

**Clinical trial results:**

**Single dose, double-blind, placebo-controlled, single center, randomized cross-over study to investigate safety, tolerability, pharmacodynamics and pharmacokinetic properties of BAY-632521 after oral dosing of a 2 mg IR tablet in 20 subjects with Raynaud's phenomenon (RP)**

**Summary**

EudraCT number	2013-001899-38
Trial protocol	DE
Global end of trial date	07 November 2014

**Results information**

Result version number	v2 (current)
This version publication date	07 September 2016
First version publication date	12 June 2016
Version creation reason	<ul style="list-style-type: none"><li>• New data added to full data set</li><li>• Correction of full data set</li></ul> Bayer sponsor contact information to be updated

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

Sponsor protocol code	BAY63-2521/16787
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01926847
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
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)	No
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	07 November 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 November 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to investigate the safety, tolerability and pharmacodynamics of a single oral dose of riociguat (BAY63-2521) administered in subjects suffering from Raynaud's phenomenon.

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	07 October 2013
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: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	21
From 65 to 84 years	2
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at one study center in Germany, between 07 October 2013 (first subject first visit) and 04 June 2014 (last subject last visit).

### Pre-assignment

Screening details:

All 23 subjects who were randomized, received either placebo or riociguat treatment once, in a cross-over fashion, during the respective intervention periods.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo - Riociguat (Adempas; BAY63-2521)

Arm description:

Subjects who followed treatment sequence placebo then riociguat (Adempas; BAY63-2521) were reported. Single oral dose of matching placebo in the first intervention period; followed by single oral dose of riociguat (Adempas; BAY63-2521) 2 milligram (mg) tablet in the second intervention period. A wash-out phase of 1 week was maintained between treatments.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each subject received a single oral dose of placebo matched to riociguat (BAY63-2521) during the first intervention period of the study.

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

Dosage and administration details:

Each subject received a single oral dose of 2 mg riociguat during the first intervention period of the study.

<b>Arm title</b>	Riociguat (Adempas; BAY63-2521)-Placebo
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Arm description:

Subjects who followed treatment sequence riociguat (Adempas; BAY63-2521) then placebo were reported. Single oral dose of riociguat (Adempas; BAY63-2521) 2 mg tablet in the first intervention period; followed by single oral dose of matching placebo in the second intervention period. A wash-out phase of 1 week was maintained between treatments.

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

Dosage and administration details:

Each subject received a single oral dose of 2 mg riociguat during the first intervention period of the study.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each subject received a single oral dose of placebo matched to riociguat (BAY63-2521) during the second intervention period of the study.

<b>Number of subjects in period 1</b>	Placebo – Riociguat (Adempas; BAY63-2521)	Riociguat (Adempas; BAY63-2521)-Placebo
Started	12	11
Completed	11	11
Not completed	1	0
Consent withdrawn by subject	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo – Riociguat (Adempas; BAY63-2521)
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Reporting group description:

Subjects who followed treatment sequence placebo then riociguat (Adempas; BAY63-2521) were reported. Single oral dose of matching placebo in the first intervention period; followed by single oral dose of riociguat (Adempas; BAY63-2521) 2 milligram (mg) tablet in the second intervention period. A wash-out phase of 1 week was maintained between treatments.

Reporting group title	Riociguat (Adempas; BAY63-2521)–Placebo
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Reporting group description:

Subjects who followed treatment sequence riociguat (Adempas; BAY63-2521) then placebo were reported. Single oral dose of riociguat (Adempas; BAY63-2521) 2 mg tablet in the first intervention period; followed by single oral dose of matching placebo in the second intervention period. A wash-out phase of 1 week was maintained between treatments.

Reporting group values	Placebo – Riociguat (Adempas; BAY63-2521)	Riociguat (Adempas; BAY63-2521)–Placebo	Total
Number of subjects	12	11	23
Age Categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	50.9 ± 15.5	50.8 ± 11.1	-
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Gender Categorical Units: Subjects			
Male	1	4	5
Female	11	7	18

Medical Grouping			
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All subjects included in the study had a confirmed medical history of Raynaud's phenomenon at screening. Subjects with diffuse cutaneous Scleroderma (SSc) were over sampled in order to enrich the study with the most fibrotic type of Scleroderma.

Units: Subjects			
Diffuse cutaneous SSc	6	6	12
Idiopathic primary	1	2	3
Limited cutaneous SSc	3	2	5
SSc overlap syndrome	2	0	2
Undifferentiated form SSc	0	1	1

## End points

### End points reporting groups

Reporting group title	Placebo – Riociguat (Adempas; BAY63-2521)
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Reporting group description:

Subjects who followed treatment sequence placebo then riociguat (Adempas; BAY63-2521) were reported. Single oral dose of matching placebo in the first intervention period; followed by single oral dose of riociguat (Adempas; BAY63-2521) 2 milligram (mg) tablet in the second intervention period. A wash-out phase of 1 week was maintained between treatments.

Reporting group title	Riociguat (Adempas; BAY63-2521)–Placebo
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Reporting group description:

Subjects who followed treatment sequence riociguat (Adempas; BAY63-2521) then placebo were reported. Single oral dose of riociguat (Adempas; BAY63-2521) 2 mg tablet in the first intervention period; followed by single oral dose of matching placebo in the second intervention period. A wash-out phase of 1 week was maintained between treatments.

Subject analysis set title	Safety analysis set (SAF)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All subjects who received one dose of the study medication were included in the safety evaluation.

Subject analysis set title	Pharmacodynamic analysis set (PDS)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All subjects who completed the study without major protocol deviations were included in the evaluation of pharmacodynamics.

Subject analysis set title	Pharmacokinetic (PK) analysis set (PKS)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All subjects who received one dose of the study medication and had a valid pharmacokinetic profile were included in the analysis of pharmacokinetic data.

Subject analysis set title	Placebo
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects received a single oral dose of matching placebo in any intervention period.

Subject analysis set title	Riociguat 2 mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects received a single oral dose of 2 mg riociguat tablet in any intervention period.

### Primary: Number of Subjects with Treatment Emergent Adverse Events (TEAE)

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAE) <sup>[1]</sup>
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End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly and another medically important serious event as judged by the investigator. Treatment-emergent adverse events were defined as adverse events/serious adverse events that started or worsened after the study drug treatment.

End point type	Primary
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End point timeframe:

From start of study drug administration until Day 7 (follow-up)

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	Placebo	Riociguat 2 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 <sup>[2]</sup>	22 <sup>[3]</sup>		
Units: Subjects	1	7		

Notes:

[2] - SAF

[3] - SAF

### Statistical analyses

No statistical analyses for this end point

### Primary: Systolic Blood Pressure (SBP) at Specified Time-points

End point title	Systolic Blood Pressure (SBP) at Specified Time-points <sup>[4]</sup>			
End point description:	SBP was measured after 10 minutes of sitting.			
End point type	Primary			
End point timeframe:	30 minutes pre-dose; 1, 2, 3 and 4 hours post-dose			

Notes:

[4] - 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	Placebo	Riociguat 2 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 <sup>[5]</sup>	22 <sup>[6]</sup>		
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
30 Minutes pre-dose	122.3 (± 14.6)	124.7 (± 14.6)		
1 Hours post-dose	124.1 (± 14.4)	120 (± 12.3)		
2 Hours post-dose	124 (± 14)	120.4 (± 12)		
3 Hours post-dose	123.8 (± 14.5)	120.9 (± 11.9)		
4 Hours post-dose	124.7 (± 14.1)	122 (± 12.6)		

Notes:

[5] - SAF

[6] - SAF

### Statistical analyses

No statistical analyses for this end point

### Primary: Diastolic Blood Pressure (DBP) at Specified Time-points

End point title	Diastolic Blood Pressure (DBP) at Specified Time-points <sup>[7]</sup>			
End point description:	DBP was measured after 10 minutes of sitting.			
End point type	Primary			

End point timeframe:

30 minutes pre-dose; 1, 2, 3 and 4 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.

<b>End point values</b>	Placebo	Riociguat 2 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 <sup>[8]</sup>	22 <sup>[9]</sup>		
Units: mmHg				
arithmetic mean (standard deviation)				
30 Minutes pre-dose	76.7 (± 8.1)	78.7 (± 7.6)		
1 Hours post-dose	77.4 (± 6.9)	77 (± 6.4)		
2 Hours post-dose	77.9 (± 6.3)	76.1 (± 5.8)		
3 Hours post-dose	76.4 (± 6.8)	76.2 (± 5.1)		
4 Hours post-dose	77.1 (± 6)	75.8 (± 5.7)		

Notes:

[8] - SAF

[9] - SAF

## Statistical analyses

No statistical analyses for this end point

## Primary: Heart Rate (HR) at Specified Time-points

End point title | Heart Rate (HR) at Specified Time-points<sup>[10]</sup>

End point description:

HR was measured after 10 minutes of sitting.

End point type | Primary

End point timeframe:

30 minutes pre-dose; 1, 2, 3 and 4 hours post-dose

Notes:

[10] - 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.

<b>End point values</b>	Placebo	Riociguat 2 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 <sup>[11]</sup>	22 <sup>[12]</sup>		
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
30 Minutes pre-dose	72.5 (± 7.1)	71.9 (± 7.2)		
1 Hours post-dose	72.9 (± 6.6)	73 (± 6.8)		
2 Hours post-dose	73.9 (± 6.1)	73.4 (± 6.5)		
3 Hours post-dose	74.3 (± 5.9)	73.8 (± 6.8)		
4 Hours post-dose	73.9 (± 6)	74.5 (± 6.9)		

Notes:

[11] - SAF

[12] - SAF

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Clinically Significant Laboratory Values and Haematology Assessment

End point title	Number of Subjects With Clinically Significant Laboratory Values and Haematology Assessment <sup>[13]</sup>
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End point description:

Laboratory parameters includes aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate dehydrogenase [LDH], creatine kinase [CK], creatinine, urea, sodium, potassium and hematology includes hematocrit, hemoglobin, erythrocytes, leukocytes, platelets parameters. Number of subjects with clinically significant laboratory findings were reported.

End point type	Primary
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End point timeframe:

Baseline up to Day 7 (follow-up)

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

End point values	Placebo	Riociguat 2 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 <sup>[14]</sup>	22 <sup>[15]</sup>		
Units: subjects	0	0		

Notes:

[14] - SAF

[15] - SAF

### Statistical analyses

No statistical analyses for this end point

### Primary: Plasma Concentration at 2 - hours After Riociguat Administration

End point title	Plasma Concentration at 2 - hours After Riociguat Administration <sup>[16]</sup>
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End point description:

A single plasma measurement for PK was done after study drug administration to evaluate the exposure at the time of the digital flow measurement. Plasma Concentration was reported based on medical grouping; diffuse cutaneous SSc, idiopathic primary SSc, limited cutaneous SSc, SSc overlap syndrome, undifferentiated form SSc. Data was planned to be reported only greater than equal to ( $\geq$ ) 2/3 of individual values were greater than ( $>$ ) lower limit of quantification (LLOQ). Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively. '99999' signified that data was not calculable as 2/3 of individual had value  $<$  LLOQ.

End point type	Primary
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End point timeframe:

At 2 hours post-dose

Notes:

[16] - 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.

<b>End point values</b>	Riociguat 2 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	21 <sup>[17]</sup>			
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)				
Diffuse cutaneous SSc (n=10)	73.54 (± 55.53)			
Idiopathic primary SSc (n=3)	54.94 (± 27.71)			
Limited cutaneous SSc (n=5)	88.07 (± 26.51)			
SSc overlap syndrome (n=2)	106.9 (± 16.16)			
Undifferentiated form SSc (n=1)	56.23 (± 99999)			

Notes:

[17] - PKS

### Statistical analyses

No statistical analyses for this end point

### Primary: Placebo Corrected Change in Digital Blood Flow at Room Temperature, Measured by Laser Doppler Perfusion Imaging

End point title	Placebo Corrected Change in Digital Blood Flow at Room Temperature, Measured by Laser Doppler Perfusion Imaging <sup>[18]</sup>
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End point description:

The digital blood flow in the index finger of the right hand was measured 2 times before and 2 hours after intake of riciguat or placebo respectively using laser doppler perfusion imaging and measured by Laser Speckle Contrast Analysis (LASCA). Mean value was calculated for the 2 measures.

End point type	Primary
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End point timeframe:

Baseline (0 minutes), 2 hours post-dose

Notes:

[18] - 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.

<b>End point values</b>	Placebo	Riociguat 2 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20 <sup>[19]</sup>	20 <sup>[20]</sup>		
Units: percent change				
arithmetic mean (standard deviation)				
Responder (n=8)	-27.1612 (± 38.4849)	135.6953 (± 113.836)		
Non-Responder (n=12)	10.2366 (± 66.5401)	-22.8392 (± 37.1348)		

Notes:

[19] - PDS

[20] - PDS

### Statistical analyses

No statistical analyses for this end point

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**Primary: Placebo Corrected Change in Digital Blood Flow During Cold Exposure, Measured by Laser Doppler Perfusion Imaging**

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End point title	Placebo Corrected Change in Digital Blood Flow During Cold Exposure, Measured by Laser Doppler Perfusion Imaging <sup>[21]</sup>
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End point description:

The digital blood flow in the index finger of the right hand was measured 2 times before and 2 hours after intake of riciguat or placebo respectively using laser doppler perfusion imaging and measured by Laser Speckle Contrast Analysis (LASCA). Mean value was calculated for the 2 measures.

End point type	Primary
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End point timeframe:

Baseline (0 minutes), 2 hours post-dose

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

End point values	Placebo	Riociguat 2 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20 <sup>[22]</sup>	20 <sup>[23]</sup>		
Units: percent change				
arithmetic mean (standard deviation)				
Responder (n=8)	-13.8552 (± 22.1774)	38.879 (± 53.2865)		
Non-Responder (n=12)	82.5718 (± 167.6288)	-20.5624 (± 12.8349)		

Notes:

[22] - PDS

[23] - PDS

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were collected from the start of study treatment until the end of follow-up (7 days post-dose)

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received a single oral dose of matching placebo in any intervention period.

Reporting group title	Riociguat 2 mg
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Reporting group description:

Subjects received a single oral dose of 2 mg riociguat tablet in any intervention period.

<b>Serious adverse events</b>	Placebo	Riociguat 2 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 22 (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>	Placebo	Riociguat 2 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	7 / 22 (31.82%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 23 (0.00%)	5 / 22 (22.73%)	
occurrences (all)	0	5	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Dyspepsia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 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 autogenerated and cannot be deleted. '99999' in the posting indicates that data were not calculated. Decimal places were automatically truncated if last decimal equals zero.

Notes: