



Clinical trial results:

A randomized, double-blind, placebo-controlled phase II study to investigate the efficacy and safety of riociguat (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg TID) in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias (IIP)

Summary

EudraCT number	2010-024332-42
Trial protocol	IT DE ES BE GB PT DK GR
Global end of trial date	14 September 2016

Results information

Result version number	v1
This version publication date	20 May 2017
First version publication date	20 May 2017

Trial information

Trial identification

Sponsor protocol code	BAY63-2521/13605
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02138825
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	14 September 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of 26-weeks of treatment with riociguat vs. placebo in patients with symptomatic PH (pulmonary hypertension) associated with IIP (idiopathic interstitial pneumonias).

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. Only after the subject voluntarily signed the informed consent form was he/she able to enter the study. If the subject was not capable of providing a signature, an oral statement of consent could have been given in the presence of a witness. Each subject was assured of the right to 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	04 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Denmark: 1

Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Italy: 6
Worldwide total number of subjects	147
EEA total number of subjects	55

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)	37
From 65 to 84 years	110
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 229 participants were enrolled into the study centers in 19 countries worldwide, from 04-Jun-2014 (first patient first visit) to 14-Sep-2016 (last patient last visit).

Pre-assignment

Screening details:

A total of 147 participants were randomized and entered the main study phase, of whom 73 were assigned to riociguat and 74 to placebo.

Period 1

Period 1 title	Main study treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Riociguat (Adempas, BAY63-2521)

Arm description:

In the main study treatment phase subjects received Riociguat titrated to optimal dose within range of 0.5 mg TID (3 times a day) to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded sham titration phase of 10 weeks followed by an open-label extension phase. During the open-label extension phase subjects were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

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

Dosage and administration details:

Active drug 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg TID/day as per individual dose titration. The starting dose will be 0.5 mg TID, and the dose will be adjusted every two weeks for ten weeks in 0.5 mg increments up to a maximum dose of 2.5 mg TID based on patient's systolic blood pressure and well-being.

Arm title	Placebo
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Arm description:

In the main study treatment phase subjects received sham titration within range of 0.5 mg TID to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded titration phase to optimal dose of Riociguat of 10 weeks followed by an open-label extension phase. During the open-label extension phase subjects were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Inactive dosed at 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg TID/day as per individual dose titration for 26 weeks.

Number of subjects in period 1	Riociguat (Adempas, BAY63-2521)	Placebo
Started	73	74
Completed	33	39
Not completed	40	35
Consent withdrawn by subject	3	1
Adverse event, non-fatal	11	3
Death	1	2
Study terminated by sponsor	10	9
Medical decision	1	-
Protocol Violation	2	2
Sponsor decision	12	18

Period 2

Period 2 title	Long-term extension
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Riociguat (Adempas, BAY63-2521)

Arm description:

In the main study treatment phase subjects received Riociguat titrated to optimal dose within range of 0.5 mg TID (3 times a day) to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded sham titration phase of 10 weeks followed by an open-label extension phase. During the open-label extension phase subjects were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

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

Dosage and administration details:

Active drug 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg TID/day as per individual dose titration. The starting dose will be 0.5 mg TID, and the dose will be adjusted every two weeks for ten weeks in 0.5 mg increments up to a maximum dose of 2.5 mg TID based on patient's systolic blood pressure and well-being.

Arm title	Placebo to Riociguat
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Arm description:

In the main study treatment phase subjects received sham titration within range of 0.5 mg TID to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded titration phase to optimal dose of Riociguat of 10 weeks followed by an open-label extension phase. During the open-label extension phase subjects were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

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

Dosage and administration details:

Active drug 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg TID/day as per individual dose titration. The starting dose will be 0.5 mg TID, and the dose will be adjusted every two weeks for ten weeks in 0.5 mg increments up to a maximum dose of 2.5 mg TID based on patient's systolic blood pressure and well-being.

Number of subjects in period 2^[1]	Riociguat (Adempas, BAY63-2521)	Placebo to Riociguat
Started	32	38
Completed	32	38

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects completing the main study treatment period entered long-term extension period.

Baseline characteristics

Reporting groups

Reporting group title	Riociguat (Adempas, BAY63-2521)
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Reporting group description:

In the main study treatment phase subjects received Riociguat titrated to optimal dose within range of 0.5 mg TID (3 times a day) to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded sham titration phase of 10 weeks followed by an open-label extension phase. During the open-label extension phase subjects were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

Reporting group title	Placebo
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Reporting group description:

In the main study treatment phase subjects received sham titration within range of 0.5 mg TID to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded titration phase to optimal dose of Riociguat of 10 weeks followed by an open-label extension phase. During the open-label extension phase subjects were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

Reporting group values	Riociguat (Adempas, BAY63-2521)	Placebo	Total
Number of subjects	73	74	147
Age categorical			
Units: Subjects			
<65 years	20	17	37
>=65 - <75 years	35	45	80
>=75 years	18	12	30
Gender categorical			
Units: Subjects			
Female	23	29	52
Male	50	45	95
Pulmonary hypertension (PH) subtype (Nice Clinical Classification)			
Units: Subjects			
PH owing to respiratory disease and /or hypoxia	73	74	147
Other	0	0	0
Classification of Idiopathic Interstitial Pneumonia			
Units: Subjects			
Idiopathic pulmonary fibrosis	54	49	103
Idiopathic nonspecific interstitial pneumonia	9	14	23
Resp. bronchiolitis-interstitial lung disease	1	0	1
Cryptogenic organizing pneumonia	0	1	1
Acute interstitial pneumonia	0	1	1
Idiopathic lymphoid interstitial pneumonia	0	2	2
Unclassifiable idiopathic interstitial pneumonias	9	7	16
World Health Organization (WHO)			

functional class			
The WHO functional assessment of pulmonary arterial hypertension ranged from functional class I (Patients with PH but without resulting limitation of physical activity) to class IV (Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure.). Changes to a lower WHO functional class resemble improvement, changes to a higher functional class resemble deterioration of pulmonary arterial hypertension (PAH).			
Units: Subjects			
Class II	16	22	38
Class III	50	45	95
Class IV	7	7	14
6 minute walking distance (6MWD) category			
The 6MWD test is designed to evaluate a patient's exercise capacity while performing an everyday activity.			
Units: Subjects			
< 320 m	43	32	75
>= 320 m and <380m	12	28	40
>= 380 m	18	14	32

End points

End points reporting groups

Reporting group title	Riociguat (Adempas, BAY63-2521)
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Reporting group description:

In the main study treatment phase subjects received Riociguat titrated to optimal dose within range of 0.5 mg TID (3 times a day) to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded sham titration phase of 10 weeks followed by an open-label extension phase. During the open-label extension phase subjects were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

Reporting group title	Placebo
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Reporting group description:

In the main study treatment phase subjects received sham titration within range of 0.5 mg TID to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded titration phase to optimal dose of Riociguat of 10 weeks followed by an open-label extension phase. During the open-label extension phase subjects were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

Reporting group title	Riociguat (Adempas, BAY63-2521)
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Reporting group description:

In the main study treatment phase subjects received Riociguat titrated to optimal dose within range of 0.5 mg TID (3 times a day) to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded sham titration phase of 10 weeks followed by an open-label extension phase. During the open-label extension phase subjects were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

Reporting group title	Placebo to Riociguat
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Reporting group description:

In the main study treatment phase subjects received sham titration within range of 0.5 mg TID to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded titration phase to optimal dose of Riociguat of 10 weeks followed by an open-label extension phase. During the open-label extension phase subjects were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

Subject analysis set title	Intent to treat (ITT)
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Subjects randomized and received at least one dose of study medication.

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:

Subjects randomized and received at least one dose of study medication.

Primary: Mean change in 6 minute walking distance (6MWD) from baseline to week 26

End point title	Mean change in 6 minute walking distance (6MWD) from baseline to week 26
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End point description:

The 6MWD test is designed to evaluate a patient's exercise capacity while performing an everyday activity.

End point type	Primary
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End point timeframe:

Baseline to 26 weeks

End point values	Riociguat (Adempas, BAY63-2521)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73 ^[1]	74 ^[2]		
Units: Meter				
arithmetic mean (standard deviation)	3.63 (± 60.8)	-15.94 (± 63.7)		

Notes:

[1] - ITT

[2] - ITT

Statistical analyses

Statistical analysis title	Riociguat vs. Placebo
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Statistical analysis description:

The evaluation of primary efficacy endpoint will be based on change from baseline in 6MWD using analysis of covariance (ANCOVA) with baseline 6MWD, treatment arm and region as factors.

Comparison groups	Riociguat (Adempas, BAY63-2521) v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2074
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	21.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.75
upper limit	51.71

Secondary: Number of participants with clinical worsening

End point title	Number of participants with clinical worsening
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End point description:

The combined endpoint "time to clinical worsening", made up of the following components, defined by the first occurrence: all-cause mortality; need for hospitalization due to worsening cardiopulmonary (CP) status, attributable to progression of disease (including but not limited to increased shortness of breath or increased leg swelling); >15% decrease in the 6MWD test; worsening of WHO functional class.

End point type	Secondary
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End point timeframe:

Up to week 26

End point values	Riociguat (Adempas, BAY63-2521)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73 ^[3]	74 ^[4]		
Units: Subjects				
number (not applicable)				
No clinical event	39	38		
>15% decrease in 6MWD	9	17		
All-cause mortality	1	0		
Hospitalization due to worsening CP status	15	7		
Worsening of WHO functional class	9	12		

Notes:

[3] - ITT

[4] - ITT

Statistical analyses

Statistical analysis title	Riociguat vs. Placebo
Statistical analysis description:	
The difference in incidences in clinical worsening and mortality will be analyzed using Mantel-Haenszel weights, stratified by region.	
Comparison groups	Riociguat (Adempas, BAY63-2521) v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3437
Method	Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to 7 days after end of treatment.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

In the main study treatment phase participants received sham titration within range of 0.5 mg TID to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, which included a blinded titration phase to optimal dose of Riociguat of 10 weeks followed by an open-label extension phase. During the open-label extension phase participants were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

Reporting group title	Riociguat (Adempas, BAY63-2521)
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Reporting group description:

In the main study treatment phase participants received Riociguat titrated to optimal dose within range of 0.5 mg TID (3 times a day) to 2.5 mg TID for 10 weeks followed by maintenance period of 16 weeks. This phase was followed by a long-term extension phase, throughout which all participants continued the treatment with Riociguat. The long-term extension phase included a blinded sham titration phase of 10 weeks followed by an open-label extension phase. During the open-label extension phase participants were to be treated with Riociguat until commercial access in the indication of PH associated with IIP or until an agreed time point is defined with the individual country, local regulatory authority and the Sponsor's global team.

Serious adverse events	Placebo	Riociguat (Adempas, BAY63-2521)	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 74 (41.89%)	36 / 73 (49.32%)	
number of deaths (all causes)	15	12	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder papilloma			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Inguinal hernia repair			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung transplant			
subjects affected / exposed	0 / 74 (0.00%)	3 / 73 (4.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	1 / 74 (1.35%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 74 (2.70%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	4 / 74 (5.41%)	6 / 73 (8.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 2	
Interstitial lung disease			
subjects affected / exposed	3 / 74 (4.05%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumothorax			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			

subjects affected / exposed	3 / 74 (4.05%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	5 / 74 (6.76%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	2 / 74 (2.70%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute interstitial pneumonitis			
subjects affected / exposed	1 / 74 (1.35%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Tibia fracture			

subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 74 (1.35%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			

subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal rhythm			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	3 / 74 (4.05%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			

subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral artery thrombosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 74 (1.35%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choroidal neovascularisation			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neovascular age-related macular degeneration			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 74 (0.00%)	4 / 73 (5.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 74 (2.70%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 74 (1.35%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			

subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 74 (6.76%)	4 / 73 (5.48%)	
occurrences causally related to treatment / all	1 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pneumonia moraxella			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 74 (1.35%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone abscess			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Riociguat (Adempas, BAY63-2521)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 74 (78.38%)	58 / 73 (79.45%)	
Investigations			
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	4 / 74 (5.41%)	3 / 73 (4.11%)	
occurrences (all)	4	3	
Blood glucose increased			
subjects affected / exposed	1 / 74 (1.35%)	5 / 73 (6.85%)	
occurrences (all)	1	5	
Vascular disorders			
Hypotension			
subjects affected / exposed	8 / 74 (10.81%)	7 / 73 (9.59%)	
occurrences (all)	8	7	
Cardiac disorders			
Right ventricular failure			
subjects affected / exposed	1 / 74 (1.35%)	5 / 73 (6.85%)	
occurrences (all)	1	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 74 (13.51%)	12 / 73 (16.44%)	
occurrences (all)	17	14	
Syncope			
subjects affected / exposed	4 / 74 (5.41%)	4 / 73 (5.48%)	
occurrences (all)	8	5	
Presyncope			

subjects affected / exposed	2 / 74 (2.70%)	4 / 73 (5.48%)	
occurrences (all)	2	4	
Headache			
subjects affected / exposed	11 / 74 (14.86%)	10 / 73 (13.70%)	
occurrences (all)	15	10	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	6 / 74 (8.11%)	5 / 73 (6.85%)	
occurrences (all)	7	12	
Fatigue			
subjects affected / exposed	9 / 74 (12.16%)	5 / 73 (6.85%)	
occurrences (all)	10	6	
Oedema			
subjects affected / exposed	2 / 74 (2.70%)	4 / 73 (5.48%)	
occurrences (all)	2	4	
Oedema peripheral			
subjects affected / exposed	12 / 74 (16.22%)	18 / 73 (24.66%)	
occurrences (all)	12	20	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 74 (16.22%)	15 / 73 (20.55%)	
occurrences (all)	15	21	
Constipation			
subjects affected / exposed	5 / 74 (6.76%)	5 / 73 (6.85%)	
occurrences (all)	5	6	
Abdominal pain upper			
subjects affected / exposed	2 / 74 (2.70%)	5 / 73 (6.85%)	
occurrences (all)	3	5	
Vomiting			
subjects affected / exposed	6 / 74 (8.11%)	9 / 73 (12.33%)	
occurrences (all)	6	12	
Nausea			
subjects affected / exposed	12 / 74 (16.22%)	14 / 73 (19.18%)	
occurrences (all)	18	15	
Gastrooesophageal reflux disease			

subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 5	4 / 73 (5.48%) 5	
Dyspepsia subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 5	4 / 73 (5.48%) 5	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	12 / 74 (16.22%) 12	10 / 73 (13.70%) 11	
Dyspnoea subjects affected / exposed occurrences (all)	18 / 74 (24.32%) 20	13 / 73 (17.81%) 16	
Epistaxis subjects affected / exposed occurrences (all)	7 / 74 (9.46%) 9	6 / 73 (8.22%) 8	
Haemoptysis subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	5 / 73 (6.85%) 5	
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	2 / 73 (2.74%) 2	
Idiopathic pulmonary fibrosis subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	4 / 73 (5.48%) 5	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5	3 / 73 (4.11%) 3	
Renal and urinary disorders			
Renal failure subjects affected / exposed occurrences (all)	0 / 74 (0.00%) 0	4 / 73 (5.48%) 4	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 4	4 / 73 (5.48%) 4	

Arthralgia subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 6	3 / 73 (4.11%) 4	
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 6	4 / 73 (5.48%) 5	
Influenza subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	2 / 73 (2.74%) 2	
Lower respiratory tract infection subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 7	4 / 73 (5.48%) 7	
Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 8	6 / 73 (8.22%) 7	
Sinusitis subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	1 / 73 (1.37%) 1	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 7	5 / 73 (6.85%) 6	
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	5 / 73 (6.85%) 7	
Respiratory tract infection subjects affected / exposed occurrences (all)	7 / 74 (9.46%) 13	6 / 73 (8.22%) 12	
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 6	0 / 73 (0.00%) 0	
Decreased appetite subjects affected / exposed occurrences (all)	9 / 74 (12.16%) 9	4 / 73 (5.48%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2014	1. Adjustment of the blinding period 2. Revision of inclusion and exclusion criteria 3. Revision of time windows 4. Addition of missing visit 5. Modification in SAE reporting 6. Addition of echocardiography assessment for screening
19 May 2015	1. Revision of the number of randomized patients 2. Addition of time point for calculating secondary and exploratory variables
24 May 2016	1. Extension of safety follow-up period from 1 month to 4 months 2. Addition of assessments to be performed in the safety follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was prematurely terminated following a recommendation from the independent data safety monitoring committee (DMC) and steering committee (SC).

Notes: