



## Clinical trial results:

**Relative bioavailability and food effect study of two oral liquid formulations in comparison to a 1 mg tablet of riociguat to characterize its pharmacokinetic properties in healthy male and female adult subjects in a randomized, open label, 5 fold crossover design**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

EudraCT number	2011-001893-24
Trial protocol	DE
Global end of trial date	21 May 2012

## Results information

Result version number	v2 (current)
This version publication date	24 July 2016
First version publication date	05 July 2015
Version creation reason	<ul style="list-style-type: none"><li>Correction of full data set</li><li>Review of results set after re-introduction of EudraCT</li></ul>

## Trial information

### Trial identification

Sponsor protocol code	BAY63-2521/14986
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01489488
WHO universal trial number (UTN)	-

Notes:

## Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, D-51368, Germany,
Public contact	Bayer Clinical Trials Contact, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Bayer Clinical Trials Contact, 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?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 May 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 May 2012
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of the study were to determine the oral bioavailability of the liquid formulations intended for pediatric use and any potential food effects in healthy adults.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects 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: -

Evidence for comparator: -

Actual start date of recruitment	09 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at a single study center in Germany in healthy adult subjects between 09 January 2012 (first subject first visit) and 03 April 2012 (last subject last visit).

### Pre-assignment

Screening details:

Out of a total of 32 randomized subjects, 30 subjects were treated with five riociguat doses, once in a crossover fashion during the respective intervention periods (1st, 2nd, 3rd, 4th, and 5th). The reasons for 2 'randomized but not treated' subjects: one subject withdrew consent and the other revealed protocol violation.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment sequence A-B-C-D-E

Arm description:

Single oral dose of 2.4 milligram (mg) riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg per milliliter [mg/mL], i.e. 16 mL) under fasting conditions (Treatment A) in the 1st intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL) under fed conditions (Treatment B) in the 2nd intervention period; followed by a single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL) under fasting conditions (Treatment C) in the 3rd intervention period; followed by single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL) under fasting conditions (Treatment D) in the 4th intervention period; and then single oral dose of riociguat immediate release (IR) tablet 1 mg under fasting conditions (Treatment E) in the 5th intervention period.

A wash-out phase of at least 5 days was maintained between treatments.

Arm type	Experimental
Investigational medicinal product name	Riociguat
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Suspension and effervescent granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Treatment A: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions.

Treatment B: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions.

Treatment C: Single oral dose of 0.3 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions.

Treatment D: Single oral dose of 0.15 mg riociguat (BAY63-2521) as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions.

Investigational medicinal product name	Riociguat, IR Tablet
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment E: Single oral dose of riociguat (BAY63-2521) IR tablet 1 mg, under fasting conditions.

<b>Arm title</b>	Treatment sequence B-C-E-A-D
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**Arm description:**

Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the first intervention period; followed by single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the second intervention period; followed by single oral dose of riociguat IR tablet 1 mg, under fasting conditions (Treatment E) in the third intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the fourth intervention period; and then single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the fifth intervention period. A wash-out phase of at least 5 days was maintained between treatments.

Arm type	Experimental
Investigational medicinal product name	Riociguat, IR Tablet
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

Treatment E: Single oral dose of riociguat (BAY63-2521) IR tablet 1 mg, under fasting conditions.

Investigational medicinal product name	Riociguat
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Suspension and effervescent granules for oral suspension
Routes of administration	Oral use

**Dosage and administration details:**

Treatment A: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions.

Treatment B: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions.

Treatment C: Single oral dose of 0.3 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions.

Treatment D: Single oral dose of 0.15 mg riociguat (BAY63-2521) as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions.

<b>Arm title</b>	Treatment sequence C-E-D-B-A
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**Arm description:**

Single oral dose of 0.3 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the first intervention period; followed by single oral dose of riociguat IR tablet 1 mg, under fasting conditions (Treatment E) in the second intervention period; followed by single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the third intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the fourth intervention period; and then single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the fifth intervention period. A wash-out phase of at least 5 days was maintained between treatments.

Arm type	Experimental
Investigational medicinal product name	Riociguat
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Suspension and effervescent granules for oral suspension
Routes of administration	Oral use

**Dosage and administration details:**

Treatment A: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions.

Treatment B: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions.

Treatment C: Single oral dose of 0.3 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions.

Treatment D: Single oral dose of 0.15 mg riociguat (BAY63-2521) as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions.

Investigational medicinal product name	Riociguat, IR Tablet
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment E: Single oral dose of riociguat (BAY63-2521) IR tablet 1 mg, under fasting conditions.

<b>Arm title</b>	Treatment sequence D-A-B-E-C
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Arm description:

Single oral dose of 0.15 mg riociguat (BAY63-2521) as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the first intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the second intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the third intervention period; followed by single oral dose of riociguat IR tablet 1 mg, under fasting conditions (Treatment E) in the fourth intervention period; and then single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the fifth intervention period. A wash-out phase of at least 5 days was maintained between treatments.

Arm type	Experimental
Investigational medicinal product name	Riociguat
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Suspension and effervescent granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Treatment A: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions.

Treatment B: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions.

Treatment C: Single oral dose of 0.3 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions.

Treatment D: Single oral dose of 0.15 mg riociguat (BAY63-2521) as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions.

Investigational medicinal product name	Riociguat, IR Tablet
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment E: Single oral dose of riociguat (BAY63-2521) IR tablet 1 mg, under fasting conditions.

<b>Arm title</b>	Treatment sequence E-D-A-C-B
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Arm description:

Single oral dose of riociguat (BAY63-2521) IR tablet 1 mg, under fasting conditions (Treatment E) in the first intervention period; followed by single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the second intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the third intervention period; followed by single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the fourth intervention period; and then single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the fifth intervention period. A wash-out phase of at least 5 days was maintained between treatments.

Arm type	Experimental
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Investigational medicinal product name	Riociguat, IR Tablet
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment E: Single oral dose of riociguat (BAY63-2521) IR tablet 1 mg, under fasting conditions.

Investigational medicinal product name	Riociguat
Investigational medicinal product code	BAY63-2521
Other name	
Pharmaceutical forms	Suspension and effervescent granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Treatment A: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions.

Treatment B: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions.

Treatment C: Single oral dose of 0.3 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions.

Treatment D: Single oral dose of 0.15 mg riociguat (BAY63-2521) as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Treatment sequence A-B-C-D-E	Treatment sequence B-C-E-A-D	Treatment sequence C-E-D-B-A
Started	6	6	6
Received all 5 treatments	6	6	6
Completed	6	6	6

<b>Number of subjects in period 1<sup>[1]</sup></b>	Treatment sequence D-A-B-E-C	Treatment sequence E-D-A-C-B
Started	6	6
Received all 5 treatments	6	6
Completed	6	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: All enrolled subjects were not treated with study drugs. As baseline included only treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment sequence A-B-C-D-E
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#### Reporting group description:

Single oral dose of 2.4 milligram (mg) riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg per milliliter [mg/mL], i.e. 16 mL) under fasting conditions (Treatment A) in the 1st intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL) under fed conditions (Treatment B) in the 2nd intervention period; followed by a single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL) under fasting conditions (Treatment C) in the 3rd intervention period; followed by single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL) under fasting conditions (Treatment D) in the 4th intervention period; and then single oral dose of riociguat immediate release (IR) tablet 1 mg under fasting conditions (Treatment E) in the 5th intervention period.

A wash-out phase of at least 5 days was maintained between treatments.

Reporting group title	Treatment sequence B-C-E-A-D
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#### Reporting group description:

Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the first intervention period; followed by single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the second intervention period; followed by single oral dose of riociguat IR tablet 1 mg, under fasting conditions (Treatment E) in the third intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the fourth intervention period; and then single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the fifth intervention period. A wash-out phase of at least 5 days was maintained between treatments.

Reporting group title	Treatment sequence C-E-D-B-A
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#### Reporting group description:

Single oral dose of 0.3 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the first intervention period; followed by single oral dose of riociguat IR tablet 1 mg, under fasting conditions (Treatment E) in the second intervention period; followed by single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the third intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the fourth intervention period; and then single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the fifth intervention period. A wash-out phase of at least 5 days was maintained between treatments.

Reporting group title	Treatment sequence D-A-B-E-C
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#### Reporting group description:

Single oral dose of 0.15 mg riociguat (BAY63-2521) as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the first intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the second intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the third intervention period; followed by single oral dose of riociguat IR tablet 1 mg, under fasting conditions (Treatment E) in the fourth intervention period; and then single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the fifth intervention period. A wash-out phase of at least 5 days was maintained between treatments.

Reporting group title	Treatment sequence E-D-A-C-B
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#### Reporting group description:

Single oral dose of riociguat (BAY63-2521) IR tablet 1 mg, under fasting conditions (Treatment E) in the first intervention period; followed by single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the second intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the third intervention period; followed by single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the fourth intervention period; and then single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the fifth intervention period. A wash-out phase of at least 5 days was maintained



between treatments.

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Reporting group values	Treatment sequence A-B-C-D-E	Treatment sequence B-C-E-A-D	Treatment sequence C-E-D-B-A
Number of subjects	6	6	6
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	36.5	34.5	30.2
standard deviation	± 6.1	± 7.1	± 5
Gender categorical Units: Subjects			
Female	3	3	3
Male	3	3	3

Reporting group values	Treatment sequence D-A-B-E-C	Treatment sequence E-D-A-C-B	Total
Number of subjects	6	6	30
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	31.2	30.5	
standard deviation	± 5	± 8.7	-
Gender categorical Units: Subjects			
Female	3	3	15
Male	3	3	15

## End points

### End points reporting groups

Reporting group title	Treatment sequence A-B-C-D-E
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#### Reporting group description:

Single oral dose of 2.4 milligram (mg) riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg per milliliter [mg/mL], i.e. 16 mL) under fasting conditions (Treatment A) in the 1st intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL) under fed conditions (Treatment B) in the 2nd intervention period; followed by a single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL) under fasting conditions (Treatment C) in the 3rd intervention period; followed by single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL) under fasting conditions (Treatment D) in the 4th intervention period; and then single oral dose of riociguat immediate release (IR) tablet 1 mg under fasting conditions (Treatment E) in the 5th intervention period.

A wash-out phase of at least 5 days was maintained between treatments.

Reporting group title	Treatment sequence B-C-E-A-D
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#### Reporting group description:

Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the first intervention period; followed by single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the second intervention period; followed by single oral dose of riociguat IR tablet 1 mg, under fasting conditions (Treatment E) in the third intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the fourth intervention period; and then single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the fifth intervention period. A wash-out phase of at least 5 days was maintained between treatments.

Reporting group title	Treatment sequence C-E-D-B-A
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#### Reporting group description:

Single oral dose of 0.3 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the first intervention period; followed by single oral dose of riociguat IR tablet 1 mg, under fasting conditions (Treatment E) in the second intervention period; followed by single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the third intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the fourth intervention period; and then single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the fifth intervention period. A wash-out phase of at least 5 days was maintained between treatments.

Reporting group title	Treatment sequence D-A-B-E-C
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#### Reporting group description:

Single oral dose of 0.15 mg riociguat (BAY63-2521) as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the first intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the second intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the third intervention period; followed by single oral dose of riociguat IR tablet 1 mg, under fasting conditions (Treatment E) in the fourth intervention period; and then single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the fifth intervention period. A wash-out phase of at least 5 days was maintained between treatments.

Reporting group title	Treatment sequence E-D-A-C-B
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#### Reporting group description:

Single oral dose of riociguat (BAY63-2521) IR tablet 1 mg, under fasting conditions (Treatment E) in the first intervention period; followed by single oral dose of 0.15 mg riociguat as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions (Treatment D) in the second intervention period; followed by single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions (Treatment A) in the third intervention period; followed by single oral dose of 0.3 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions (Treatment C) in the fourth intervention period; and then single oral dose of 2.4 mg riociguat as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions (Treatment B) in the fifth intervention period. A wash-out phase of at least 5 days was maintained

between treatments.

Subject analysis set title	Riociguat (BAY63-2521) 2.4 mg suspension, fasted
Subject analysis set type	Sub-group analysis
Subject analysis set description: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions in any intervention period.	
Subject analysis set title	Riociguat (BAY63-2521) 2.4 mg suspension, fed
Subject analysis set type	Sub-group analysis
Subject analysis set description: Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions in any intervention period.	
Subject analysis set title	Riociguat (BAY63-2521) 0.3 mg suspension, fasted
Subject analysis set type	Sub-group analysis
Subject analysis set description: Single oral dose of 0.3 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions in any intervention period.	
Subject analysis set title	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject analysis set type	Sub-group analysis
Subject analysis set description: Single oral dose of 0.15 mg riociguat (BAY63-2521) as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions in any intervention period.	
Subject analysis set title	Riociguat (BAY63-2521) 1 mg IR tablet, fasted
Subject analysis set type	Sub-group analysis
Subject analysis set description: Single oral dose of riociguat (BAY63-2521) IR tablet 1 mg, under fasting conditions in any intervention period.	
Subject analysis set title	Pharmacokinetic (PK) analysis set (PKS)
Subject analysis set type	Sub-group analysis
Subject analysis set description: PKS included all subjects who completed all five periods of this trial with at least one valid PK profile.	

**Primary: Area Under the Concentration Versus Time Curve From Zero to Infinity (AUC) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose**

End point title	Area Under the Concentration Versus Time Curve From Zero to Infinity (AUC) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose <sup>[1]</sup>
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End point description:

AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. AUC is defined as area under concentration versus time curve from time 0 (pre-dose) to extrapolated infinite time. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Primary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[2]</sup>	29 <sup>[3]</sup>	29 <sup>[4]</sup>	29 <sup>[5]</sup>
Units: microgram*hour per liter (mcg*h/L)				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 27, 25, 29)	780.599 (± 48.68)	662.469 (± 45.03)	91.005 (± 43.4)	46.828 (± 59.49)
Analyte M1 (BAY60-4552) (N=29, 28, 16, 8, 29)	555.013 (± 38.14)	513.447 (± 40.62)	77.78 (± 39.39)	45.735 (± 22)

Notes:

[2] - PKS

[3] - PKS

[4] - PKS

[5] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[6]</sup>			
Units: microgram*hour per liter (mcg*h/L)				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 27, 25, 29)	311.162 (± 46.41)			
Analyte M1 (BAY60-4552) (N=29, 28, 16, 8, 29)	237.386 (± 31.93)			

Notes:

[6] - PKS

## Statistical analyses

No statistical analyses for this end point

## Primary: Maximum Observed Drug Concentration (C<sub>max</sub>) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose

End point title	Maximum Observed Drug Concentration (C <sub>max</sub> ) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose <sup>[7]</sup>
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End point description:

C<sub>max</sub> refers to the highest measured drug concentration which is obtained by collecting a series of plasma samples and measuring the concentrations of drug in each sample. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Primary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[8]</sup>	29 <sup>[9]</sup>	29 <sup>[10]</sup>	29 <sup>[11]</sup>
Units: microgram(s)/liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	78.0386 (± 31.3)	48.3776 (± 22.4)	9.7814 (± 32.93)	4.9024 (± 34.99)
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	19.44999 (± 42.64)	17.32912 (± 59.29)	2.37407 (± 53.44)	1.41143 (± 42.54)

Notes:

[8] - PKS

[9] - PKS

[10] - PKS

[11] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[12]</sup>			
Units: microgram(s)/liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	35.8421 (± 29.55)			
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	8.90839 (± 48.75)			

Notes:

[12] - PKS

## Statistical analyses

No statistical analyses for this end point

## Primary: Area Under the Concentration Versus Time Curve From Zero to Infinity Divided by Dose (AUC/D) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose

End point title	Area Under the Concentration Versus Time Curve From Zero to Infinity Divided by Dose (AUC/D) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose <sup>[13]</sup>
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End point description:

Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Primary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

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: EudraCT format does autoaddition of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[14]</sup>	29 <sup>[15]</sup>	29 <sup>[16]</sup>	29 <sup>[17]</sup>
Units: hour per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 27, 25, 29)	0.32525 (± 48.68)	0.276029 (± 45.03)	0.303351 (± 43.4)	0.312185 (± 59.49)
Analyte M1 (BAY60-4552) (N=29, 28, 16, 8, 29)	0.239183 (± 38.14)	0.22127 (± 40.62)	0.268155 (± 39.39)	0.315351 (± 22)

Notes:

[14] - PKS

[15] - PKS

[16] - PKS

[17] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[18]</sup>			
Units: hour per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 27, 25, 29)	0.311162 (± 46.41)			
Analyte M1 (BAY60-4552) (N=29, 28, 16, 8, 29)	0.245524 (± 31.93)			

Notes:

[18] - PKS

Attachments (see zip file)	AUC by D_Analyte_Statistical Analysis/AUC by AUC by D_Riociguat_Statistical Analysis/AUC by
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## Statistical analyses

No statistical analyses for this end point

## Primary: Maximum Observed Drug Concentration Adjusted by Dose (C<sub>max</sub>/D) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose

End point title	Maximum Observed Drug Concentration Adjusted by Dose (C <sub>max</sub> /D) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose <sup>[19]</sup>
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End point description:

Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Primary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

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: EudraCT format does autoaddition of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[20]</sup>	29 <sup>[21]</sup>	29 <sup>[22]</sup>	29 <sup>[23]</sup>
Units: 1 per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	0.032516 (± 31.3)	0.020157 (± 22.4)	0.032605 (± 32.93)	0.032683 (± 34.99)
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	0.008382 (± 42.64)	0.007468 (± 59.29)	0.008184 (± 53.44)	0.009732 (± 42.54)

Notes:

[20] - PKS

[21] - PKS

[22] - PKS

[23] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[24]</sup>			
Units: 1 per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	0.035842 (± 29.55)			
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	0.009213 (± 48.75)			

Notes:

[24] - PKS

Attachments (see zip file)	Cmax by D_Riociguat_Statistical Analysis/Cmax by Cmax by D_Analyte_Statistical analysis/Cmax by
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## Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Concentration Versus Time Curve From Zero to Infinity Divided by Dose per Kilogram Body Weight (AUC,norm) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose

End point title	Area Under the Concentration Versus Time Curve From Zero to Infinity Divided by Dose per Kilogram Body Weight (AUC,norm) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose
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End point description:

AUC is a measure of the plasma concentration of the drug over time. It is used to characterize drug absorption. AUCnorm is defined as AUC divided by dose per kg body weight. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[25]</sup>	29 <sup>[26]</sup>	29 <sup>[27]</sup>	29 <sup>[28]</sup>
Units: kilogram*hour per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 27, 25, 29)	21.9493 (± 52.4)	18.6276 (± 50.07)	20.73 (± 43.8)	20.9657 (± 58.75)
Analyte M1 (BAY60-4552) (N=29, 28, 16, 8, 29)	16.1411 (± 39.5)	14.8904 (± 37.9)	18.1793 (± 42.16)	20.4818 (± 22.27)

Notes:

[25] - PKS

[26] - PKS

[27] - PKS

[28] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[29]</sup>			
Units: kilogram*hour per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 27, 25, 29)	20.9986 (± 49.46)			
Analyte M1 (BAY60-4552) (N=29, 28, 16, 8, 29)	16.569 (± 33.11)			

Notes:

[29] - PKS

## Statistical analyses



**Secondary: Maximum Observed Plasma Concentration Divided by Dose per Kilogram Body Weight (C<sub>max,norm</sub>) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose**

End point title	Maximum Observed Plasma Concentration Divided by Dose per Kilogram Body Weight (C <sub>max,norm</sub> ) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose
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End point description:

C<sub>max</sub> refers to the highest measured drug concentration which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. C<sub>max,norm</sub> is defined as C<sub>max</sub> divided by dose per kg body weight. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[30]</sup>	29 <sup>[31]</sup>	29 <sup>[32]</sup>	29 <sup>[33]</sup>
Units: kilogram per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	2.19433 (± 31.33)	1.36031 (± 25.26)	2.2003 (± 29.91)	2.20556 (± 32.23)
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	0.56565 (± 38.01)	0.50397 (± 51.69)	0.55235 (± 48.93)	0.65492 (± 38.01)

Notes:

[30] - PKS

[31] - PKS

[32] - PKS

[33] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[34]</sup>			
Units: kilogram per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	2.41878 (± 28.06)			
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	0.62179 (± 43.25)			

Notes:

[34] - PKS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Reach Maximum Drug Concentration in Plasma (tmax) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose

End point title	Time to Reach Maximum Drug Concentration in Plasma (tmax) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose
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End point description:

tmax refers to the time after dosing when a drug attains its highest measurable concentration (Cmax). It is obtained by collecting a series of blood samples at various times after dosing, and measuring them for drug content. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[35]</sup>	29 <sup>[36]</sup>	29 <sup>[37]</sup>	29 <sup>[38]</sup>
Units: hour				
median (full range (min-max))				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	1.5 (0.75 to 4)	4 (3 to 12)	1 (0.5 to 3)	1 (0.5 to 4)
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	12 (4 to 36)	12 (4 to 24)	12 (2 to 12.017)	8 (2 to 12)

Notes:

[35] - PKS

[36] - PKS

[37] - PKS

[38] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[39]</sup>			
Units: hour				
median (full range (min-max))				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	1 (0.5 to 3)			
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	12 (3 to 15)			

Notes:

[39] - PKS

## Statistical analyses

**Secondary: Terminal Half Life (t<sub>1/2</sub>) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose**

End point title	Terminal Half Life (t <sub>1/2</sub> ) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose
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End point description:

Half life associated with terminal slope refers to the elimination of the drug. It is the time taken for the blood plasma concentration to reach half the concentration in the terminal phase of elimination. It is expressed in hours and derived from the terminal slope of the concentration versus time curve. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[40]</sup>	29 <sup>[41]</sup>	29 <sup>[42]</sup>	29 <sup>[43]</sup>
Units: hour				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 27, 25, 29)	9.1937 (± 41.09)	9.4197 (± 33.18)	7.8429 (± 39.25)	6.8434 (± 42.31)
Analyte M1 (BAY60-4552) (N=29, 28, 16, 8, 29)	14.5067 (± 25.81)	15.3798 (± 25.5)	16.6117 (± 36.58)	11.9893 (± 37.4)

Notes:

[40] - PKS

[41] - PKS

[42] - PKS

[43] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[44]</sup>			
Units: hour				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 27, 25, 29)	7.9115 (± 43.17)			
Analyte M1 (BAY60-4552) (N=29, 28, 16, 8, 29)	14.4817 (± 33.58)			

Notes:

[44] - PKS

**Statistical analyses**

**Secondary: Mean Residence Time (MRT) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose**

End point title	Mean Residence Time (MRT) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose
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End point description:

MRT is an average duration of the drug in the body, and is expressed in hours. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[45]</sup>	29 <sup>[46]</sup>	29 <sup>[47]</sup>	29 <sup>[48]</sup>
Units: hour				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 27, 25, 29) Analyte M1 (BAY60-4552) (N=29, 28, 16, 8, 29)	11.2926 (± 33.77) 26.426 (± 21.97)	13.3653 (± 30.97) 28.752 (± 23.5)	10.801 (± 32.53) 27 (± 30.79)	10.1044 (± 36.81) 21.019 (± 34.53)

Notes:

[45] - PKS

[46] - PKS

[47] - PKS

[48] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[49]</sup>			
Units: hour				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 27, 25, 29) Analyte M1 (BAY60-4552) (N=29, 28, 16, 8, 29)	10.3793 (± 37.6) 25.791 (± 30.32)			

Notes:

[49] - PKS

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Area Under the Concentration Versus Time Curve From Zero to Last Quantifiable Concentration (AUC[0-tlast]) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose

End point title	Area Under the Concentration Versus Time Curve From Zero to Last Quantifiable Concentration (AUC[0-tlast]) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose
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End point description:

AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. AUC(0-tlast) is defined as AUC from time zero to the last data point above the lower limit of quantification. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[50]</sup>	29 <sup>[51]</sup>	29 <sup>[52]</sup>	29 <sup>[53]</sup>
Units: mcg*h/L				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	767.0408 (± 48.98)	648.7076 (± 45.5)	81.6691 (± 45.56)	36.3776 (± 64.66)
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	524.0023 (± 38.21)	481.743 (± 40.72)	44.9594 (± 60.75)	18.7457 (± 76.77)

Notes:

[50] - PKS

[51] - PKS

[52] - PKS

[53] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[54]</sup>			
Units: mcg*h/L				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	298.7707 (± 47.65)			
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	210.8965 (± 36.71)			

Notes:

[54] - PKS

## Statistical analyses

**Secondary: Area Under the Concentration Versus Time Curve From Zero to Last Quantifiable Concentration Divided by Dose per Kilogram Body Weight (AUC[0-tlast]norm) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose**

End point title	Area Under the Concentration Versus Time Curve From Zero to Last Quantifiable Concentration Divided by Dose per Kilogram Body Weight (AUC[0-tlast]norm) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose
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End point description:

AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. AUC(0-tlast),norm is defined as AUC from time zero to the last data point above the lower limit of quantification divided by dose per kg body weight. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[55]</sup>	29 <sup>[56]</sup>	29 <sup>[57]</sup>	29 <sup>[58]</sup>
Units: kilogram*hour per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	21.568 (± 52.6)	18.2407 (± 50.5)	18.3713 (± 45.82)	16.3661 (± 66.1)
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	15.2392 (± 39.21)	14.0102 (± 37.87)	10.4602 (± 60.64)	8.6983 (± 74.02)

Notes:

[55] - PKS

[56] - PKS

[57] - PKS

[58] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[59]</sup>			
Units: kilogram*hour per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	20.1623 (± 50.4)			
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	14.7201 (± 36.54)			

Notes:

[59] - PKS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration Versus Time Curve From Zero to Last Quantifiable Concentration Divided by Dose (AUC[0-tlast]/D) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose

End point title	Area Under the Concentration Versus Time Curve From Zero to Last Quantifiable Concentration Divided by Dose (AUC[0-tlast]/D) of Riociguat and its Analyte M1 (BAY60-4552) After a Single Dose
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End point description:

AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. AUC(0-tlast)/D is defined as AUC from time zero to the last data point above the lower limit of quantification divided by dose. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In below table, "n" signifies the number of subjects that were evaluable in specified category of each group.

End point type	Secondary
----------------	-----------

End point timeframe:

0 hour (pre-dose), 15, 30, 45 minutes; 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post-dose

End point values	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29 <sup>[60]</sup>	29 <sup>[61]</sup>	29 <sup>[62]</sup>	29 <sup>[63]</sup>
Units: hour per liter				
geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	0.3196 (± 48.98)	0.270295 (± 45.5)	0.27223 (± 45.56)	0.242517 (± 64.66)
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	0.225819 (± 38.21)	0.207607 (± 40.72)	0.155002 (± 60.75)	0.129255 (± 76.77)

Notes:

[60] - PKS

[61] - PKS

[62] - PKS

[63] - PKS

End point values	Riociguat (BAY63-2521) 1 mg IR tablet, fasted			
Subject group type	Subject analysis set			
Number of subjects analysed	29 <sup>[64]</sup>			
Units: hour per liter				

geometric mean (geometric coefficient of variation)				
Riociguat (BAY63-2521) (N=29, 29, 29, 29, 29)	0.298771 ( $\pm$ 47.65)			
Analyte M1 (BAY60-4552) (N=29, 29, 29, 28, 29)	0.218126 ( $\pm$ 36.71)			

Notes:

[64] - PKS

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the date of informed consent signed until last follow-up visit

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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### Reporting groups

Reporting group title	Riociguat (BAY63-2521) 2.4 mg suspension, fasted
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Reporting group description:

Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fasting conditions in any intervention period.

Reporting group title	Riociguat (BAY63-2521) 2.4 mg suspension, fed
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Reporting group description:

Single oral dose of 2.4 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 16 mL), under fed conditions in any intervention period.

Reporting group title	Riociguat (BAY63-2521) 0.3 mg suspension, fasted
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Reporting group description:

Single oral dose of 0.3 mg riociguat (BAY63-2521) as pediatric high-concentration suspension (0.15 mg/mL, i.e. 2 mL), under fasting conditions in any intervention period.

Reporting group title	Riociguat (BAY63-2521) 0.15 mg suspension, fasted
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Reporting group description:

Single oral dose of 0.15 mg riociguat (BAY63-2521) as pediatric low-concentration suspension (0.03 mg/mL, i.e. 5 mL), under fasting conditions in any intervention period.

Reporting group title	Riociguat (BAY63-2521) 1 mg IR tablet, fasted
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Reporting group description:

Single oral dose of riociguat (BAY63-2521) IR tablet 1 mg, under fasting conditions in any intervention period.

Serious adverse events	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Riociguat (BAY63-2521) 0.15 mg suspension, fasted	Riociguat (BAY63-2521) 1 mg IR tablet, fasted	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Riociguat (BAY63-2521) 2.4 mg suspension, fasted	Riociguat (BAY63-2521) 2.4 mg suspension, fed	Riociguat (BAY63-2521) 0.3 mg suspension, fasted
Total subjects affected by non-serious adverse events subjects affected / exposed	20 / 30 (66.67%)	19 / 30 (63.33%)	18 / 30 (60.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Orthostatic hypotension			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Discomfort			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	3 / 30 (10.00%)	3 / 30 (10.00%)	2 / 30 (6.67%)
occurrences (all)	3	3	3
Feeling hot			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Catheter site pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast			

disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Nasal obstruction			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	2 / 30 (6.67%)
occurrences (all)	1	1	2
Oropharyngeal pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	1 / 30 (3.33%)
occurrences (all)	2	3	1
Headache			
subjects affected / exposed	14 / 30 (46.67%)	14 / 30 (46.67%)	14 / 30 (46.67%)
occurrences (all)	16	16	18
Sinus headache			

subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 5	2 / 30 (6.67%) 2	0 / 30 (0.00%) 0
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Eye disorders Abnormal sensation in eye subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Erythema of eyelid subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Eye pain subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Gastrointestinal disorders Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 2	0 / 30 (0.00%) 0
Gingival bleeding subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 4	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1
Toothache			

subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Proteinuria subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Myalgia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Tooth infection subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Oral herpes subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	2 / 30 (6.67%) 2

<b>Non-serious adverse events</b>	Riociguat (BAY63-2521) 0.15 mg suspension, fasted	Riociguat (BAY63-2521) 1 mg IR tablet, fasted	
Total subjects affected by non-serious adverse events subjects affected / exposed	17 / 30 (56.67%)	17 / 30 (56.67%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Discomfort			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 30 (6.67%)	4 / 30 (13.33%)	
occurrences (all)	2	4	
Feeling hot			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Catheter site pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Nasal obstruction			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	10 / 30 (33.33%)	10 / 30 (33.33%)	
occurrences (all)	12	11	
Sinus headache			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
Eye disorders			
Abnormal sensation in eye subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	2 / 30 (6.67%) 2	
Erythema of eyelid subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
Eye pain subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Gastrointestinal disorders			
Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
Gingival bleeding subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
Vomiting			



subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Proteinuria			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

Occurrence of "±" in relation with geometric CV(%) is auto-generated and cannot be deleted. Decimal places were automatically truncated if last decimal equals zero.
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Notes: