-proBNP) or brain-type natriuretic peptide (BNP) were tested for the subjects. When both tests were available, NT-proBNP was chosen over BNP and the same test was performed at every required visit. Number of subjects with BNP data at baseline: n=7			
Units: Picograms per milliliter (pg/mL)			
arithmetic mean	10.46		
standard deviation	± 9.10	-	
Quality of life evaluated by SF-10 questionnaire physical summary score			
SF-10 is a parent-completed health survey for children that contains 10 questions adapted from the Child Health Questionnaire. It is scored to produce physical and psychosocial health summary measures. Each of the 10 questions responses is scored with a point value from 1 to 6 (1 is the worst possible condition and 6 is the best possible condition). The SF-10 physical and psychosocial measures are scored such that higher scores indicate more favorable functioning.			
Units: Scores on a scale			
arithmetic mean	30.964		
standard deviation	± 13.335	-	
Quality of life evaluated by SF-10 questionnaire psychosocial summary score			
SF-10 is a parent-completed health survey for children that contains 10 questions adapted from the Child Health Questionnaire. It is scored to produce physical and psychosocial health summary measures. Each of the 10 questions responses is scored with a point value from 1 to 6 (1 is the worst possible condition and 6 is the best possible condition). The SF-10 physical and psychosocial measures are scored such that higher scores indicate more favorable functioning.			
Units: Scores on a scale			
arithmetic mean	48.765		
standard deviation	± 8.263	-	
Quality of life evaluated by PedsQL total scale score			
PedsQL Generic Core Scales were designed to measure health-related quality of life in children and adolescents. It has 4 dimensions: physical functioning, emotional functioning, social functioning and school functioning. 3 Summary Scores of PedsQL were calculated from the scales including total scale			

score, physical health summary score (physical functioning) and psychosocial health summary score (emotional, social and school functioning). Responses of the questions are transformed to a 0-100 scale. Higher scores indicate better quality of life. Number of subjects with data at baseline: n=21			
Units: Scores on a scale			
arithmetic mean	69.77		
standard deviation	± 16.29	-	
Quality of life evaluated by PedsQL physical health summary score			
PedsQL Generic Core Scales were designed to measure health-related quality of life in children and adolescents. It has 4 dimensions: physical functioning, emotional functioning, social functioning and school functioning. 3 Summary Scores of PedsQL were calculated from the scales including total scale score, physical health summary score (physical functioning) and psychosocial health summary score (emotional, social and school functioning). Responses of the questions are transformed to a 0-100 scale. Higher scores indicate better quality of life. Number of subjects with data at baseline: n=21			
Units: Scores on a scale			
arithmetic mean	64.43		
standard deviation	± 15.80	-	
Quality of life evaluated by PedsQL psychosocial health summary score			
PedsQL Generic Core Scales were designed to measure health-related quality of life in children and adolescents. It has 4 dimensions: physical functioning, emotional functioning, social functioning and school functioning. 3 Summary Scores of PedsQL were calculated from the scales including total scale score, physical health summary score (physical functioning) and psychosocial health summary score (emotional, social and school functioning). Responses of the questions are transformed to a 0-100 scale. Higher scores indicate better quality of life. Number of subjects with data at baseline: n=21			
Units: Scores on a scale			
arithmetic mean	72.62		
standard deviation	± 19.20	-	
Estimate right atrial pressure			
Estimate right atrial pressure was measured by echocardiography. Number of subjects with estimate right atrial pressure data at baseline: n=18			
Units: millimetre of mercury (mmHg)			
arithmetic mean	9.2		
standard deviation	± 2.9	-	
Left ventricular eccentricity index			
Left ventricular eccentricity index was measured by echocardiography. Number of subjects with left ventricular eccentricity index data at baseline: n=17			
Units: Index			
arithmetic mean	2.099		
standard deviation	± 1.275	-	
Pulmonary artery acceleration time			
Pulmonary artery acceleration time was measured by echocardiography. Number of subjects with pulmonary artery acceleration time data at baseline: n=17			
Units: Millisecond (msec)			
arithmetic mean	91.568		
standard deviation	± 36.853	-	
Right ventricular cardiac index			
Right ventricular cardiac index was measured by echocardiography. Number of subjects with right ventricular cardiac index data at baseline: n=16			
Units: Liter/minute/square meter (L/min/m <sup>2</sup> )			
arithmetic mean	4.343		
standard deviation	± 1.599	-	
Right ventricular cardiac output			
Right ventricular cardiac output was measured by echocardiography. Number of subjects with right ventricular cardiac output data at baseline: n=16			
Units: Liter per minute (L/min)			
arithmetic mean	5.511		

standard deviation	± 2.093	-	
Right atrial diastolic area			
Right atrial diastolic area was measured by echocardiography. Number of subjects with right atrial diastolic area data at baseline: n=18			
Units: Square centimeter (cm <sup>2</sup> )			
arithmetic mean	16.944		
standard deviation	± 11.071	-	
Right atrial diastolic area index			
Right atrial diastolic area index was measured by echocardiography. Number of subjects with right atrial diastolic area index data at baseline: n=18			
Units: Index			
arithmetic mean	12.788		
standard deviation	± 6.977	-	
Right atrial systolic area			
Right atrial systolic area was measured by echocardiography. Number of subjects with right atrial systolic area data at baseline: n=18			
Units: Square centimeter (cm <sup>2</sup> )			
arithmetic mean	12.017		
standard deviation	± 9.391	-	
Right atrial systolic area index			
Right atrial systolic area index was measured by echocardiography. Number of subjects with right atrial systolic area index data at baseline: n=18			
Units: Index			
arithmetic mean	8.996		
standard deviation	± 6.021	-	
Right ventricular fractional area change			
Right ventricular fractional area change was measured by echocardiography. Number of subjects with right ventricular fractional area change data at baseline: n=17			
Units: Percentage (%)			
arithmetic mean	25.7		
standard deviation	± 8.5	-	
Right ventricular diastolic area			
Right ventricular diastolic area was measured by echocardiography. Number of subjects with right ventricular diastolic area data at baseline: n=17			
Units: Square centimeter (cm <sup>2</sup> )			
arithmetic mean	27.155		
standard deviation	± 11.993	-	
Right ventricular diastolic area index			
Right ventricular diastolic area index was measured by echocardiography. Number of subjects with right ventricular diastolic area index data at baseline: n=17			
Units: Index			
arithmetic mean	20.722		
standard deviation	± 6.564	-	
Right ventricular systolic area			
Right ventricular systolic area was measured by echocardiography. Number of subjects with right ventricular systolic area data at baseline: n=17			
Units: Square centimeter (cm <sup>2</sup> )			
arithmetic mean	20.235		
standard deviation	± 9.343	-	
Right ventricular systolic area index			
Right ventricular systolic area index was measured by echocardiography. Number of subjects with right ventricular systolic area index data at baseline: n=17			
Units: Index			
arithmetic mean	15.613		
standard deviation	± 5.745	-	



Systolic pulmonary artery pressure			
Systolic pulmonary artery pressure was measured by echocardiography. Number of subjects with systolic pulmonary artery pressure data at baseline: n=6			
Units: millimetre of mercury (mmHg)			
arithmetic mean	117.2		
standard deviation	± 51.6	-	
Tricuspid annular plane systolic excursion			
Tricuspid annular plane systolic excursion was measured by echocardiography. Number of subjects with tricuspid annular plane systolic excursion data at baseline: n=17			
Units: Millimeter (mm)			
arithmetic mean	18.82		
standard deviation	± 4.21	-	
Tricuspid regurgitation peak velocity			
Tricuspid regurgitation peak velocity was measured by echocardiography. Number of subjects with tricuspid regurgitation peak velocity data at baseline: n=11			
Units: Meter/second (m/s)			
arithmetic mean	4.915		
standard deviation	± 1.100	-	
Pericardial effusion			
Pericardial effusion was measured by echocardiography. Number of subjects with pericardial effusion data at baseline: n=2			
Units: Millimeter (mm)			
arithmetic mean	1.280		
standard deviation	± 0.212	-	
Platelets			
Hematology parameters were collected and analyzed.			
Units: Giga per liter (Giga/L)			
arithmetic mean	218.8		
standard deviation	± 50.6	-	
Lymphocytes/leucocytes ratio			
Hematology parameters were collected and analyzed.			
Units: Percentage of leucocytes in blood			
arithmetic mean	48.98		
standard deviation	± 8.15	-	
Neutrophils/leucocytes ratio			
Hematology parameters were collected and analyzed.			
Units: Percentage of leucocytes in blood			
arithmetic mean	18.71		
standard deviation	± 10.37	-	
Alanine aminotransferase			
Clinical chemistry parameters were collected and analyzed.			
Units: Units per liter (U/L)			
arithmetic mean	18.71		
standard deviation	± 10.37	-	
Aspartate aminotransferase			
Clinical chemistry parameters were collected and analyzed.			
Units: Units per liter (U/L)			
arithmetic mean	23.76		
standard deviation	± 8.38	-	
Urea			
Clinical chemistry parameters were collected and analyzed. Number of subjects with urea data at baseline: n=11			
Units: microgram per deciliter (mg/dL)			

arithmetic mean	25.17		
standard deviation	$\pm 7.23$	-	
Gamma glutamyl transferase			
Clinical chemistry parameters were collected and analyzed. Number of subjects with gamma glutamyl transferase data at baseline: n=20			
Units: Units per liter (U/L)			
arithmetic mean	16.9		
standard deviation	$\pm 14.5$	-	
Blood urea nitrogen			
Clinical chemistry parameters were collected and analyzed. Number of subjects with blood urea nitrogen data at baseline: n=17			
Units: microgram per deciliter (mg/dL)			
arithmetic mean	11.8		
standard deviation	$\pm 4.7$	-	
Estimated Glomerular Filtration Rate (eGFR)			
Clinical chemistry parameters were collected and analyzed.			
Units: milliliter/minute/1.73 square meter			
arithmetic mean	117.877		
standard deviation	$\pm 30.649$	-	
Sodium			
Clinical chemistry parameters were collected and analyzed. Number of subjects with blood urea nitrogen data at baseline: n=22			
Units: millimole per Liter (mmol/L)			
arithmetic mean	140.5		
standard deviation	$\pm 2.0$	-	

## End points

### End points reporting groups

Reporting group title	Riociguat $\geq 6$ to $< 18$ years
Reporting group description: Subjects with age $\geq 6$ to $< 18$ years received riociguat up to 2.5 mg three times a day (titration between 0.5 mg and 2.5 mg) for up to 8 weeks during the individual dose titration (IDT) phase, and followed with the last dose administered in the IDT phase for up to 16 weeks during the maintenance phase. Down-titration of the dose for safety reasons was allowed at any time.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: All subject who was assigned to receive study medication and had received at least one dose of the study medication.	
Subject analysis set title	Riociguat 0.5 mg or equivalent - PK
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received riociguat at 0.5 mg or body weight-adjusted dose equivalent to the exposure of 0.5 mg dose in adults at the day of PK measurement	
Subject analysis set title	Riociguat 1.0 mg or equivalent - PK
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received riociguat at 1.0 mg or body weight-adjusted dose equivalent to the exposure of 1.0 mg dose in adults at the day of PK measurement	
Subject analysis set title	Riociguat 2.0 mg or equivalent - PK
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received riociguat at 2.0 mg or body weight-adjusted dose equivalent to the exposure of 2.0 mg dose in adults at the day of PK measurement	
Subject analysis set title	Riociguat 2.5 mg or equivalent - PK
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received riociguat at 2.5 mg or body weight-adjusted dose equivalent to the exposure of 2.5 mg dose in adults at the day of PK measurement	

### Primary: Number of subjects with any treatment-emergent adverse events

End point title	Number of subjects with any treatment-emergent adverse events <sup>[1]</sup>
End point description: An adverse event (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. A serious AE (SAE) is any untoward medical occurrence that at any dose is resulting in death, is lifethreatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity. AEs occurring between start of study drug and up to 2 days after the last dose were defined as treatment-emergent AEs (TEAEs).	
End point type	Primary
End point timeframe: From start of study drug up to 2 days after the last dose of study drug in the main study part, up to 24 weeks plus/minus 5 days.	

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	24 <sup>[2]</sup>			
Units: Subjects				
Any TEAE	20			
Any serious TEAE	4			

Notes:

[2] - SAF

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in heart rate from baseline

End point title	Change in heart rate from baseline <sup>[3]</sup>
End point description:	
Mean change in heart rate from baseline is reported.	
End point type	Primary
End point timeframe:	
Baseline and Week 24 (plus/minus 5 days)	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[4]</sup>			
Units: Beats per minute (BPM)				
arithmetic mean (standard deviation)	4.1 ( $\pm$ 10.1)			

Notes:

[4] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in blood pressure from baseline

End point title	Change in blood pressure from baseline <sup>[5]</sup>
End point description:	
Mean changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline are reported.	
End point type	Primary
End point timeframe:	
Baseline and Week 24 (plus/minus 5 days)	

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[6]</sup>			
Units: millimetre of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP	-3.1 ( $\pm$ 10.5)			
DBP	-2.4 ( $\pm$ 10.0)			

Notes:

[6] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in respiratory rate from baseline

End point title	Change in respiratory rate from baseline <sup>[7]</sup>
End point description:	
Mean change in respiratory rate from baseline by age subgroups ( $\geq 6$ to $< 12$ years and $\geq 12$ to $< 18$ years) were reported.	
End point type	Primary
End point timeframe:	
Baseline and Week 24 (plus/minus 5 days)	

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	18 <sup>[8]</sup>			
Units: Breath per minute				
arithmetic mean (standard deviation)	0.3 ( $\pm$ 3.3)			

Notes:

[8] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with transitions from baseline in bone age compared to chronological age

End point title	Number of subjects with transitions from baseline in bone age compared to chronological age <sup>[9]</sup>
End point description:	
X-ray of left hand was performed for each subject and bone age was determined centrally by a specialist. For each subject, the bone age was compared to the chronological age and assigned to one of the categories - "delayed", "in accordance" or "advanced", indicating the advancement or delay in the growth of the bone. Number of subjects who transitioned to another category different from baseline was calculated and reported.	
End point type	Primary

End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[10]</sup>			
Units: Subjects				
Transitioned from Delayed to In Accordance	0			
Transitioned from Delayed to Advanced	0			
Transitioned from In Accordance to Delayed	1			
Transitioned from In Accordance to Advanced	3			
Transitioned from In Accordance to Missing	1			
Transitioned from Advanced to Delayed	1			
Transitioned from Advanced to In Accordance	0			

Notes:

[10] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Primary: Change in hematology parameters (platelets) from baseline

End point title	Change in hematology parameters (platelets) from baseline <sup>[11]</sup>
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End point description:

Hematology parameters were collected. Parameters with a decrease or increase in the mean value compared to baseline were reported.

End point type	Primary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	20 <sup>[12]</sup>			
Units: Giga per Liter (Giga/L)				
arithmetic mean (standard deviation)	-4.4 ( $\pm$ 51.1)			

Notes:

[12] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in hematology parameters (lymphocytes/leucocytes ratio) from baseline

End point title	Change in hematology parameters (lymphocytes/leucocytes ratio) from baseline <sup>[13]</sup>
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End point description:

Hematology parameters were collected. Parameters with a decrease or increase in the mean value compared to baseline were reported.

End point type	Primary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

End point values	Riociguat $\geq 6$ to $<18$ years			
Subject group type	Reporting group			
Number of subjects analysed	20 <sup>[14]</sup>			
Units: Percentage of leucocytes in blood				
arithmetic mean (standard deviation)	-4.77 ( $\pm$ 11.08)			

Notes:

[14] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in hematology parameters (neutrophils/leucocytes ratio) from baseline

End point title	Change in hematology parameters (neutrophils/leucocytes ratio) from baseline <sup>[15]</sup>
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End point description:

Hematology parameters were collected. Parameters with a decrease or increase in the mean value compared to baseline were reported.

End point type	Primary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	20 <sup>[16]</sup>			
Units: Percentage of leucocytes in blood				
arithmetic mean (standard deviation)	5.71 ( $\pm$ 11.73)			

Notes:

[16] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in clinical chemistry (alanine aminotransferase) from baseline

End point title	Change in clinical chemistry (alanine aminotransferase) from baseline <sup>[17]</sup>
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End point description:

Clinical chemistry parameters were collected and analyzed. Parameters with a trend to lower or higher mean values from baseline were reported.

End point type	Primary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[18]</sup>			
Units: Units per liter (U/L)				
arithmetic mean (standard deviation)	-1.01 ( $\pm$ 9.86)			

Notes:

[18] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in clinical chemistry (aspartate aminotransferase) from baseline

End point title	Change in clinical chemistry (aspartate aminotransferase) from baseline <sup>[19]</sup>
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End point description:

Clinical chemistry parameters were collected and analyzed. Parameters with a trend to lower or higher mean values from baseline were reported.

End point type	Primary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was



planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[20]</sup>			
Units: Units per liter (U/L)				
arithmetic mean (standard deviation)	-1.94 ( $\pm$ 6.52)			

Notes:

[20] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Primary: Change in clinical chemistry (eGFR) from baseline

End point title	Change in clinical chemistry (eGFR) from baseline <sup>[21]</sup>
End point description:	
Clinical chemistry parameters were collected and analyzed. Parameters with a trend to lower or higher mean values from baseline were reported. eGFR = estimated glomerular filtration rate	
End point type	Primary
End point timeframe:	
Baseline and Week 24 (plus/minus 5 days)	

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[22]</sup>			
Units: milliliter/minute/1.73 square meter				
arithmetic mean (standard deviation)	-4.459 ( $\pm$ 25.686)			

Notes:

[22] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Primary: Change in clinical chemistry (sodium) from baseline

End point title	Change in clinical chemistry (sodium) from baseline <sup>[23]</sup>
End point description:	
Clinical chemistry parameters were collected and analyzed. Parameters with a trend to lower or higher mean values from baseline were reported.	
End point type	Primary
End point timeframe:	
Baseline and Week 24 (plus/minus 5 days)	

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	19 <sup>[24]</sup>			
Units: millimole per Liter (mmol/L)				
arithmetic mean (standard deviation)	-1.0 ( $\pm$ 1.9)			

Notes:

[24] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in clinical chemistry (blood urea nitrogen) from baseline

End point title	Change in clinical chemistry (blood urea nitrogen) from baseline <sup>[25]</sup>
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End point description:

Clinical chemistry parameters were collected and analyzed. Parameters with a trend to lower or higher mean values from baseline were reported.

End point type	Primary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[26]</sup>			
Units: microgram per deciliter (mg/dL)				
arithmetic mean (standard deviation)	1.3 ( $\pm$ 4.3)			

Notes:

[26] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in clinical chemistry (urea) from baseline

End point title	Change in clinical chemistry (urea) from baseline <sup>[27]</sup>
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End point description:

Clinical chemistry parameters were collected and analyzed. Parameters with a trend to lower or higher mean values from baseline were reported.

End point type	Primary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	9 <sup>[28]</sup>			
Units: microgram per deciliter (mg/dL)				
arithmetic mean (standard deviation)	4.06 ( $\pm$ 10.52)			

Notes:

[28] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Primary: Change in clinical chemistry (gamma glutamyl transferase) from baseline

End point title	Change in clinical chemistry (gamma glutamyl transferase) from baseline <sup>[29]</sup>
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End point description:

Clinical chemistry parameters were collected and analyzed. Parameters with a trend to lower or higher mean values from baseline were reported.

End point type	Primary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	18 <sup>[30]</sup>			
Units: Units per liter (U/L)				
arithmetic mean (standard deviation)	1.7 ( $\pm$ 4.0)			

Notes:

[30] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Primary: Plasma concentration of riociguat at Week 0

End point title	Plasma concentration of riociguat at Week 0 <sup>[31]</sup>
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End point description:

Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation in statistics. Means at any time were only calculated if at least 2/3 of the individual data were measured

and were above the limit of quantification (LOQ). Geometric mean and percentage geometric coefficient of variation (%CV) were reported. W = Week. Occurrence of "±" in relation with coefficient of variation is auto-generated by the database.

End point type	Primary
End point timeframe:	
Week 0 (30-90 minutes post-dose; 2.5-4 hours post-dose)	

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat 1.0 mg or equivalent - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	22 <sup>[32]</sup>			
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)				
W0 (30-90 min post-dose)	15.340 (± 90.536)			
W0 (2.5-4 h post-dose)	17.791 (± 55.690)			

Notes:

[32] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Primary: Plasma concentration of riociguat at Week 4

End point title	Plasma concentration of riociguat at Week 4 <sup>[33]</sup>
End point description:	
Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation in statistics, Means at any time were only calculated if at least 2/3 of the individual data were measured and were above the limit of quantification (LOQ). Geometric mean and percentage geometric coefficient of variation (%CV) were reported. "99999" denotes that value was not calculated due to very low number of subjects. Occurrence of "±" in relation with coefficient of variation is auto-generated by the database.	
End point type	Primary
End point timeframe:	
Week 4 (pre-dose)	

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat 0.5 mg or equivalent - PK	Riociguat 1.0 mg or equivalent - PK	Riociguat 2.0 mg or equivalent - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1 <sup>[34]</sup>	2 <sup>[35]</sup>	17 <sup>[36]</sup>	
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)	4.510 (± 99999)	65.585 (± 47.727)	31.126 (± 89.790)	

Notes:

[34] - Subjects in SAF with evaluable data

[35] - Subjects in SAF with evaluable data

[36] - SAF

## Statistical analyses

No statistical analyses for this end point

### Primary: Plasma concentration of riociguat at Week 8

End point title	Plasma concentration of riociguat at Week 8 <sup>[37]</sup>
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End point description:

Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation in statistics, Means at any time were only calculated if at least 2/3 of the individual data were measured and were above the limit of quantification (LOQ). Geometric mean and percentage geometric coefficient of variation (%CV) were reported. "99999" denotes that value was not calculated due to very low number of subjects. Occurrence of "±" in relation with coefficient of variation is auto-generated by the database.

End point type	Primary
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End point timeframe:

Week 8 (pre-dose)

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

End point values	Riociguat 0.5 mg or equivalent - PK	Riociguat 1.0 mg or equivalent - PK	Riociguat 2.0 mg or equivalent - PK	Riociguat 2.5 mg or equivalent - PK
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2 <sup>[38]</sup>	1 <sup>[39]</sup>	1 <sup>[40]</sup>	15 <sup>[41]</sup>
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)				
Riociguat	11.650 (± 244.238)	27.100 (± 99999)	14.000 (± 99999)	32.381 (± 137.719)
BAY60-4552	23.065 (± 91.296)	13.200 (± 99999)	49.600 (± 99999)	65.849 (± 26.864)

Notes:

[38] - Subjects in SAF with evaluable data

[39] - Subjects in SAF with evaluable data

[40] - Subjects in SAF with evaluable data

[41] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Plasma concentration of BAY60-4552 at Week 0

End point title	Plasma concentration of BAY60-4552 at Week 0 <sup>[42]</sup>
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End point description:

BAY60-4552 is riociguat's active metabolite. Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation in statistics, Means at any time were only calculated if at least 2/3 of the individual data were measured and were above the limit of quantification (LOQ).

Geometric mean and percentage geometric coefficient of variation (%CV) were reported. W = Week; n = number of subjects. "99999" denotes that value was not calculated due to very low number of subjects.

End point type	Primary
End point timeframe:	
Week 0 (30-90 minutes post-dose; 2.5-4 hours post-dose)	

Notes:

[42] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat 1.0 mg or equivalent - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	22 <sup>[43]</sup>			
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)				
W0 (30-90 min post-dose)	99999 (± 99999)			
W0 (2.5-4 h post-dose)	3.922 (± 94.399)			

Notes:

[43] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Primary: Plasma concentration of BAY60-4552 at Week 4

End point title	Plasma concentration of BAY60-4552 at Week 4 <sup>[44]</sup>
End point description:	
BAY60-4552 is riociguat's active metabolite. Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation in statistics. Means at any time were only calculated if at least 2/3 of the individual data were measured and were above the limit of quantification (LOQ). Geometric mean and percentage geometric coefficient of variation (%CV) were reported. "99999" denotes that value was not calculated due to very low number of subjects. Occurrence of "±" in relation with coefficient of variation is auto-generated by the database.	
End point type	Primary
End point timeframe:	
Week 4 (pre-dose)	

Notes:

[44] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

<b>End point values</b>	Riociguat 0.5 mg or equivalent - PK	Riociguat 1.0 mg or equivalent - PK	Riociguat 2.0 mg or equivalent - PK	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1 <sup>[45]</sup>	2 <sup>[46]</sup>	17 <sup>[47]</sup>	
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)	12.700 (± 99999)	48.822 (± 193.584)	38.579 (± 27.242)	

Notes:

[45] - Subjects in SAF with evaluable data

[46] - Subjects in SAF with evaluable data

[47] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Plasma concentration of BAY60-4552 at Week 8

End point title	Plasma concentration of BAY60-4552 at Week 8 <sup>[48]</sup>
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End point description:

BAY60-4552 is riociguat's active metabolite. Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation in statistics, Means at any time were only calculated if at least 2/3 of the individual data were measured and were above the limit of quantification (LOQ). Geometric mean and percentage geometric coefficient of variation (%CV) were reported. "99999" denotes that value was not calculated due to very low number of subjects. Occurrence of "±" in relation with coefficient of variation is auto-generated by the database.

End point type	Primary
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End point timeframe:

Week 8 (pre-dose)

Notes:

[48] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the nature of this trial, only descriptive statistics were performed. This trial was planned as fully exploratory, based on a small number of subjects, and without any inferential statistics.

End point values	Riociguat 0.5 mg or equivalent - PK	Riociguat 1.0 mg or equivalent - PK	Riociguat 2.0 mg or equivalent - PK	Riociguat 2.5 mg or equivalent - PK
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2 <sup>[49]</sup>	1 <sup>[50]</sup>	1 <sup>[51]</sup>	15 <sup>[52]</sup>
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)	23.065 (± 91.296)	13.200 (± 99999)	49.600 (± 99999)	65.849 (± 26.864)

Notes:

[49] - Subjects in SAF with evaluable data

[50] - Subjects in SAF with evaluable data

[51] - Subjects in SAF with evaluable data

[52] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in 6-minute walking distance from baseline

End point title	Change in 6-minute walking distance from baseline
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End point description:

6-minute walking distance (6MWD) is a exercise test used to assess aerobic capacity and endurance. The distance covered over a time of 6 minutes is used as the outcome by which to compare changes in performance capacity. An increase in the distance walked indicates improvement in basic mobility.

End point type	Secondary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	19 <sup>[53]</sup>			
Units: Meter				
arithmetic mean (standard deviation)	23.01 ( $\pm$ 68.80)			

Notes:

[53] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with change in WHO functional class from baseline

End point title	Number of subjects with change in WHO functional class from baseline
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End point description:

The World Health Organization (WHO) functional class describes how severe a patient's pulmonary hypertension (PH) symptoms are. There are four different classes – I is the mildest and IV the most severe form of PH. Number of subjects per change in number of classes was reported.

End point type	Secondary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[54]</sup>			
Units: Subjects				
-3 classes	0			
-2 classes	0			
-1 classes	0			
0 classes	21			
1 classes	0			
2 classes	0			
3 classes	0			

Notes:

[54] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in NT-proBNP from baseline

End point title	Change in NT-proBNP from baseline
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End point description:

Laboratory biomarkers N-terminal prohormone brain-type natriuretic peptide (NT-proBNP) or brain-type natriuretic peptide (BNP) were tested for the subjects. When both tests were available, NT-proBNP was chosen over BNP and the same test was performed at every required visit.

End point type	Secondary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[55]</sup>			
Units: picograms per milliliter (pg/mL)				
arithmetic mean (standard deviation)	-65.77 ( $\pm$ 585.41)			

Notes:

[55] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in BNP from baseline

End point title	Change in BNP from baseline
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End point description:

Laboratory biomarkers N-terminal prohormone brain-type natriuretic peptide (NT-proBNP) or brain-type natriuretic peptide (BNP) were tested for the subjects. When both tests were available, NT-proBNP was chosen over BNP and the same test was performed at every required visit.

End point type	Secondary
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End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	6 <sup>[56]</sup>			
Units: Picograms per milliliter (pg/mL)				
arithmetic mean (standard deviation)	7.45 ( $\pm$ 10.65)			

Notes:

[56] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in quality of life evaluated by SF-10 questionnaire from baseline

End point title	Change in quality of life evaluated by SF-10 questionnaire from
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## End point description:

SF-10 is a parent-completed health survey for children that contains 10 questions adapted from the Child Health Questionnaire. It is scored to produce physical and psychosocial health summary measures. Each of the 10 questions responses is scored with a point value from 1 to 6 (1 is the worst possible condition and 6 is the best possible condition). The SF-10 physical and psychosocial measures are scored such that higher scores indicate more favorable functioning.

## End point type

Secondary

## End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

End point values	Riociguat $\geq 6$ to $<18$ years			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[57]</sup>			
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Physical summary score	5.79 ( $\pm$ 12.46)			
Psychosocial summary score	1.10 ( $\pm$ 6.85)			

Notes:

[57] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in quality of life evaluated by PedsQL scale

## End point title

Change in quality of life evaluated by PedsQL scale

## End point description:

The PedsQL Generic Core Scales were designed to measure health-related quality of life in children and adolescents. It has 4 dimensions: physical functioning, emotional functioning, social functioning and school functioning. 3 Summary Scores of PedsQL were calculated from the scales including total scale score (23 questions), physical health summary score (physical functioning, 8 questions) and psychosocial health summary score (emotional, social and school functioning, 15 questions). Responses of the questions are transformed to a 0-100 scale. Higher scores indicate better quality of life.

## End point type

Secondary

## End point timeframe:

Baseline and Week 24 (plus/minus 5 days)

End point values	Riociguat $\geq 6$ to $<18$ years			
Subject group type	Reporting group			
Number of subjects analysed	19 <sup>[58]</sup>			
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Total scale score	3.49 ( $\pm$ 10.81)			
Physical health summary score	4.28 ( $\pm$ 13.51)			
Psychosocial health summary score	3.07 ( $\pm$ 11.21)			

Notes:

[58] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with clinical worsening

End point title	Number of subjects with clinical worsening
End point description: Clinical worsening was defined as: hospitalization for right heart failure, death, lung transplantation, Pott's anastomosis and atrioseptostomy, worsening of PAH symptoms, which must include either an increase in WHO functional class or appearance/worsening symptoms of right heart failure and need for additional PAH therapy.	
End point type	Secondary
End point timeframe: Up to Week 24 (plus/minus 5 days)	

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	24 <sup>[59]</sup>			
Units: Subjects	2			

Notes:

[59] - SAF

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in estimated right atrial pressure from baseline

End point title	Change in estimated right atrial pressure from baseline
End point description: Estimated right atrial pressure was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[60]</sup>			
Units: millimetre of mercury (mmHg)				
arithmetic mean (standard deviation)	-0.6 ( $\pm$ 3.6)			

Notes:

[60] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in left ventricular eccentricity index from baseline

End point title	Change in left ventricular eccentricity index from baseline
End point description:	Left ventricular eccentricity index was measured by echocardiography.
End point type	Secondary
End point timeframe:	Baseline and Week 24 (plus/minus 5 days)

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	15 <sup>[61]</sup>			
Units: Index				
arithmetic mean (standard deviation)	0.002 ( $\pm$ 0.907)			

Notes:

[61] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in pericardial effusion from baseline

End point title	Change in pericardial effusion from baseline
End point description:	Pericardial effusion was measured by echocardiography. "99999" denotes that value was not calculated due to very low number of subjects.
End point type	Secondary
End point timeframe:	Baseline and Week 24 (plus/minus 5 days)

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	1 <sup>[62]</sup>			
Units: Millimeter (mm)				
arithmetic mean (standard deviation)	1.040 ( $\pm$ 99999)			

Notes:

[62] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in pulmonary artery acceleration time from baseline

End point title	Change in pulmonary artery acceleration time from baseline
End point description: Pulmonary artery acceleration time was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	15 <sup>[63]</sup>			
Units: Millisecond (msec)				
arithmetic mean (standard deviation)	-7.777 ( $\pm$ 35.898)			

Notes:

[63] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right ventricular cardiac index from baseline

End point title	Change in right ventricular cardiac index from baseline
End point description: Right ventricular cardiac index was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	13 <sup>[64]</sup>			
Units: Liter/minute/square meter (L/min/m <sup>2</sup> )				
arithmetic mean (standard deviation)	0.188 ( $\pm$ 2.094)			

Notes:

[64] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right ventricular cardiac output from baseline

End point title	Change in right ventricular cardiac output from baseline
End point description:	Right ventricular cardiac output was measured by echocardiography.
End point type	Secondary
End point timeframe:	Baseline and Week 24 (plus/minus 5 days)

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	13 <sup>[65]</sup>			
Units: Liter per minute (L/min)				
arithmetic mean (standard deviation)	0.457 ( $\pm$ 3.066)			

Notes:

[65] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right atrial diastolic area from baseline

End point title	Change in right atrial diastolic area from baseline
End point description:	Right atrial diastolic area was measured by echocardiography.
End point type	Secondary
End point timeframe:	Baseline and Week 24 (plus/minus 5 days)

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[66]</sup>			
Units: Square centimeter (cm <sup>2</sup> )				
arithmetic mean (standard deviation)	1.078 ( $\pm$ 3.330)			

Notes:

[66] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right atrial diastolic area index from baseline

End point title	Change in right atrial diastolic area index from baseline
End point description: Right atrial diastolic area index was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[67]</sup>			
Units: Index				
arithmetic mean (standard deviation)	0.643 ( $\pm$ 2.314)			

Notes:

[67] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right atrial systolic area from baseline

End point title	Change in right atrial systolic area from baseline
End point description: Right atrial systolic area was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[68]</sup>			
Units: Square centimeter (cm <sup>2</sup> )				
arithmetic mean (standard deviation)	0.424 ( $\pm$ 3.758)			

Notes:

[68] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right atrial systolic area index from baseline

End point title	Change in right atrial systolic area index from baseline
End point description: Right atrial systolic area index was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[69]</sup>			
Units: Index				
arithmetic mean (standard deviation)	0.329 ( $\pm$ 2.417)			

Notes:

[69] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right ventricular fractional area change from baseline

End point title	Change in right ventricular fractional area change from baseline
End point description: Right ventricular fractional area change was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	



<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	15 <sup>[70]</sup>			
Units: Percentage (%)				
arithmetic mean (standard deviation)	-4.3 ( $\pm$ 7.3)			

Notes:

[70] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right ventricular diastolic area from baseline

End point title	Change in right ventricular diastolic area from baseline
End point description: Right ventricular diastolic area was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	15 <sup>[71]</sup>			
Units: Square centimeter (cm <sup>2</sup> )				
arithmetic mean (standard deviation)	0.618 ( $\pm$ 4.519)			

Notes:

[71] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right ventricular diastolic area index from baseline

End point title	Change in right ventricular diastolic area index from baseline
End point description: Right ventricular diastolic area index was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	15 <sup>[72]</sup>			
Units: Index				
arithmetic mean (standard deviation)	0.451 ( $\pm$ 3.562)			

Notes:

[72] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right ventricular systolic area from baseline

End point title	Change in right ventricular systolic area from baseline
End point description: Right ventricular systolic area was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	15 <sup>[73]</sup>			
Units: Square centimeter (cm <sup>2</sup> )				
arithmetic mean (standard deviation)	1.725 ( $\pm$ 3.847)			

Notes:

[73] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in right ventricular systolic area index from baseline

End point title	Change in right ventricular systolic area index from baseline
End point description: Right ventricular systolic area index was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	15 <sup>[74]</sup>			
Units: Index				
arithmetic mean (standard deviation)	1.244 ( $\pm$ 3.277)			

Notes:

[74] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in systolic pulmonary artery pressure from baseline

End point title	Change in systolic pulmonary artery pressure from baseline
End point description: Systolic pulmonary artery pressure was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	3 <sup>[75]</sup>			
Units: millimetre of mercury (mmHg)				
arithmetic mean (standard deviation)	5.7 ( $\pm$ 49.0)			

Notes:

[75] - Subjects in SAF with evaluable data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in tricuspid annular plane systolic excursion from baseline

End point title	Change in tricuspid annular plane systolic excursion from baseline
End point description: Tricuspid annular plane systolic excursion (TAPSE) was measured by echocardiography.	
End point type	Secondary
End point timeframe: Baseline and Week 24 (plus/minus 5 days)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	15 <sup>[76]</sup>			
Units: Millimeter (mm)				
arithmetic mean (standard deviation)	-1.27 ( $\pm$ 3.87)			

Notes:

[76] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in tricuspid regurgitation peak velocity from baseline

End point title	Change in tricuspid regurgitation peak velocity from baseline
End point description:	Ttricuspid regurgitation peak velocity was measured by echocardiography.
End point type	Secondary
End point timeframe:	Baseline and Week 24 (plus/minus 5 days)

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[77]</sup>			
Units: Meter/second (m/s)				
arithmetic mean (standard deviation)	-0.085 ( $\pm$ 0.726)			

Notes:

[77] - Subjects in SAF with evaluable data

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Taste and texture (Questions 1 to 4) of the oral suspension of Riociguat at Week 0

End point title	Taste and texture (Questions 1 to 4) of the oral suspension of Riociguat at Week 0
End point description:	To assess the taste and texture of oral suspension of Riociguat, a questionnaire including 7 questions was used. Responses to Questions 1 to 4 were reported in this endpoint. Questions 1 and 2 were asked before the subjects received the suspension; whereas questions 3 and 4 were asked right after administration of the suspension. Subjects were asked to respond to the 4 questions as "yes" (= positive answer), "I do not know/unsure" (= indifferent answer) or "No" (= negative answer).
End point type	Other pre-specified
End point timeframe:	At the beginning of the treatment (Week 0)

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[78]</sup>			
Units: Subjects				
Like the look of the drink - Yes	4			
Like the look of the drink - No	2			
Like the look of the drink - Unsure	9			
Like the look of the drink - Missing	1			
Like the smell of the drink - Yes	4			
Like the smell of the drink - No	2			
Like the smell of the drink - Unsure	9			
Like the smell of the drink - Missing	1			
Like the drink - Yes	9			
Like the drink - No	1			
Like the drink - Unsure	5			
Like the drink - Missing	1			
Like to drink again - Yes	12			
Like to drink again - No	0			
Like to drink again - Unsure	3			
Like to drink again - Missing	1			

Notes:

[78] - Subjects in SAF with assessment

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Taste and texture (Questions 1 to 4) the oral suspension of Riociguat at Week 24

End point title	Taste and texture (Questions 1 to 4) the oral suspension of Riociguat at Week 24
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End point description:

To assess the taste and texture of oral suspension of Riociguat, a questionnaire including 7 questions was used. Responses to Questions 1 to 4 were reported in this endpoint. Questions 1 and 2 were asked before the subjects received the suspension; whereas questions 3 and 4 were asked right after administration of the suspension. Subjects were asked to respond to the 4 questions as "yes" (= positive answer), "I do not know/unsure" (= indifferent answer) or "No" (= negative answer).

End point type	Other pre-specified
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End point timeframe:

Week 24 (plus/minus 5 days)

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[79]</sup>			
Units: Subjects				
Like the look of the drink - Yes	6			
Like the look of the drink - No	1			
Like the look of the drink - Unsure	6			
Like the look of the drink - Missing	1			
Like the smell of the drink - Yes	7			
Like the smell of the drink - No	2			
Like the smell of the drink - Unsure	4			
Like the smell of the drink - Missing	1			
Like the drink - Yes	6			
Like the drink - No	4			
Like the drink - Unsure	3			
Like the drink - Missing	1			
Like to drink again - Yes	6			
Like to drink again - No	3			
Like to drink again - Unsure	4			
Like to drink again - Missing	1			

Notes:

[79] - Subjects in SAF with assessment

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Taste and texture (Question 5) of the oral suspension of Riociguat at Week 0

End point title	Taste and texture (Question 5) of the oral suspension of Riociguat at Week 0
End point description:	
To assess the taste and texture of oral suspension of Riociguat, a questionnaire including 7 questions was used. Number of subjects per responses to Questions 5 "Taste of the drink" was reported in this endpoint. Question 5 was only asked to subjects who answered "No" to Question 3 "Did you like the drink" or Question 4 "Would you like to drink this again". Subjects were asked to answer "yes", "I do not know/unsure" or "No" to each taste including "sweet, sour, bitter, salty, disgusting and fruity".	
End point type	Other pre-specified
End point timeframe:	
At the beginning of the treatment (Week 0)	

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	1 <sup>[80]</sup>			
Units: Subjects				
Sweet - Yes	1			
Sour - No	1			
Bitter - No	1			
Salty - No	1			

Disgusting - No	1			
Fruity - Yes	1			

Notes:

[80] - Subjects in SAF with assessment

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Taste and texture (Question 5) of the oral suspension of Riociguat at Week 24

End point title	Taste and texture (Question 5) of the oral suspension of Riociguat at Week 24
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End point description:

To assess the taste and texture of oral suspension of Riociguat, a questionnaire including 7 questions was used. Number of subjects per responses to Questions 5 "Taste of the drink" was reported in this endpoint. Question 5 was only asked to subjects who answered "No" to Question 3 "Did you like the drink" or Question 4 "Would you like to drink this again". Subjects were asked to answer "yes", "I do not know/unsure" or "No" to each taste including "sweet, sour, bitter, salty, disgusting and fruity".

End point type	Other pre-specified
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End point timeframe:

Week 24 (plus/minus 5 days)

<b>End point values</b>	Riociguat $\geq 6$ to $<18$ years			
Subject group type	Reporting group			
Number of subjects analysed	4 <sup>[81]</sup>			
Units: Subjects				
Sweet - Yes	2			
Sweet - No	1			
Sweet - Unsure	1			
Sour - Yes	1			
Sour - No	3			
Bitter - No	3			
Bitter - Unsure	1			
Salty - No	4			
Disgusting - Yes	4			
Fruity - No	2			
Fruity - Unsure	2			

Notes:

[81] - Subjects in SAF with assessment

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Taste and texture (Question 6) of the oral suspension of Riociguat at Week 0

End point title	Taste and texture (Question 6) of the oral suspension of
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## End point description:

To assess the taste and texture of oral suspension of Riociguat, a questionnaire including 7 questions was used. Number of subjects per responses to Questions 6 "Drink feels in mouth" was reported in this endpoint. Question 6 was only asked to subjects who answered "No" to Question 3 "Did you like the drink" or Question 4 "Would you like to drink this again". Subjects were asked to answer "yes", "I do not know/unsure" or "No" to each feeling including "like sand, sticky, gooey, slimy, creamy".

## End point type

Other pre-specified

## End point timeframe:

At the beginning of the treatment (Week 0)

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	1 <sup>[82]</sup>			
Units: Subjects				
Like Sand - No	1			
Sticky - No	1			
Gooey - No	1			
Slimy - No	1			
Creamy - No	1			

Notes:

[82] - Subjects in SAF with assessment

## Statistical analyses

No statistical analyses for this end point

**Other pre-specified: Taste and texture (Question 6) of the oral suspension of Riociguat in mouth at Week 24**

## End point title

Taste and texture (Question 6) of the oral suspension of Riociguat in mouth at Week 24

## End point description:

To assess the taste and texture of oral suspension of Riociguat, a questionnaire including 7 questions was used. Number of subjects per responses to Questions 6 "Drink feels in mouth" was reported in this endpoint. Question 6 was only asked to subjects who answered "No" to Question 3 "Did you like the drink" or Question 4 "Would you like to drink this again". Subjects were asked to answer "yes", "I do not know/unsure" or "No" to each feeling including "like sand, sticky, gooey, slimy, creamy".

## End point type

Other pre-specified

## End point timeframe:

Week 24 (plus/minus 5 days)

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	4 <sup>[83]</sup>			
Units: Subjects				
Like sand - No	3			
Like sand - Unsure	1			



Sticky - Yes	1			
Sticky - No	3			
Goosey - No	3			
Goosey - Unsure	1			
Slimy - Yes	2			
Slimy - No	1			
Slimy - Unsure	1			
Creamy - No	2			
Creamy - Unsure	2			

Notes:

[83] - Subjects in SAF with assessment

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Taste and texture (Question 7) of the oral suspension of Riociguat in mouth at Week 0

End point title	Taste and texture (Question 7) of the oral suspension of Riociguat in mouth at Week 0
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End point description:

To assess the taste and texture of oral suspension of Riociguat, a questionnaire including 7 questions was used. Number of subjects per responses to Questions 7 "Did you like the taste after swallowing" was reported in this endpoint. Question 7 was only asked to subjects who answered "No" to Question 3 "Did you like the drink" or Question 4 "Would you like to drink this again". Subjects were asked to respond as "yes" (= positive answer), "I do not know/unsure"(= indifferent answer) or "No" (= negative answer).

End point type	Other pre-specified
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End point timeframe:

At the beginning of the treatment (Week 0)

<b>End point values</b>	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	1 <sup>[84]</sup>			
Units: Subjects				
Like the taste after swallowing - Yes	1			
Like the taste after swallowing - No	0			
Like the taste after swallowing - Unsure	0			

Notes:

[84] - Subjects in SAF with assessment

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Taste and texture (Question 7) of the oral suspension of Riociguat in mouth at Week 24

End point title	Taste and texture (Question 7) of the oral suspension of Riociguat in mouth at Week 24
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End point description:

To assess the taste and texture of oral suspension of Riociguat, a questionnaire including 7 questions was used. Number of subjects per responses to Questions 7 "Did you like the taste after swallowing" was reported in this endpoint. Question 7 was only asked to subjects who answered "No" to Question 3 "Did you like the drink" or Question 4 "Would you like to drink this again". Subjects were asked to respond as "yes" (= positive answer), "I do not know/unsure"(= indifferent answer) or "No" (= negative answer).

End point type	Other pre-specified
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End point timeframe:

Week 24 (plus/minus 5 days)

End point values	Riociguat >=6 to <18 years			
Subject group type	Reporting group			
Number of subjects analysed	4 <sup>[85]</sup>			
Units: Subjects				
Like the taste after swallowing - Yes	0			
Like the taste after swallowing - No	3			
Like the taste after swallowing - Unsure	1			

Notes:

[85] - Subjects in SAF with assessment

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Expression assessment on the taste and texture of oral suspension of Riociguat - Week 0

End point title	Expression assessment on the taste and texture of oral suspension of Riociguat - Week 0
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End point description:

The facial expression of the subjects concerning appearance, smell and taste of the suspension of Riociguat was captured by the investigators as "comfortable", "indifferent" and "displeased".

End point type	Other pre-specified
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End point timeframe:

At the beginning of the treatment (Week 0)

End point values	Riociguat >=6 to <18 years			
Subject group type	Reporting group			
Number of subjects analysed	16 <sup>[86]</sup>			
Units: Subjects				
Comfortable	7			
Indifferent	8			
Displeased	0			
Missing	1			

Notes:

[86] - Subjects in SAF with assessment

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Expression assessment on the taste and texture of oral suspension of Riociguat - Week 24

End point title	Expression assessment on the taste and texture of oral suspension of Riociguat - Week 24
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End point description:

The facial expression of the subjects concerning appearance, smell and taste of the suspension of Riociguat was captured by the investigators as "comfortable", "indifferent" and "displeased".

End point type	Other pre-specified
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End point timeframe:

Week 24 (plus/minus 5 days)

End point values	Riociguat $\geq 6$ to $< 18$ years			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[87]</sup>			
Units: Subjects				
Comfortable	6			
Indifferent	5			
Displeased	2			
Missing	1			

Notes:

[87] - Subjects in SAF with assessment

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study drug up to 2 days after the last dose of study drug in the main study part, up to 24 weeks plus/minus 5 days.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Riociguat $\geq 6$ to $< 18$ years
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Reporting group description:

Subjects with age  $\geq 6$  to  $< 18$  years received riociguat up to 2.5 mg three times a day (titration between 0.5 mg and 2.5 mg) for up to 8 weeks during the individual dose titration (IDT) phase, and followed with the last dose administered in the IDT phase for up to 16 weeks during the maintenance phase. Down-titration of the dose for safety reasons was allowed at any time.

Serious adverse events	Riociguat $\geq 6$ to $< 18$ years		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 24 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Right ventricular failure			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pain of skin			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin swelling			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Vascular device infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Riociguat $\geq 6$ to $< 18$ years		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 24 (62.50%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	11		

General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Gastrointestinal disorders Abdominal pain alternative assessment type: Systematic subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 5		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)  Nasopharyngitis subjects affected / exposed occurrences (all)  Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2  4 / 24 (16.67%) 7  4 / 24 (16.67%) 4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2015	Amendment 3 introduced the following changes: The wording describing the LTE part of the study was changed ("study" was replaced with "phase" and "optional" was added) to clarify that the subjects can volunteer to participate in the LTE, which is a part of this study. Clarification of primary completion and end of study. Pharmacodynamics was deleted from primary objective. Addition of a safety follow up visit for subjects participating in the LTE phase.
31 May 2016	Amendment 5 introduced the following changes: The collection of the following parameters: GGT, UA, T-Bil, Alb, Na, K, Ca, and P at visit 0, 5 and 9 were added for safety reasons. Addition of the statement that all laboratory parameters are recorded to the eCRF when obtained as medically required according to a local package insert of bosentan or medical practice at any time. The collection of RHC parameters in the eCRF was included. The echocardiography parameter of right heart dimensions was introduced in the study and all Echo parameters were listed as main secondary variables. Central reading of the echocardiographic parameters were added. Taste and texture was downgraded from secondary efficacy endpoint to other endpoint.
09 January 2017	Amendment 6 introduced the following changes: A new exclusion criterion "patients with pulmonary hypertension associated with idiopathic interstitial pneumonia (PH-IIP)" was added. The study population was broadened to include patients treated with PAH medications including ERA (besides bosentan), PCAs or combination of these. Parents and patients questionnaires were added. Exclusion criteria were changed regarding the pretreatment with PDE5 inhibitors. Clarification that pretreatment with PDE5i was allowed but up to 3 three days prior to start of riociguat treatment (Visit 1) was added. BNP was added as an alternative for NT-proBNP.
13 March 2018	Amendment 9 introduced the following changes: The inclusion of patients with ostium secundum atrial septal defect $\leq 1$ cm without hemodynamic alterations was allowed. The inclusion of patients with patent foramen ovale $\leq 1$ cm was allowed. The definition of "effective" methods was added in inclusion criterion 7.
23 August 2019	Amendment 12 introduced the following changes: Description of the pregnancy testing (to be performed in 4-weekly intervals starting at Visit 1 until 4 weeks after the patient stopped intake of study drug) in the optional LTE phase was added. The conditions for transitioning into the optional LTE phase was clarified. The dosing recommendation for patients with body weight $\geq 12$ to $<14$ kg was added.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The results should be interpreted with caution due to the limited number of subjects. The number of subjects with clinical worsening events was too low to produce valid Kaplan-Meier estimates for the time to clinical worsening.

Notes:

