



Clinical trial results:

Long-term extension, multi-centre, multi-national study to evaluate the safety and tolerability of oral BAY63-2521(1 mg, 1.5 mg, 2 mg, or 2.5 mg tid) in patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

Summary

EudraCT number	2008-003539-19
Trial protocol	DE NL FR AT IT IE ES BE CZ PT DK SK GB
Global end of trial date	18 August 2019

Results information

Result version number	v1 (current)
This version publication date	02 September 2020
First version publication date	02 September 2020

Trial information

Trial identification

Sponsor protocol code	BAY 63-2521/11349
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00910429
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	18 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2019
Global end of trial reached?	Yes
Global end of trial date	18 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety and tolerability of BAY63-2521 in patients with inoperable Chronic Thromboembolic Pulmonary Hypertension (CTEPH) or recurrent or persisting pulmonary hypertension after surgical treatment.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. 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	30 June 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Japan: 14
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	China: 30
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 51
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Slovakia: 2

Country: Number of subjects enrolled	Swaziland: 2
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Mexico: 8
Worldwide total number of subjects	237
EEA total number of subjects	128

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)	141
From 65 to 84 years	96
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 71 centers in 25 countries or regions, between 01-JUL-2009 (first subject first visit) and 19-AUG-2019 (last subject last visit)

Pre-assignment

Screening details:

Of the 243 subjects who completed CHEST-1, 237 entered CHEST-2. 155 subjects were from the former riociguat treatment group, and 82 were from the former placebo group.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Study titration phase was from week 1 to week 8, in titration phase, blinded with respect to the riociguat dose. Study main phase was starting from week 12 to the end of study. In study main phase, unblinded with respect to riociguat dose.

Arms

Are arms mutually exclusive?	Yes
Arm title	Riociguat-Former Riociguat 1.0-2.5 mg

Arm description:

Subjects were from the former riociguat (BAY 63-2521) treatment group of CHEST-1 (2007-000072-16)

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

Dosage and administration details:

Subjects from the riociguat 1.0-2.5mg group of CHEST-1 entered the extension study (CHEST-2) on the same dose as they received on the last day of CHEST-1 (Visit7). If the investigator requested a dose increase above that level via the IVRS, the subject received a sham titration. However, if the investigator requested a dose decrease (e.g. for safety reasons), dose modifications were possible, but without a subsequent re-increase before Visit5.

Arm title	Riociguat-Former Placebo
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Arm description:

Subjects were from the former placebo group of CHEST-1

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

Dosage and administration details:

For subjects from the CHEST-1 placebo arm, the starting dose in CHEST-2 was 1.0 mg riociguat tid. The individual riociguat dose was titrated every 2weeks according to the peripheral SBP measured at trough before intake of the next morning dose. At the end of the titration phase (Visit5), subjects reached riociguat doses between 0.5mg tid and 2.5mg tid.

Number of subjects in period 1	Riociguat-Former Riociguat 1.0-2.5 mg	Riociguat-Former Placebo
Started	155	82
Completed	116	61
Not completed	39	21
Consent withdrawn by subject	3	2
Drug non-compliance	1	-
Adverse event, non-fatal	10	5
Death	18	12
Lost to follow-up	2	1
Protocol deviation	1	-
Lack of efficacy	4	1

Baseline characteristics

Reporting groups

Reporting group title	Riociguat-Former Riociguat 1.0-2.5 mg
Reporting group description:	
Subjects were from the former riociguat (BAY 63-2521) treatment group of CHEST-1 (2007-000072-16)	
Reporting group title	Riociguat-Former Placebo
Reporting group description:	
Subjects were from the former placebo group of CHEST-1	

Reporting group values	Riociguat-Former Riociguat 1.0-2.5 mg	Riociguat-Former Placebo	Total
Number of subjects	155	82	237
Age Categorical Units: Subjects			
Adults (18-64 years)	91	50	141
From 65-84 years	64	32	96
Age Continuous Units: years			
arithmetic mean	59	59.2	
standard deviation	± 13.8	± 12.4	-
Gender Categorical Units: Subjects			
Female	104	49	153
Male	51	33	84
Race / Ethnicity Units: Subjects			
White	105	60	165
Black or African American	7	1	8
Asian	34	19	53
Hispanic or Latino	8	2	10
Multiple races	1	0	1

End points

End points reporting groups

Reporting group title	Riociguat-Former Riociguat 1.0-2.5 mg
Reporting group description:	
Subjects were from the former riociguat (BAY 63-2521) treatment group of CHEST-1 (2007-000072-16)	
Reporting group title	Riociguat-Former Placebo
Reporting group description:	
Subjects were from the former placebo group of CHEST-1	
Subject analysis set title	Long-term safety analysis set(SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All 237 subjects who completed 16 weeks of treatment in the double-blind CHEST-1 study entered long term extension CHEST-2 study. Baseline of CHEST-2 was Week 0 of CHEST-1. All 237 subjects were included in the long-term safety set	

Primary: Number of subjects with treatment-emergent adverse events (TEAE)

End point title	Number of subjects with treatment-emergent adverse events (TEAE) ^[1]
End point description:	
Analyses of drug-related TEAEs were based on the assessment of causal relationship to study medication.	
End point type	Primary
End point timeframe:	
From administration of first dose of study medication up to 2 days after end of treatment with study medication.	

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-Former Riociguat 1.0-2.5 mg	Riociguat-Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	82		
Units: Subjects				
Any TEAE	153	82		
Any drug-related TEAE	77	44		
Any serious TEAE	96	56		
Any drug-related serious TEAE	14	7		
Any TEAE leading to death	22	13		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with death

End point title	Number of subjects with death ^[2]
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End point description:

Analyses of deaths were based on the assessment of causal relationship to study medication. The safety follow-up visit was to be performed 30 days after the last dose of riociguat.

End point type Primary

End point timeframe:

From baseline to safety follow-up visit

Notes:

[2] - 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- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	82		
Units: Subjects				
Death	22	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with treatment-emergent high laboratory abnormalities in Hematology and Coagulation

End point title Percentage of subjects with treatment-emergent high laboratory abnormalities in Hematology and Coagulation

End point description:

Percentage of subjects with a treatment-emergent shift in hematology and coagulation parameters from normal or low at baseline to a high value at a timepoint after the start of treatment. The percentage was calculated by comparing the number of subjects with a normal or low value at baseline who had at least one high value after the start of treatment with the number of subjects with a normal or low value at baseline who also had at least one valid value after start of treatment.

A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type Secondary

End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	82		
Units: Percentage				
number (not applicable)				
Activated partial thromboplastin time (sec)	97.1	90.5		
Basophils (Giga/L)	1.4	0.0		

Basophils / Leukocytes (%)	18.4	16.4		
Eosinophils (Giga/L)	0.7	5.4		
Eosinophils / Leukocytes (%)	3.7	9.7		
Erythrocytes (T/L)	18.0	24.2		
Hematocrit (%)	41.2	38.0		
Hemoglobin (g/dL)	12.5	10.8		
Leukocytes (Giga/L)	8.0	16.4		
Lymphocytes (Giga/L)	0.0	1.4		
Lymphocytes / Leukocytes (%)	8.8	7.4		
Monocytes (Giga/L)	3.7	8.6		
Monocytes / Leukocytes (%)	15.6	16.4		
Neutrophils (Giga/L)	11.3	23.3		
Neutrophils / Leukocytes (%)	31.7	32.9		
Platelets (Giga/L)	17.2	20.6		
Prothrombin international normalized ratio	92.3	75		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with treatment-emergent low laboratory abnormalities in Hematology and coagulation

End point title	Percentage of subjects with treatment-emergent low laboratory abnormalities in Hematology and coagulation
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End point description:

Percentage of subjects with a treatment-emergent shift in hematology and coagulation parameters from normal or high at baseline to a low value at a timepoint after the start of treatment. The percentage was calculated by comparing the number of subjects with a normal or high value at baseline who had at least one low value after the start of treatment with the number of subjects with a normal or high value at baseline who also had at least one valid value after start of treatment.

A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type	Secondary
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End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	82		
Units: Percentage				
number (not applicable)				
Activated partial thromboplastin time (sec)	2.9	2.7		
Erythrocytes (T/L)	21.1	29.7		
Hematocrit (%)	9.3	17.6		
Hemoglobin (g/dL)	30.0	36.2		

Leukocytes (Giga/L)	25.4	25.4		
Lymphocytes (Giga/L)	30.0	22.4		
Lymphocytes / Leukocytes (%)	39.3	42.9		
Monocytes (Giga/L)	0.7	0.0		
Monocytes / Leukocytes (%)	3.6	2.7		
Neutrophils (Giga/L)	10.8	5.6		
Neutrophils / Leukocytes (%)	5.8	10.1		
Platelets (Giga/L)	19.8	19.4		
Prothrombin INR	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of hemoglobin in Hematology and coagulation

End point title	Change from baseline of hemoglobin in Hematology and coagulation
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End point description:

Hemoglobin is a standard Hematology and coagulation parameter. A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type	Secondary
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End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[3]	82 ^[4]		
Units: gram/deciliter (g/dL)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	14.49 (± 1.82)	14.36 (± 1.70)		
Change from baseline to Termination visit	1.04 (± 1.58)	-1.37 (± 1.71)		

Notes:

[3] - Baseline: N=140 Termination Visit: N=5

[4] - Baseline: N=76 Termination visit: N=3

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with treatment-emergent high laboratory abnormalities in Clinical chemistry

End point title	Percentage of subjects with treatment-emergent high laboratory abnormalities in Clinical chemistry
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End point description:

Percentage of subjects per treatment group with a treatment-emergent shift in clinical chemistry parameters from normal or low at baseline to a high value at a timepoint after the start of treatment. The percentage was calculated by comparing the number of subjects with a normal or low value at baseline who had at least one high value after the start of treatment with the number of subjects with a normal or low value at baseline who also had at least one valid value after start of treatment.

A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type	Secondary
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End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat-Former Riociguat 1.0-2.5 mg	Riociguat-Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	82		
Units: Percentage				
number (not applicable)				
Alanine aminotransferase (U/L)	11.5	13.7		
Albumin (g/dL)	0.0	0.0		
Alkaline phosphatase (U/L)	22.0	19.4		
Aspartate aminotransferase (U/L)	16.4	14.1		
Bilirubin (mg/dL)	17.2	15.6		
Calcium (mg/dL)	2.6	0.0		
Creatine kinase (U/L)	28.4	30.3		
Creatinine (mg/dL)	32.5	31.0		
Gamma glutamyltransferase (U/L)	22.3	24.1		
Glutamate dehydrogenase (U/L)	43.0	34.0		
Phosphate (mg/dL)	7.9	5.0		
Potassium (mmol/L)	4.3	6.7		
Protein (g/dL)	2.7	0.0		
Pseudocholinesterase (U/mL)	2.1	0.0		
Sodium (mmol/L)	1.4	3.9		
Triacylglycerol lipase (U/L)	18.8	18.8		
Urate (mg/dL)	13.6	35.7		
Urea (mg/dL)	22.9	36.7		
eGFR MDRD method(mL/min/1.73 m2)	0.0	0.0		
Creatinine clearance (mL/min)	11.5	8.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with treatment-emergent low laboratory abnormalities in Clinical chemistry

End point title	Percentage of subjects with treatment-emergent low laboratory abnormalities in Clinical chemistry
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End point description:

Percentage of subjects per treatment group with a treatment-emergent shift in clinical chemistry parameters from normal or high at baseline to a low value at a timepoint after the start of treatment. The percentage was calculated by comparing the number of subjects with a normal or high value at baseline who had at least one low value after the start of treatment with the number of subjects with a normal or high value at baseline who also had at least one valid value after start of treatment. A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type	Secondary
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End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	82		
Units: Percentage				
number (not applicable)				
Albumin (g/dL)	2.0	0.0		
Alkaline phosphatase (U/L)	2.1	0.0		
Bilirubin (mg/dL)	0.0	0.0		
Calcium (mg/dL)	14.3	6.3		
Creatine kinase (U/L)	6.4	6.8		
Creatinine (mg/dL)	4.1	3.9		
Gamma glutamyltransferase (U/L)	0.0	0.0		
Phosphate (mg/dL)	10.5	9.5		
Potassium (mmol/L)	18.4	18.9		
Protein (g/dL)	6.3	2.8		
Pseudocholinesterase (U/mL)	10.0	14.7		
Sodium (mmol/L)	4.3	6.6		
Triacylglycerol lipase (U/L)	0.0	0.0		
Urate (mg/dL)	2.7	2.6		
Urea (mg/dL)	0.0	1.3		
eGFR MDRDmethod (mL/min/1.73 m ²)	26.7	22.4		
Creatinine clearance (mL/min)	29.2	40.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of urate in Clinical chemistry.

End point title	Change from baseline of urate in Clinical chemistry.
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End point description:

Urate is a standard clinical chemistry parameter. A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type	Secondary
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End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[5]	82 ^[6]		
Units: milligram/deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	6.767 (± 1.859)	6.999 (± 2.193)		
Change from baseline to Termination visit	0.310 (± 2.916)	-1.290 (± 1.120)		

Notes:

[5] - Baseline: N=147 Termination visit: N=5

[6] - Baseline: N=77 Termination visit: N=3

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of Systolic blood pressure (SBP)

End point title	Change of Systolic blood pressure (SBP)
End point description:	
SBP was measured after the subject had been at rest for 10 minutes in a supine position. Low SBP was defined as SBP <95 mmHg, normal SBP as SBP 95–140mmHg, and high SBP as SBP >140 mmHg. A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.	
End point type	Other pre-specified
End point timeframe:	
From baseline to Termination visit, up to 10 years	

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[7]	82 ^[8]		
Units: millimetre(s) of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	118.81 (± 14.96)	124.26 (± 16.14)		
Change from baseline to Termination visit	-3.96 (± 17.34)	-5.02 (± 14.79)		

Notes:

[7] - Baseline: N=155 Termination visit: N=126

[8] - Baseline: N=82 Termination visit: N=65

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of Diastolic blood pressure (DBP)

End point title	Change of Diastolic blood pressure (DBP)
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End point description:

DBP was measured after the subject had been at rest for 10 minutes in a supine position.

A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type	Other pre-specified
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End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[9]	82 ^[10]		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (Week 0)	75.34 (± 9.75)	78.55 (± 9.46)		
Change from baseline to Termination visit	-6.16 (± 13.77)	-7.26 (± 11.09)		

Notes:

[9] - Baseline: N=155 Termination visit: N=126

[10] - Baseline: N=82 Termination visit: N=66

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of Heart rate

End point title	Change of Heart rate
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End point description:

Heart rate was measured after the subject had been at rest for 10 minutes in a supine position.

A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type	Other pre-specified
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End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[11]	82 ^[12]		
Units: beats/minute (BPM)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	77.66 (± 12.12)	76.11 (± 12.10)		
Change from baseline to Termination visit	-0.89 (± 13.85)	3.77 (± 14.69)		

Notes:

[11] - Baseline: N=155 Termination visit: N=126

[12] - Baseline: N=82 Termination visit: N=65

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of Weight

End point title	Change of Weight
End point description:	
Weight was evaluated for safety.	
A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.	
End point type	Other pre-specified
End point timeframe:	
From baseline to Termination visit, up to 10 years	

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[13]	82 ^[14]		
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	74.01 (± 18.76)	77.29 (± 16.42)		
From baseline to Termination visit	-0.87 (± 5.86)	-2.97 (± 7.27)		

Notes:

[13] - Baseline: N=155 Termination visit: N=123

[14] - Baseline: N=82 Termination visit: N=64

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of oxygen saturation (SaO2)

End point title	Change of oxygen saturation (SaO2)
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End point description:

SaO₂ is one parameters of blood gas. The sample was obtained with the participant resting in a sitting or supine position for at least 10 minutes.

A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type	Other pre-specified
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End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[15]	82 ^[16]		
Units: Percentage				
arithmetic mean (standard deviation)				
Baseline (Week 0)	93.9 (± 2.7)	93.6 (± 2.4)		
From baseline to Termination visit	0.0 (± 2.6)	-2.3 (± 5.5)		

Notes:

[15] - Baseline: N=154 Termination visit: N=3

[16] - Baseline: N=81 Termination visit: N=3

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of arterial partial oxygen pressure (PaO₂)

End point title	Change of arterial partial oxygen pressure (PaO ₂)
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End point description:

PaO₂ is one parameter of blood gas. The sample was obtained with the participant resting in a sitting or supine position for at least 10 minutes.

A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type	Other pre-specified
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End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[17]	82 ^[18]		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (Week 0)	69.66 (± 11.90)	69.19 (± 10.96)		
From baseline to Termination visit	-1.67 (± 8.02)	2.00 (± 24.73)		

Notes:

[17] - Baseline: N=154 Termination visit: N=3

[18] - Baseline: N=81 Termination visit: N=4

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of arterial partial pressure of carbon dioxide (PaCO₂)

End point title	Change of arterial partial pressure of carbon dioxide (PaCO ₂)
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End point description:

PaCO₂ is one parameter of blood gas. The sample was obtained with the participant resting in a sitting or supine position for at least 10 minutes.

A termination visit was only to be performed in the case of premature termination of study medication or if the sponsor announced the official end of the study.

End point type	Other pre-specified
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End point timeframe:

From baseline to Termination visit, up to 10 years

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[19]	82 ^[20]		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (Week 0)	33.20 (± 4.61)	33.52 (± 4.60)		
From baseline to Termination visit	-0.33 (± 1.53)	-2.25 (± 4.50)		

Notes:

[19] - Baseline: N=154 Termination visit: N=3

[20] - Baseline: N=81 Termination visit: N=4

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of RR duration from Electrocardiogram (ECG)

End point title	Change of RR duration from Electrocardiogram (ECG)
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End point description:

Heart rate from ECG is derived from the RR duration, unless arrhythmias such as atrial fibrillation or ventricular extra beats require additional calculations. ECGs were recorded after the subject had been at rest for 15 minutes in a supine position.

Analyses up to Month 48. After this timepoint, data was available for considerably fewer participants in the analysis set. "99999" denotes that value was not calculated due to very low number of subjects.

End point type	Other pre-specified
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End point timeframe:

From baseline to Month 48

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[21]	82 ^[22]		
Units: millisecond (msec)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	812.90 (± 144.31)	828.47 (± 147.54)		
Change from baseline to Month 48	152.00 (± 236.17)	99999 (± 99999)		

Notes:

[21] - Baseline: N=149 Month 48: N=2

[22] - Baseline: N=75 Month 48: N=0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of PR duration from ECG

End point title	Change of PR duration from ECG
End point description:	
PR duration was evaluated as part of ECG. ECGs were recorded after the subject had been at rest for 15 minutes in a supine position.	
Analyses up to Month 48. After this timepoint, data was available for considerably fewer participants in the analysis set. "99999" denotes that value was not calculated due to very low number of subjects.	
End point type	Other pre-specified
End point timeframe:	
From baseline to Month 48	

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[23]	82 ^[24]		
Units: msec				
arithmetic mean (standard deviation)				
Baseline (Week 0)	173.22 (± 26.49)	174.92 (± 24.35)		
Change from baseline to Month 48	-10.00 (± 11.31)	99999 (± 99999)		

Notes:

[23] - Baseline: N=147 Month 48: N=2

[24] - Baseline: N=72 Month 48: N=0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of QRS duration from ECG

End point title	Change of QRS duration from ECG
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End point description:

QRS duration was evaluated as part of ECG. ECGs were recorded after the subject had been at rest for 15 minutes in a supine position.

Analyses up to Month 48. After this timepoint, data was available for considerably fewer participants in the analysis set. "99999" denotes that value was not calculated due to very low number of subjects.

End point type	Other pre-specified
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End point timeframe:

From baseline to Month 48

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[25]	82 ^[26]		
Units: msec				
arithmetic mean (standard deviation)				
Baseline (Week 0)	104.30 (± 17.85)	104.11 (± 18.24)		
Change from baseline to Month 48	3.00 (± 4.24)	99999 (± 99999)		

Notes:

[25] - Baseline: N=148 Month 48: N=2

[26] - Baseline: N=74 Month 48: N=0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of QT duration in ECG

End point title	Change of QT duration in ECG
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End point description:

QT duration was evaluated as part of ECG. ECGs were recorded after the subject had been at rest for 15 minutes in a supine position.

Analyses up to Month 48. After this timepoint, data was available for considerably fewer participants in the analysis set. "99999" denotes that value was not calculated due to very low number of subjects.

End point type	Other pre-specified
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End point timeframe:

From baseline to Month 48

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[27]	82 ^[28]		
Units: msec				
arithmetic mean (standard deviation)				
Baseline (Week 0)	405.82 (± 31.29)	408.45 (± 30.98)		
Change from baseline to Month 48	42.00 (± 39.60)	99999 (± 99999)		

Notes:

[27] - Baseline: N=114 Month 48: N=2

[28] - Baseline: N=53 Month 48: N=0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Six-minute walking distance (6MWD) test

End point title	Change in Six-minute walking distance (6MWD) test
End point description: 6MWD is exercise testing and is one of efficacy evaluation	
End point type	Other pre-specified
End point timeframe: From baseline to End of study visit	

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[29]	82 ^[30]		
Units: meters				
median (full range (min-max))				
Baseline (Week 0)	361.0 (150 to 557)	372.0 (170 to 474)		
Change from baseline to End of study visit	31.0 (-447 to 230)	12.5 (-448 to 215)		

Notes:

[29] - Baseline: N=155 End of study visit: N=155

[30] - Baseline: N=82 End of study visit: N=82

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Pulmonary vascular resistance (PVR)

End point title	Change in Pulmonary vascular resistance (PVR)
End point description: Pulmonary vascular resistance (PVR) was measured only if right-heart catheterization was performed as part of a regular diagnostic work-up.	

Analyses up to Month 48 due to limited data. "99999" denotes that value was not calculated due to very low number of subjects.

End point type	Other pre-specified
End point timeframe:	
From baseline to Month 45 and Month 48	

End point values	Riociguat-Former Riociguat 1.0-2.5 mg	Riociguat-Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[31]	82 ^[32]		
Units: dyn*s*cm-5				
arithmetic mean (standard deviation)				
Baseline (Week 0)	796.64 (± 435.24)	761.83 (± 388.87)		
Change from baseline to Month 45	99999 (± 99999)	-1243.48 (± 99999)		
Change from baseline to Month 48	-148.29 (± 74.39)	99999 (± 99999)		

Notes:

[31] - Baseline: N=146 Month 45: N=0 Month 48: N=2

[32] - Baseline: N=80 Month 45: N=1 Month 48: N=0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in N-terminal prohormone of brain natriuretic peptide (NT-proBNP)

End point title	Change in N-terminal prohormone of brain natriuretic peptide (NT-proBNP)
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End point description:

NT-proBNP levels in the blood are used for diagnosis of acute congestive heart failure (CHF) and may be useful to establish prognosis in heart failure

End point type	Other pre-specified
End point timeframe:	
From baseline to End of study visit	

End point values	Riociguat-Former Riociguat 1.0-2.5 mg	Riociguat-Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[33]	82 ^[34]		
Units: picograms/millilitre (pg/mL)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	1553.19 (± 2435.94)	1404.23 (± 1745.48)		
Change from baseline to End of study visit	-125.99 (± 2503.78)	-187.96 (± 1438.96)		

Notes:

[33] - Baseline: N=135 End of study visit: N=135

[34] - Baseline: N=69 End of study visit: N=69

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in World Health Organization (WHO) functional class

End point title	Change in World Health Organization (WHO) functional class
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End point description:

The subject's functional class was determined according to the WHO classification: I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope. II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope. IV: Patients with PH with inability to carry out any physical activity without symptoms. These subjects manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

End point type	Other pre-specified
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End point timeframe:

From baseline to End of study (EOS) visit

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[35]	82 ^[36]		
Units: Subjects				
Baseline-class I	3	0		
Baseline-class II	48	25		
Baseline-class III	100	54		
Baseline-class IV	4	2		
Baseline-Missing	0	1		
Change from baseline to EOS visit- -2	7	4		
Change from baseline to EOS visit- -1	44	24		
Change from baseline to EOS visit- 0	72	38		
Change from baseline to EOS visit- +1	11	2		
Change from baseline to EOS visit- +2	13	7		
Change from baseline to EOS visit- +3	7	6		
Change from baseline to EOS visit- +4	1	0		

Notes:

[35] - Baseline: N=155 End of study visit: N=155

[36] - Baseline: N=82 End of study visit: N=81

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of subjects with clinical worsening

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

Time to clinical worsening was a parameter that combined death and events reflective of persistent clinical worsening of the subject's underlying diagnosis of pulmonary hypertension (PH).

End point type	Other pre-specified
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End point timeframe:

From the baseline to End of study visit

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	82		
Units: Subjects				
Pulmonary endarterectomy	4	3		
Hospitalization due to PH	7	3		
Start of new PH treatment	21	9		
Decrease in 6MWD due to PH	4	2		
Persistent worsening of functional class due to PH	7	2		
Death	22	13		
Any clinical worsening	45	23		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of clinical worsening events

End point title	Incidence of clinical worsening events
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End point description:

Time to clinical worsening was a parameter that combined death and events reflective of persistent clinical worsening of the subject's underlying diagnosis of pulmonary hypertension (PH).

End point type	Other pre-specified
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End point timeframe:

From the baseline to End of study visit

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	82		
Units: Percentage per 100 person-years				
number (not applicable)				
Pulmonary endarterectomy	0.73	1.04		
Hospitalization due to PH	1.65	1.04		
Start of new PH treatment	4.40	3.81		
Decrease in 6MWD due to PH	0.73	0.69		
Persistent worsening of functional class due to PH	1.28	0.69		
Death	4.04	4.50		
Any clinical worsening event	12.85	11.77		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in Borg CR 10 Scale

End point title	Change from baseline in Borg CR 10 Scale
End point description:	
The Borg CR10 Scale was measured in conjunction with the 6MWD test. The test was explained to the subject before starting the 6MWD test. Subjects were asked to rank their exertion at the end of the 6MWD test. Low values indicate low levels of exertion; high values indicate more intense exertion reported by the participant. The score ranges from 0 ("Nothing at all") to 10 ("Extremely strong – Maximal").	
End point type	Other pre-specified
End point timeframe:	
From baseline to Week 12	

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[37]	82 ^[38]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline (Week 0)	4.36 (± 2.30)	4.45 (± 2.26)		
Change from baseline to Week 12	-1.04 (± 2.35)	-0.70 (± 1.93)		

Notes:

[37] - Baseline: N=155 Week 12: N=143

[38] - Baseline: N=82 Week 12: N=75

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in score of EQ-5D questionnaire

End point title	Change in score of EQ-5D questionnaire
End point description: The EQ-5D is a standardized instrument for use as a measure of health outcome. The EQ-5D is a self report questionnaire. The utility score is calculated based on five questions concerning problems with mobility, self-care, usual activities, pain/discomfort and anxiety/depression. An increase in the utility score represents an improvement in quality of life. The score ranges from -0.594 (worst answer in all five questions) to 1 (best answer in all five questions).	
End point type	Other pre-specified
End point timeframe: From baseline to End of study visit	

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[39]	82 ^[40]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline (Week 0)	0.6406 (± 0.2509)	0.6569 (± 0.2518)		
Change from baseline to End of study Visit	-0.1008 (± 0.4965)	-0.1230 (± 0.5213)		

Notes:

[39] - Baseline: N=154 End of study visit: N=154

[40] - Baseline: N=81 End of study visit: N=81

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in score of Living with Pulmonary Hypertension (LPH) questionnaire

End point title	Change in score of Living with Pulmonary Hypertension (LPH) questionnaire
End point description: The LPH questionnaire is designed to measure the effects of PH and PH-specific treatments on an individual's quality of life. The LPH is a self-report questionnaire and was completed by the subject. The LPH total score can range from 0 (best) to 105 (worst).	
End point type	Other pre-specified
End point timeframe: From baseline to End of study visit	

End point values	Riociguat- Former Riociguat 1.0- 2.5 mg	Riociguat- Former Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 ^[41]	82 ^[42]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline (Week 0)	42.19 (± 22.05)	46.01 (± 22.93)		
Change from baseline to End of study Visit	-2.64 (± 29.26)	-0.56 (± 30.83)		

Notes:

[41] - Baseline: N=152 End of study visit: N=152

[42] - Baseline: N=80 End of study visit: N=80

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From administration of first dose of study medication up to 2 days after end of treatment with study medication.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Former Riociguat 1.0-2.5 mg
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Reporting group description:

Subjects from the riociguat 1.0-2.5 mg group of CHEST-1 entered the extension study(CHEST-2) with the same dose as they received on the last day of CHEST-1 (Visit7).

Reporting group title	Former Placebo
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Reporting group description:

Subjects from the placebo group of CHEST-1 entered the extension study (CHEST-2),the starting dose in CHEST-2 was 1.0 mg riociguat tid.

Serious adverse events	Former Riociguat 1.0-2.5 mg	Former Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 155 (61.94%)	56 / 82 (68.29%)	
number of deaths (all causes)	22	13	
number of deaths resulting from adverse events	22	13	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	3 / 155 (1.94%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			

subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transitional cell carcinoma			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal neoplasm			

subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 155 (1.94%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporal arteritis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 155 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Angioplasty			
subjects affected / exposed	0 / 155 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colostomy			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal dialysis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Removal of internal fixation			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenectomy			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transurethral prostatectomy			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreectomy			

subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava filter insertion			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterosalpingo-oophorectomy			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee operation			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical conisation			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ablation			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery therapeutic procedure			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract operation			

subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary endarterectomy			
subjects affected / exposed	2 / 155 (1.29%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 155 (0.65%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Fatigue			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oedema peripheral			
subjects affected / exposed	1 / 155 (0.65%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic mass			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Bartholin's cyst			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Adenomyosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (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	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchospasm			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 155 (1.29%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	4 / 155 (2.58%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	1 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiogenic pulmonary oedema			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 155 (1.29%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	16 / 155 (10.32%)	13 / 82 (15.85%)	
occurrences causally related to treatment / all	1 / 29	0 / 15	
deaths causally related to treatment / all	0 / 2	0 / 3	
Pulmonary oedema			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			

subjects affected / exposed	4 / 155 (2.58%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric decompensation			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular cognitive impairment			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Angiogram pulmonary			
subjects affected / exposed	0 / 155 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation cardiac			
subjects affected / exposed	8 / 155 (5.16%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colonoscopy			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigation			
subjects affected / exposed	2 / 155 (1.29%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hip fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 155 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			

subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			

subjects affected / exposed	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	5 / 155 (3.23%)	5 / 82 (6.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	5 / 155 (3.23%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 155 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	5 / 155 (3.23%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 5	0 / 1	
Cardiac failure			
subjects affected / exposed	8 / 155 (5.16%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cor pulmonale chronic			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	13 / 155 (8.39%)	8 / 82 (9.76%)	
occurrences causally related to treatment / all	0 / 24	0 / 13	
deaths causally related to treatment / all	0 / 5	0 / 1	
Supraventricular extrasystoles			

subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute right ventricular failure			
subjects affected / exposed	3 / 155 (1.94%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	14 / 155 (9.03%)	11 / 82 (13.41%)	
occurrences causally related to treatment / all	3 / 16	5 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar stroke			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 155 (2.58%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	3 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (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	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	6 / 155 (3.87%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gingival bleeding			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			

subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal haemorrhage			

subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 155 (1.29%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic kidney disease			
subjects affected / exposed	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	3 / 155 (1.94%)	5 / 82 (6.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endocrine disorders			
Myxoedema			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal osteoarthritis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 155 (1.29%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 155 (1.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	17 / 155 (10.97%)	7 / 82 (8.54%)	
occurrences causally related to treatment / all	0 / 20	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pyelonephritis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 155 (1.94%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 155 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 155 (1.29%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdiaphragmatic abscess			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 155 (1.94%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone abscess			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 155 (0.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 155 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoproteinaemia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steroid diabetes			
subjects affected / exposed	1 / 155 (0.65%)	0 / 82 (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	Former Riociguat 1.0-2.5 mg	Former Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 155 (95.48%)	79 / 82 (96.34%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	12 / 155 (7.74%)	10 / 82 (12.20%)	
occurrences (all)	13	13	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	7 / 155 (4.52%)	7 / 82 (8.54%)	
occurrences (all)	12	9	
Chest pain			

subjects affected / exposed	15 / 155 (9.68%)	8 / 82 (9.76%)	
occurrences (all)	20	10	
Fatigue			
subjects affected / exposed	10 / 155 (6.45%)	8 / 82 (9.76%)	
occurrences (all)	10	8	
Oedema			
subjects affected / exposed	6 / 155 (3.87%)	8 / 82 (9.76%)	
occurrences (all)	8	13	
Oedema peripheral			
subjects affected / exposed	38 / 155 (24.52%)	27 / 82 (32.93%)	
occurrences (all)	58	40	
Pyrexia			
subjects affected / exposed	9 / 155 (5.81%)	4 / 82 (4.88%)	
occurrences (all)	11	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	27 / 155 (17.42%)	17 / 82 (20.73%)	
occurrences (all)	34	23	
Dyspnoea			
subjects affected / exposed	25 / 155 (16.13%)	15 / 82 (18.29%)	
occurrences (all)	29	23	
Epistaxis			
subjects affected / exposed	17 / 155 (10.97%)	11 / 82 (13.41%)	
occurrences (all)	20	15	
Haemoptysis			
subjects affected / exposed	8 / 155 (5.16%)	6 / 82 (7.32%)	
occurrences (all)	10	9	
Hypoxia			
subjects affected / exposed	8 / 155 (5.16%)	9 / 82 (10.98%)	
occurrences (all)	8	10	
Productive cough			
subjects affected / exposed	8 / 155 (5.16%)	3 / 82 (3.66%)	
occurrences (all)	9	4	
Pulmonary hypertension			

subjects affected / exposed occurrences (all)	8 / 155 (5.16%) 16	7 / 82 (8.54%) 8	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	8 / 155 (5.16%) 8	9 / 82 (10.98%) 10	
Investigations Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all) Blood potassium decreased subjects affected / exposed occurrences (all) International normalised ratio increased subjects affected / exposed occurrences (all)	10 / 155 (6.45%) 15 1 / 155 (0.65%) 1 13 / 155 (8.39%) 19	2 / 82 (2.44%) 2 5 / 82 (6.10%) 9 6 / 82 (7.32%) 6	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all)	4 / 155 (2.58%) 4 9 / 155 (5.81%) 10 12 / 155 (7.74%) 16	5 / 82 (6.10%) 5 3 / 82 (3.66%) 3 7 / 82 (8.54%) 8	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) Palpitations subjects affected / exposed occurrences (all) Supraventricular extrasystoles	12 / 155 (7.74%) 13 13 / 155 (8.39%) 15	6 / 82 (7.32%) 11 9 / 82 (10.98%) 11	

subjects affected / exposed occurrences (all)	2 / 155 (1.29%) 3	5 / 82 (6.10%) 8	
Ventricular extrasystoles subjects affected / exposed occurrences (all)	4 / 155 (2.58%) 4	5 / 82 (6.10%) 8	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	34 / 155 (21.94%) 47	20 / 82 (24.39%) 28	
Headache subjects affected / exposed occurrences (all)	14 / 155 (9.03%) 19	12 / 82 (14.63%) 21	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	15 / 155 (9.68%) 24	9 / 82 (10.98%) 9	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	8 / 155 (5.16%) 11	8 / 82 (9.76%) 8	
Abdominal pain upper subjects affected / exposed occurrences (all)	13 / 155 (8.39%) 16	7 / 82 (8.54%) 9	
Constipation subjects affected / exposed occurrences (all)	14 / 155 (9.03%) 17	9 / 82 (10.98%) 11	
Diarrhoea subjects affected / exposed occurrences (all)	30 / 155 (19.35%) 37	17 / 82 (20.73%) 27	
Dyspepsia subjects affected / exposed occurrences (all)	17 / 155 (10.97%) 22	11 / 82 (13.41%) 12	
Gastritis subjects affected / exposed occurrences (all)	4 / 155 (2.58%) 5	6 / 82 (7.32%) 6	
Gastrooesophageal reflux disease			

subjects affected / exposed occurrences (all)	9 / 155 (5.81%) 10	4 / 82 (4.88%) 5	
Nausea subjects affected / exposed occurrences (all)	19 / 155 (12.26%) 23	16 / 82 (19.51%) 27	
Toothache subjects affected / exposed occurrences (all)	10 / 155 (6.45%) 10	4 / 82 (4.88%) 4	
Vomiting subjects affected / exposed occurrences (all)	15 / 155 (9.68%) 19	8 / 82 (9.76%) 8	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	9 / 155 (5.81%) 10	3 / 82 (3.66%) 3	
Rash subjects affected / exposed occurrences (all)	2 / 155 (1.29%) 2	6 / 82 (7.32%) 6	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	28 / 155 (18.06%) 33	10 / 82 (12.20%) 19	
Back pain subjects affected / exposed occurrences (all)	27 / 155 (17.42%) 40	11 / 82 (13.41%) 14	
Muscle spasms subjects affected / exposed occurrences (all)	8 / 155 (5.16%) 12	4 / 82 (4.88%) 6	
Musculoskeletal pain subjects affected / exposed occurrences (all)	8 / 155 (5.16%) 8	5 / 82 (6.10%) 6	
Pain in extremity subjects affected / exposed occurrences (all)	16 / 155 (10.32%) 16	8 / 82 (9.76%) 11	
Infections and infestations			

Bronchitis			
subjects affected / exposed	24 / 155 (15.48%)	11 / 82 (13.41%)	
occurrences (all)	39	15	
Influenza			
subjects affected / exposed	7 / 155 (4.52%)	5 / 82 (6.10%)	
occurrences (all)	7	8	
Nasopharyngitis			
subjects affected / exposed	55 / 155 (35.48%)	24 / 82 (29.27%)	
occurrences (all)	108	47	
Pneumonia			
subjects affected / exposed	11 / 155 (7.10%)	4 / 82 (4.88%)	
occurrences (all)	12	4	
Upper respiratory tract infection			
subjects affected / exposed	26 / 155 (16.77%)	13 / 82 (15.85%)	
occurrences (all)	32	25	
Urinary tract infection			
subjects affected / exposed	15 / 155 (9.68%)	9 / 82 (10.98%)	
occurrences (all)	24	15	
Respiratory tract infection			
subjects affected / exposed	12 / 155 (7.74%)	8 / 82 (9.76%)	
occurrences (all)	27	17	
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	5 / 155 (3.23%)	7 / 82 (8.54%)	
occurrences (all)	5	8	
Hypokalaemia			
subjects affected / exposed	16 / 155 (10.32%)	9 / 82 (10.98%)	
occurrences (all)	20	14	
Decreased appetite			
subjects affected / exposed	6 / 155 (3.87%)	6 / 82 (7.32%)	
occurrences (all)	6	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2009	Amendment 3: This amendment was implemented in response to recommendations from a series of investigator meetings conducted on a global level. The major changes concerned: - Clarifications and additions of exclusion criteria, including mandatory withdrawal from the trial if a subject misses study medication for longer than 3 days at a stretch (9 missing doses) during the titration phase - Specification of 6MWD test - Change of Modified Borg Dyspnoea score to Borg CR10 Scale - Collection of healthcare resource information - Addition of definition of physical training program - Specification of timelines for study medication dosing - Addition of methodology for blood pressure measurement - Addition of dizziness and syncope as undesirable effects - Extension of visit window from Vn on to 14 days - Addition of role of SC and DMC
21 March 2010	Amendment 4: This amendment was implemented in response to recommendations from the SC and a series of investigator meetings conducted on a global level. The major changes concerned: - Abolition of mandatory overnight stays at Visit1 - Clarification of contraception methods in exclusion criteria - Clarification of pregnancy testing - Change in assessment periods - Clarification of use of the Modified Borg Dyspnoea Score in subjects who were enrolled before approval of CHEST-1 amendment3 in their country - Collection of smoking status information - Smoking added as interaction. Clearance of riociguat was found to be increased in smokers compared to non-smokers in study12166 in subjects with PH. - Addition of vomiting and gastritis as undesirable effects - Visit window for safety follow-up visit extended from 30 (+2) days to 30 (+5) days.
14 February 2011	Amendment 5: This amendment modified the protocol to correct some typographical errors and to add laboratory measurements for calcium and phosphate for subjects included under amendment6 of CHEST-1.
12 December 2012	Amendment 8: This amendment was initiated as an update based on the results of CHEST-1 and the overall riociguat development program. Changes to the protocol focused on operational aspects and were to facilitate some of the study-related activities. Among others, central laboratory and ECG collection was stopped and instead performed locally upon decision of the investigator. Visit procedures at individual visits were reduced, but all other aspects of safety monitoring remained unchanged. Other changes concerned: - Clarification of SAE definition: any hospitalization required to conduct a routine RHC was excluded from the definition - Change in 6MWD test: two conditions related to supplemental oxygen were removed. - DMC: a statement was added that DMC would stop when all patients are on open label dose of riociguat.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported