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 symptomatic Pulmonary Arterial Hypertension (PAH).

Summary

EudraCT number	2008-003610-94
Trial protocol	DE FR SE AT GB IE BE CZ DK IT NL ES PT GR
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 63-2521/12935

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00863681
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	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 treatment naive patients and patients pretreated with an Endothelin Receptor Antagonist or a Prostacycline Analogue with symptomatic Pulmonary Arterial Hypertension (PAH).

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/legal representatives. Participating subjects/legal representatives signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. The assent of a minor was also requested where such a person was able to express his own will. His refusal or the withdrawal of his consent was not to be disregarded. 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	11 March 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: 17
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	China: 73
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	United Kingdom: 15

Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Brazil: 26
Country: Number of subjects enrolled	Mexico: 16
Worldwide total number of subjects	396
EEA total number of subjects	160

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)	306
From 65 to 84 years	90
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 97 centers in 27 countries between 12-MAR-2009 (first subject first visit) and 19-AUG-2019 (last subject last visit);

Pre-assignment

Screening details:

Of the 405 subjects who completed PATENT-1 study, 396 subjects entered PATENT-2 study. 231 subjects were from the former riociguat 1.0-2.5mg group, 109 were from the former placebo group and 56 were from the former riociguat 1.0-1.5mg group.

Period 1

Period 1 title	Overall period (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 from the former riociguat (BAY 63-2521) 1.0 - 2.5 mg treatment group in PATENT-1 (2008-003482-68)

Arm type	Experimental
Investigational medicinal product name	Riociguat
Investigational medicinal product code	BAY 63-2521
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects from the riociguat 1.0-2.5 mg individual dose titration group of PATENT-1 entered the extension study on the same dose level as they received on the last day of PATENT-1. These subjects received sham titration during the titration phase of PATENT-2. To maintain the blinding of PATENT-1, the PATENT-2 study medication (open-label riociguat) was blinded with respect to the dose during the titration phase, and investigators did not know at which dose level a subject entered the PATENT-2 study. The individual dose was not increased above the dose received on the last day of PATENT-1. 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, dose modifications were possible.

Arm title	Riociguat-Former Placebo

Arm description:

Subjects were from the former placebo group of PATENT-1

Arm type	Experimental
Investigational medicinal product name	Riociguat
Investigational medicinal product code	BAY 63-2521
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects from the placebo group of the PATENT-1 study started at Visit 1 of the PATENT-2 study with a riociguat dose of 1.0 mg tid and were up-titrated in a blinded manner. 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, subjects reached riociguat doses between 0.5mg tid and 2.5mg tid.

Arm title	Riociguat-Former Riociguat 1.0–1.5 mg

Arm description:

Subjects from the former riociguat (BAY 63-2521) 1.0 - 1.5 mg treatment group in PATENT-1

Arm type	Experimental
Investigational medicinal product name	Riociguat
Investigational medicinal product code	BAY 63-2521
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects from the PATENT-1 riociguat 1.0-1.5mg group entered the extension study PATENT-2 on the same dose level as they received on the last day of PATENT-1. For subjects with a starting dose of 1.5mg riociguat tid in PATENT-2, the individual optimal riociguat dose was to be determined every 2 weeks according to the peripheral SBP measured at trough before intake of the next morning dose. At the end of the titration phase, subjects reached riociguat doses between 0.5mg tid and 2.5mg tid. For subjects with a starting dose of 1.0mg or 0.5mg riociguat tid in PATENT-2, the dose was not to be further increased until Visit5. If the investigator requested a dose increase above that level via the IVRS, the subject underwent a sham titration. However, if the investigator requested a dose decrease, dose modifications were possible, but without a subsequent re-increase before Visit5. Subjects who did not tolerate the lowest riociguat dose (0.5mg tid) were to be withdrawn from the study.

Number of subjects in period 1	Riociguat-Former Riociguat 1.0–2.5 mg	Riociguat-Former Placebo	Riociguat-Former Riociguat 1.0–1.5 mg
Started	231	109	56
Completed	140	66	38
Not completed	91	43	18
Consent withdrawn by subject	12	5	2
Adverse event, non-fatal	28	10	6
Other	2	-	-
Death	40	23	6
Non-compliance with study drug	1	3	-
Lost to follow-up	3	-	3
Missing	1	-	-
Protocol deviation	2	-	-
Lack of efficacy	2	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Riociguat-Former Riociguat 1.0–2.5 mg
Reporting group description:	
Subjects from the former riociguat (BAY 63-2521) 1.0 - 2.5 mg treatment group in PATENT-1 (2008-003482-68)	
Reporting group title	Riociguat-Former Placebo
Reporting group description:	
Subjects were from the former placebo group of PATENT-1	
Reporting group title	Riociguat-Former Riociguat 1.0–1.5 mg
Reporting group description:	
Subjects from the former riociguat (BAY 63-2521) 1.0 - 1.5 mg treatment group in PATENT-1	

Reporting group values	Riociguat-Former Riociguat 1.0–2.5 mg	Riociguat-Former Placebo	Riociguat-Former Riociguat 1.0–1.5 mg
Number of subjects	231	109	56
Age Categorical Units: Subjects			
Adults (18-64 years)	174	87	45
From 65-84 years	57	22	11
Age Continuous Units: years			
arithmetic mean	50.4	48.8	48.2
standard deviation	± 16.4	± 15.9	± 16.3
Gender Categorical Units: Subjects			
Female	186	87	44
Male	45	22	12
Race / Ethnicity Units: Subjects			
White	148	66	28
Black or African American	2	1	1
Asian	74	33	20
Hispanic or Latino	7	8	7
Multiple	0	1	0

Reporting group values	Total		
Number of subjects	396		
Age Categorical Units: Subjects			
Adults (18-64 years)	306		
From 65-84 years	90		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender Categorical Units: Subjects			
Female	317		
Male	79		
Race / Ethnicity Units: Subjects			
White	242		
Black or African American	4		
Asian	127		
Hispanic or Latino	22		
Multiple	1		

End points

End points reporting groups

Reporting group title	Riociguat-Former Riociguat 1.0–2.5 mg
Reporting group description:	
Subjects from the former riociguat (BAY 63-2521) 1.0 - 2.5 mg treatment group in PATENT-1 (2008-003482-68)	
Reporting group title	Riociguat-Former Placebo
Reporting group description:	
Subjects were from the former placebo group of PATENT-1	
Reporting group title	Riociguat-Former Riociguat 1.0–1.5 mg
Reporting group description:	
Subjects from the former riociguat (BAY 63-2521) 1.0 - 1.5 mg treatment group in PATENT-1	
Subject analysis set title	long-term safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All 396 subjects who received 1 of 3 blinded treatments for 12 weeks in the double-blind PATENT-1 study entered long term extension PATENT-2 study. Baseline of PATENT-2 was Week 0 of PATENT-1. All 396 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 in PATENT-2 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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	109	56	
Units: Subjects				
Any TEAE	229	108	56	
Any drug-related TEAE	138	74	30	
Any serious TEAE	161	76	39	
Any drug-related serious TEAE	25	16	3	
Any TEAE leading to death	42	25	6	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subject with death

End point title	Number of subject with death[2]

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 end of 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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	109	56	
Units: Subjects				
Death	48	30	7	

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	109	56	
Units: Percentage				
number (not applicable)				
aPTT (Sec)	68.1	80.0	79.2	
Basophils (Giga/L)	1.0	1.1	2.0	
Basophils/Leukocytes (%)	16.4	12.1	10.4	
Eosinophils (Giga/L)	1.9	2.2	2.0	
Eosinophils/Leukocytes (%)	8.7	3.4	10.4	
Erythrocytes (T/L)	13.7	21.8	35.0	
Hematocrit (%)	35.6	37.7	48.6	
Hemoglobin (g/dL)	8.9	16.5	24.4	
Leukocytes (Giga/L)	10.9	13.6	22.2	
Lymphocytes (Giga/L)	1.4	3.4	0.0	
Lymphocytes/Leukocytes (%)	11.4	19.5	6.5	
Monocytes (Giga/L)	6.3	3.3	0.0	
Monocytes/Leukocytes (%)	20.0	18.0	22.2	
Neutrophils (Giga/L)	14.2	18.8	28.3	
Neutrophils/Leukocytes (%)	42.5	38.3	52.3	
Platelets (Giga/L)	14.9	9.7	15.6	
Prothrombin INR	56.3	74.0	58.6	

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

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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	109	56	
Units: Percentage				
number (not applicable)				
aPTT (Sec)	12.8	13.5	8.5	
Erythrocytes (T/L)	31.0	22.8	25.0	
Hematocrit (%)	22.1	23.3	26.7	
Hemoglobin (g/dL)	48.2	38.0	46.2	
Leukocytes (Giga/L)	25.7	23.6	25.6	
Lymphocytes (Giga/L)	29.3	29.3	32.6	
Lymphocytes/Leukocytes (%)	50.3	44.6	64.3	
Monocytes (Giga/L)	0.5	1.1	2.0	
Monocytes/Leukocytes (%)	2.4	3.3	14.3	
Neutrophils (Giga/L)	9.4	4.4	8.5	
Neutrophils/Leukocytes (%)	6.9	4.5	6.5	
Platelets (Giga/L)	23.8	29.5	26.8	
Prothrombin INR	0.0	0.0	0.0	

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

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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	109	56	
Units: Percentage				
number (not applicable)				

Alanine Aminotransferase (U/L)	13.4	12.0	8.7	
Albumin (g/dL)	0.5	1.0	0.0	
Alkaline Phosphatase (U/L)	15.7	23.4	15.6	
Aspartate Aminotransferase (U/L)	11.6	11.5	10.6	
Bilirubin (mg/dL)	14.5	11.8	28.9	
Calcium(mg/dL)	2.5	0.0	0.0	
Creatine Kinase (U/L)	23.8	24.7	19.1	
Creatinine (mg/dL)	29.4	39.7	45.5	
Gamma Glutamyl Transferase(U/L)	18.2	17.1	25.0	
Glutamate Dehydrogenase (U/L)	40.0	37.7	56.8	
Phosphate (mg/dL)	2.6	0.0	0.0	
Potassium (mmol/L)	4.6	4.9	8.0	
Protein (g/dL)	2.3	4.9	3.8	
Pseudocholinesterase (U/mL)	0.5	0.0	0.0	
Sodium (mmol/L)	0.5	1.9	3.8	
Triacylglycerol Lipase (U/L)	22.6	19.3	12.2	
Urate (mg/dL)	24.3	25.3	29.3	
Urea (mg/dL)	20.1	18.9	30.4	
eGFR - MDRD Method (mL/min/1.73 m*2)	0.0	0.0	0.0	
Creatinine Clearance (mL/min)	12.1	15.4	13.3	

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

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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	109	56	
Units: Percentage				
number (not applicable)				

Alanine Aminotransferase (U/L)	0.0	0.0	0.0	
Albumin (g/dL)	4.1	4.0	0.0	
Alkaline Phosphatase (U/L)	3.3	4.0	0.0	
Bilirubin (mg/dL)	0.0	1.0	0.0	
Calcium (mg/dL)	25.0	10.0	20.0	
Creatine Kinase (U/L)	8.7	5.1	12.2	
Creatinine (mg/dL)	4.5	6.9	5.8	
Gamma Glutamyl Transferase (U/L)	0.0	0.0	0.0	
Phosphate (mg/dL)	5.3	15.4	33.3	
Potassium (mmol/L)	24.9	32.6	29.8	
Protein (g/dL)	9.0	10.3	8.5	
Pseudocholinesterase (U/mL)	11.0	11.1	8.0	
Sodium (mmol/L)	8.5	13.0	11.8	
Triacylglycerol Lipase (U/L)	0.0	0.0	0.0	
Urate (mg/dL)	3.6	5.0	3.8	
Urea (mg/dL)	0.9	1.0	0.0	
eGFR - MDRD Method(mL/min/1.73 m*2)	19.0	17.4	23.3	
Creatinine Clearance (mL/min)	45.7	30.3	48.4	

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 participant 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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[3]	109[4]	56[5]	
Units: millimetre(s) of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	114.36 (± 14.78)	113.75 (± 12.76)	110.88 (± 12.49)	
Change from baseline to Termination visit	-0.88 (± 15.82)	-1.30 (± 15.62)	-0.99 (± 16.12)	

Notes:

[3] - Baseline: N=231 Termination visit: N=169

[4] - Baseline: N=109 Termination visit: N=80

[5] - Baseline: N=56 Termination visit: N=41

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)

End point description:

DBP was measured after the participants 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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[6]	109[7]	56[8]	
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (Week 0)	72.03 (± 10.53)	71.84 (± 9.06)	69.61 (± 9.89)	
Change from baseline to Termination visit	-3.33 (± 12.90)	-4.00 (± 11.72)	-2.13 (± 9.65)	

Notes:

[6] - Baseline: N=231 Termination visit: N=169

[7] - Baseline: N=109 Termination visit: N=80

[8] - Baseline: N=56 Termination visit: N=41

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of Heart rate

End point title	Change of Heart rate

End point description:

Heart rate was measured after the participant 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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[9]	109[10]	56[11]	
Units: beats/minute (BPM)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	76.47 (± 11.04)	77.30 (± 12.53)	76.04 (± 10.83)	
Change from baseline to Termination visit	0.75 (± 13.92)	0.18 (± 14.07)	-1.10 (± 14.74)	

Notes:

[9] - Baseline: N=231 Termination visit: N=169

[10] - Baseline: N=109 Termination visit: N=80

[11] - Baseline: N=56 Termination visit: N=41

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[12]	109[13]	56[14]	
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	68.24 (± 18.25)	69.03 (± 16.94)	69.62 (± 15.01)	
From baseline to Termination visit	-1.67 (± 6.45)	0.04 (± 6.04)	-1.79 (± 8.08)	

Notes:

[12] - Baseline: N=231 Termination visit: N=169

[13] - Baseline: N=109 Termination visit: N=81

[14] - Baseline: N=56 Termination visit: N=41

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)

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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[15]	109[16]	56[17]	
Units: Percentage				
arithmetic mean (standard deviation)				
Baseline (Week 0)	95.10 (± 2.61)	94.32 (± 3.18)	94.00 (± 2.95)	
From baseline to Termination visit	-1.14 (± 3.48)	-0.56 (± 4.45)	-4.30 (± 5.23)	

Notes:

[15] - Baseline: N=227 Termination visit: N=15

[16] - Baseline: N=109 Termination visit: N=9

[17] - Baseline: N=56 Termination visit: N=2

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 (PaO2)

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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[18]	109[19]	56[20]	
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (Week 0)	76.99 (± 17.60)	74.54 (± 17.84)	72.12 (± 13.63)	
From baseline to Termination visit	-4.77 (± 17.42)	7.14 (± 58.00)	-8.05 (± 2.76)	

Notes:

[18] - Baseline: N=227 Termination visit: N=15

[19] - Baseline: N=109 Termination visit: N=9

[20] - Baseline: N=56 Termination visit: N=2

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 (PaCO2)

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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[21]	109[22]	56[23]	
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (Week 0)	32.94 (± 4.62)	32.46 (± 4.63)	33.40 (± 4.41)	
From baseline to Termination visit	-1.87 (± 3.72)	-0.68 (± 5.70)	2.00 (± 4.24)	

Notes:

[21] - Baseline: N=227 Termination visit: N=15

[22] - Baseline: N=109 Termination visit: N=9

[23] - Baseline: N=56 Termination visit: N=2

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)

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 participant 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.

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[24]	109[25]	56[26]	
Units: millisecond (msec)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	817.69 (± 125.61)	828.96 (± 146.32)	822.33 (± 130.27)	
Change rom baseline to Month 48	59.07 (± 109.89)	75.69 (± 181.94)	89.61 (± 113.25)	

Notes:

[24] - Baseline: N=218 Month 48: N=15

[25] - Baseline: N=103 Month 48: N=7

[26] - Baseline: N=53 Month 48: N=6

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 participant 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.

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[27]	109[28]	56[29]	
Units: msec				
arithmetic mean (standard deviation)				

Baseline (Week 0)	171.07 (± 27.76)	173.97 (± 32.90)	171.74 (± 25.77)	
Change from baseline to Month 48	7.51 (± 16.29)	16.50 (± 19.41)	-3.22 (± 17.18)	

Notes:

[27] - Baseline: N=211 Month 48: N=15

[28] - Baseline: N=102 Month 48: N=6

[29] - Baseline: N=53 Month 48: N=6

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

End point description:

QRS duration was evaluated as part of ECG. ECGs were recorded after the participant 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.

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[30]	109[31]	56[32]	
Units: msec				
arithmetic mean (standard deviation)				
Baseline (Week 0)	99.59 (± 17.38)	100.09 (± 16.15)	103.22 (± 19.82)	
Change from baseline to Month 48	5.07 (± 8.56)	11.14 (± 18.69)	-0.44 (± 7.52)	

Notes:

[30] - Baseline: N=213 Month 48: N=15

[31] - Baseline: N=103 Month 48: N=7

[32] - Baseline: N=53 Month 48: N=6

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

End point description:

QT duration was evaluated as part of ECG. ECGs were recorded after the participant 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.

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[33]	109[34]	56[35]	
Units: msec				
arithmetic mean (standard deviation)				
Baseline (Week 0)	401.56 (± 31.35)	406.67 (± 35.44)	405.10 (± 30.52)	
Change from baseline to Month 48	10.93 (± 27.58)	16.89 (± 16.78)	27.34 (± 28.61)	

Notes:
[33] - Baseline: N=177 Month 48: N=9
[34] - Baseline: N=76 Month 48: N=3
[35] - Baseline: N=40 Month 48: N=4

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[36]	109[37]	56[38]	
Units: meters				
median (full range (min-max))				
Baseline (Week 0)	375.0 (160 to 468)	395.0 (174 to 450)	376.0 (158 to 448)	
Change from baseline to End of study visit	19.0 (-448 to 309)	9.0 (-446 to 275)	1.5 (-448 to 492)	

Notes:
[36] - Baseline: N=231 End of study visit: N=231
[37] - Baseline: N=109 End of study visit: N=109
[38] - Baseline: N=56 End of study visit: N=56

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.
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

End point values	Riociguat-Former Riociguat 1.0–2.5 mg	Riociguat-Former Placebo	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[39]	109[40]	56[41]	
Units: dyn*s*cm-5				
arithmetic mean (standard deviation)				
Baseline (Week 0)	802.40 (± 452.97)	835.45 (± 476.52)	855.70 (± 552.92)	
Change from baseline to Termination Visit	34.25 (± 104.83)	0 (± 0)	0 (± 0)	

Notes:

[39] - Baseline: N=228 Termination Visit: N=2

[40] - Baseline: N=103 Termination Visit: N=0

[41] - Baseline: N=56 Termination Visit: 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)

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[42]	109[43]	56[44]	
Units: picograms/millilitre (pg/mL)				
arithmetic mean (standard deviation)				
Baseline (Week 0)	996.30 (± 1627.48)	1135.68 (± 1533.20)	1220.11 (± 1457.90)	
Change from baseline to End of study visit	82.52 (± 2253.30)	202.42 (± 3466.94)	115.77 (± 1918.81)	

Notes:

[42] - Baseline: N=210 End of study visit: N=210

[43] - Baseline: N=97 End of study visit: N=97

[44] - Baseline: N=47 End of study visit: N=47

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

End point description:

The subject's functional class was determined according to the WHO classification: I: Subjects 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: Subjects 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: Subjects 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: Subjects with PH with inability to carry out any physical activity without symptoms. These participants 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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[45]	109[46]	56[47]	
Units: Subjects				
Baseline (Week 0)-class I	5	3	4	
Baseline (Week 0)-class II	98	54	17	
Baseline (Week 0)-class III	128	49	35	
Baseline (Week 0)-class IV	0	2	0	
Baseline (Week 0)-Missing	0	1	0	
Change from baseline to EOS visit- -2	5	0	1	
Change from baseline to EOS visit- -1	50	16	13	
Change from baseline to EOS visit- 0	101	52	28	
Change from baseline to EOS visit- +1	23	15	6	
Change from baseline to EOS visit- +2	33	17	5	

Change from baseline to EOS visit- +3	19	8	3	

Notes:

[45] - Baseline: N=231 End of study visit: N=231

[46] - Baseline: N=109 End of study visit: N=108

[47] - Baseline: N=56 End of study visit: N=56

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

End point description:

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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	109	56	
Units: Subjects				
Any clinical worsening	87	41	18	
Heart/lung transplantation	3	0	2	
Atrial septostomy	1	1	0	
Hospitalization due to pulmonary hypertension	29	12	8	
Start of new pulmonary hypertension treatment	52	20	14	
Decrease in 6MWD due to pulmonary hypertension	7	6	2	
Persistent worsening of functional class due to PH	8	2	1	
Death	48	30	7	

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

End point description:

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

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	109	56	
Units: Percentage per 100 person-years				
number (not applicable)				
Any clinical worsening event	193	87	43	
Heart/Lung Transplantation	3	0	2	
Atrial Septostomy	1	1	0	
Hospitalization due to PH	39	15	13	
Start of new PH treatment	85	32	17	
Decrease in 6MWD due to PH	9	7	2	
Persistent worsening of functional class due to PH	8	2	2	
Death	48	30	7	

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 participant before starting the 6MWD test. Participants 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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[48]	109[49]	56[50]	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline (Week 0)	3.87 (± 2.24)	3.80 (± 2.26)	3.41 (± 1.77)	

Change from baseline to Week 12	-0.58 (± 1.84)	-0.54 (± 1.91)	-0.52 (± 1.64)	

Notes:

[48] - Baseline: N=231 Week 12: N=216

[49] - Baseline: N=109 Week 12: N=101

[50] - Baseline: N=56 Week 12: N=54

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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[51]	109[52]	56[53]	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline (Week 0)	0.6883 (± 0.2339)	0.6929 (± 0.2302)	0.6338 (± 0.2744)	
Change from baseline to EOS Visit	-0.2452 (± 0.5894)	-0.2812 (± 0.5944)	-0.0925 (± 0.4376)	

Notes:

[51] - Baseline: N=230 End of study visit: N=230

[52] - Baseline: N=107 End of study visit: N=107

[53] - Baseline: N=55 End of study visit: N=55

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 participant. 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	Riociguat-Former Riociguat 1.0–1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231[54]	109[55]	56[56]	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline (Week 0)	41.77 (± 22.18)	41.94 (± 23.34)	45.10 (± 22.08)	
Change from baseline to EOS Visit	4.99 (± 34.04)	12.28 (± 32.76)	-4.07 (± 31.40)	

Notes:

[54] - Baseline: N=225 End of study visit: N=225

[55] - Baseline: N=105 End of study visit: N=105

[56] - Baseline: N=55 End of study visit: N=55

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Former Riociguat 1.0- 2.5 mg

Reporting group description:

Patients from the PATENT-1 1.0 - 2.5 mg Dose Arm will enter the extension trial (PATENT-2)with the same dose which they have received on the last day of PATENT-1 (Visit 6).

Reporting group title	Former Riociguat 1.0 - 1.5 mg

Reporting group description:

Patients from the PATENT-1 1.0 - 1.5 mg Dose Arm will enter the extension trial (PATENT-2)with the same dose which they have received on the last day of PATENT-1 (Visit 6).

Reporting group title	Former Placebo

Reporting group description:

Patients from the PATENT-1 Placebo Arm will enter the extension trial (PATENT-2)with the starting dose 1 mg Riociguat tid.

Serious adverse events	Former Riociguat 1.0- 2.5 mg	Former Riociguat 1.0 - 1.5 mg	Former Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	161 / 231 (69.70%)	39 / 56 (69.64%)	76 / 109 (69.72%)
number of deaths (all causes)	48	7	30
number of deaths resulting from adverse events	42	6	25
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast neoplasm			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer metastatic			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal neoplasm			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lymphatic system neoplasm			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriovenous fistula			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	5 / 231 (2.16%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Raynaud's phenomenon			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vasculitis			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocele			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial septal defect repair			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac pacemaker insertion			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel decompression			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric polypectomy			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hysterectomy			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung transplant			

subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteotomy			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prophylaxis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central venous catheterisation			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swan ganz catheter placement			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin neoplasm excision			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental operation			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein operation			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder polypectomy			

subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Balloon atrial septostomy			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Trapeziectomy			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 2	0 / 0	1 / 3

Injection site pain			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Sudden cardiac death			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
General physical health deterioration			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exercise tolerance decreased			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug intolerance			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent stenosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Social circumstances			
Homicide			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ovarian cyst			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst ruptured			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal oedema			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial dysplasia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diaphragm muscle weakness			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	11 / 231 (4.76%)	1 / 56 (1.79%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 12	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	8 / 231 (3.46%)	2 / 56 (3.57%)	4 / 109 (3.67%)
occurrences causally related to treatment / all	5 / 12	0 / 2	0 / 5
deaths causally related to treatment / all	2 / 3	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	3 / 231 (1.30%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal obstruction			

subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal oedema			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 231 (0.87%)	1 / 56 (1.79%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			

subjects affected / exposed	3 / 231 (1.30%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	17 / 231 (7.36%)	6 / 56 (10.71%)	6 / 109 (5.50%)
occurrences causally related to treatment / all	0 / 21	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Pulmonary thrombosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary veno-occlusive disease			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sleep apnoea syndrome			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nasal cavity mass			

subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	31 / 231 (13.42%)	11 / 56 (19.64%)	14 / 109 (12.84%)
occurrences causally related to treatment / all	2 / 50	1 / 13	0 / 28
deaths causally related to treatment / all	2 / 9	0 / 1	0 / 7
Acute interstitial pneumonitis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity pneumonitis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lead dislodgement			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Biopsy			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheterisation cardiac			
subjects affected / exposed	18 / 231 (7.79%)	3 / 56 (5.36%)	4 / 109 (3.67%)
occurrences causally related to treatment / all	0 / 24	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest X-ray abnormal			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endoscopy			
subjects affected / exposed	1 / 231 (0.43%)	2 / 56 (3.57%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endoscopy upper gastrointestinal tract			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemoglobin decreased			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular pressure increased			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transplant evaluation			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Brain herniation			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Facial bones fracture			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femur fracture			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Snake bite			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous haematoma			

subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative hypotension			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			

subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest injury			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Heart disease congenital			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	3 / 231 (1.30%)	1 / 56 (1.79%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 231 (0.87%)	2 / 56 (3.57%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	5 / 231 (2.16%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	8 / 231 (3.46%)	1 / 56 (1.79%)	7 / 109 (6.42%)
occurrences causally related to treatment / all	0 / 13	0 / 3	0 / 8
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 2
Cardiac failure acute			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cor pulmonale chronic			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			

subjects affected / exposed	26 / 231 (11.26%)	7 / 56 (12.50%)	6 / 109 (5.50%)
occurrences causally related to treatment / all	0 / 47	0 / 9	0 / 8
deaths causally related to treatment / all	0 / 6	0 / 1	0 / 3
Supraventricular extrasystoles			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Acute coronary syndrome			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulseless electrical activity			

subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute right ventricular failure			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac dysfunction			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral infarction			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma hepatic			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 231 (0.87%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	26 / 231 (11.26%)	5 / 56 (8.93%)	15 / 109 (13.76%)
occurrences causally related to treatment / all	10 / 43	0 / 5	12 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem syndrome			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Central nervous system vasculitis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 231 (2.16%)	1 / 56 (1.79%)	6 / 109 (5.50%)
occurrences causally related to treatment / all	0 / 5	0 / 1	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spontaneous haematoma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choroidal neovascularisation			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic nerve disorder			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	3 / 231 (1.30%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	3 / 231 (1.30%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			

subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			

subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toothache			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic congestion			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fixed eruption			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyoderma gangrenosum			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	4 / 231 (1.73%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture delayed union			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	3 / 231 (1.30%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scleroderma			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sjogren's syndrome			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	3 / 231 (1.30%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			

subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma muscle			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Connective tissue disorder			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint instability			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic scleroderma			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	5 / 231 (2.16%)	2 / 56 (3.57%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 231 (0.87%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometritis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	7 / 231 (3.03%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 231 (0.43%)	1 / 56 (1.79%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 231 (0.00%)	2 / 56 (3.57%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 231 (0.87%)	2 / 56 (3.57%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periodontitis			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 231 (1.73%)	6 / 56 (10.71%)	7 / 109 (6.42%)
occurrences causally related to treatment / all	0 / 4	0 / 7	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumonia viral			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 231 (1.73%)	2 / 56 (3.57%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal abscess			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter infection			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteritis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma infection			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			

subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric infection			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection pseudomonal			
subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	2 / 231 (0.87%)	3 / 56 (5.36%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serratia infection			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastroenteritis norovirus			

subjects affected / exposed	0 / 231 (0.00%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial colitis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	2 / 231 (0.87%)	1 / 56 (1.79%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			

subjects affected / exposed	2 / 231 (0.87%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 56 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 56 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	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 Riociguat 1.0 - 1.5 mg	Former Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	218 / 231 (94.37%)	54 / 56 (96.43%)	106 / 109 (97.25%)
Vascular disorders			
Haematoma			
subjects affected / exposed	7 / 231 (3.03%)	3 / 56 (5.36%)	2 / 109 (1.83%)
occurrences (all)	8	3	2
Hypotension			
subjects affected / exposed	32 / 231 (13.85%)	10 / 56 (17.86%)	10 / 109 (9.17%)
occurrences (all)	39	13	14
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	17 / 231 (7.36%)	3 / 56 (5.36%)	6 / 109 (5.50%)
occurrences (all)	23	4	8
Chest discomfort			

subjects affected / exposed	15 / 231 (6.49%)	6 / 56 (10.71%)	6 / 109 (5.50%)
occurrences (all)	26	7	6
Chest pain			
subjects affected / exposed	32 / 231 (13.85%)	7 / 56 (12.50%)	16 / 109 (14.68%)
occurrences (all)	44	7	25
Fatigue			
subjects affected / exposed	20 / 231 (8.66%)	4 / 56 (7.14%)	12 / 109 (11.01%)
occurrences (all)	23	6	20
Oedema			
subjects affected / exposed	9 / 231 (3.90%)	4 / 56 (7.14%)	9 / 109 (8.26%)
occurrences (all)	11	6	11
Oedema peripheral			
subjects affected / exposed	64 / 231 (27.71%)	17 / 56 (30.36%)	31 / 109 (28.44%)
occurrences (all)	108	26	51
Pyrexia			
subjects affected / exposed	24 / 231 (10.39%)	3 / 56 (5.36%)	7 / 109 (6.42%)
occurrences (all)	45	3	8
Peripheral swelling			
subjects affected / exposed	7 / 231 (3.03%)	5 / 56 (8.93%)	4 / 109 (3.67%)
occurrences (all)	7	7	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	66 / 231 (28.57%)	13 / 56 (23.21%)	28 / 109 (25.69%)
occurrences (all)	94	20	42
Dyspnoea			
subjects affected / exposed	33 / 231 (14.29%)	12 / 56 (21.43%)	15 / 109 (13.76%)
occurrences (all)	54	15	21
Epistaxis			
subjects affected / exposed	30 / 231 (12.99%)	12 / 56 (21.43%)	16 / 109 (14.68%)
occurrences (all)	42	18	20
Haemoptysis			
subjects affected / exposed	20 / 231 (8.66%)	2 / 56 (3.57%)	9 / 109 (8.26%)
occurrences (all)	46	6	10
Nasal congestion			

subjects affected / exposed	8 / 231 (3.46%)	3 / 56 (5.36%)	6 / 109 (5.50%)
occurrences (all)	9	4	7
Productive cough			
subjects affected / exposed	12 / 231 (5.19%)	2 / 56 (3.57%)	8 / 109 (7.34%)
occurrences (all)	16	2	10
Pulmonary hypertension			
subjects affected / exposed	6 / 231 (2.60%)	3 / 56 (5.36%)	4 / 109 (3.67%)
occurrences (all)	8	4	6
Pulmonary arterial hypertension			
subjects affected / exposed	15 / 231 (6.49%)	2 / 56 (3.57%)	13 / 109 (11.93%)
occurrences (all)	20	2	20
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 231 (4.33%)	1 / 56 (1.79%)	8 / 109 (7.34%)
occurrences (all)	10	1	14
Depression			
subjects affected / exposed	13 / 231 (5.63%)	3 / 56 (5.36%)	6 / 109 (5.50%)
occurrences (all)	13	5	7
Insomnia			
subjects affected / exposed	21 / 231 (9.09%)	5 / 56 (8.93%)	10 / 109 (9.17%)
occurrences (all)	24	5	13
Investigations			
Blood potassium decreased			
subjects affected / exposed	8 / 231 (3.46%)	3 / 56 (5.36%)	4 / 109 (3.67%)
occurrences (all)	10	3	6
International normalised ratio increased			
subjects affected / exposed	9 / 231 (3.90%)	4 / 56 (7.14%)	4 / 109 (3.67%)
occurrences (all)	11	5	4
Weight decreased			
subjects affected / exposed	8 / 231 (3.46%)	0 / 56 (0.00%)	6 / 109 (5.50%)
occurrences (all)	9	0	7
Weight increased			
subjects affected / exposed	6 / 231 (2.60%)	5 / 56 (8.93%)	1 / 109 (0.92%)
occurrences (all)	8	7	1
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	12 / 231 (5.19%)	1 / 56 (1.79%)	2 / 109 (1.83%)
occurrences (all)	13	1	3
Contusion			
subjects affected / exposed	17 / 231 (7.36%)	1 / 56 (1.79%)	3 / 109 (2.75%)
occurrences (all)	24	1	4
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	3 / 231 (1.30%)	3 / 56 (5.36%)	3 / 109 (2.75%)
occurrences (all)	3	3	3
Cardiac failure			
subjects affected / exposed	6 / 231 (2.60%)	4 / 56 (7.14%)	2 / 109 (1.83%)
occurrences (all)	6	4	2
Palpitations			
subjects affected / exposed	22 / 231 (9.52%)	5 / 56 (8.93%)	14 / 109 (12.84%)
occurrences (all)	27	9	14
Right ventricular failure			
subjects affected / exposed	7 / 231 (3.03%)	3 / 56 (5.36%)	6 / 109 (5.50%)
occurrences (all)	10	3	6
Tachycardia			
subjects affected / exposed	9 / 231 (3.90%)	4 / 56 (7.14%)	4 / 109 (3.67%)
occurrences (all)	10	7	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	67 / 231 (29.00%)	15 / 56 (26.79%)	31 / 109 (28.44%)
occurrences (all)	118	22	57
Headache			
subjects affected / exposed	46 / 231 (19.91%)	10 / 56 (17.86%)	34 / 109 (31.19%)
occurrences (all)	102	14	61
Hypoaesthesia			
subjects affected / exposed	9 / 231 (3.90%)	4 / 56 (7.14%)	3 / 109 (2.75%)
occurrences (all)	9	4	3
Presyncope			
subjects affected / exposed	5 / 231 (2.16%)	2 / 56 (3.57%)	8 / 109 (7.34%)
occurrences (all)	5	4	9
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	30 / 231 (12.99%)	6 / 56 (10.71%)	14 / 109 (12.84%)
occurrences (all)	35	6	29
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	6 / 231 (2.60%)	1 / 56 (1.79%)	6 / 109 (5.50%)
occurrences (all)	6	1	7
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	14 / 231 (6.06%)	0 / 56 (0.00%)	6 / 109 (5.50%)
occurrences (all)	20	0	7
Abdominal pain			
subjects affected / exposed	17 / 231 (7.36%)	4 / 56 (7.14%)	9 / 109 (8.26%)
occurrences (all)	24	4	11
Abdominal pain upper			
subjects affected / exposed	18 / 231 (7.79%)	2 / 56 (3.57%)	7 / 109 (6.42%)
occurrences (all)	19	2	8
Constipation			
subjects affected / exposed	22 / 231 (9.52%)	2 / 56 (3.57%)	10 / 109 (9.17%)
occurrences (all)	26	2	11
Diarrhoea			
subjects affected / exposed	50 / 231 (21.65%)	11 / 56 (19.64%)	34 / 109 (31.19%)
occurrences (all)	81	22	62
Dyspepsia			
subjects affected / exposed	34 / 231 (14.72%)	8 / 56 (14.29%)	14 / 109 (12.84%)
occurrences (all)	68	9	22
Gastritis			
subjects affected / exposed	7 / 231 (3.03%)	3 / 56 (5.36%)	10 / 109 (9.17%)
occurrences (all)	8	3	12
Gastrooesophageal reflux disease			
subjects affected / exposed	16 / 231 (6.93%)	6 / 56 (10.71%)	13 / 109 (11.93%)
occurrences (all)	19	6	16
Nausea			
subjects affected / exposed	46 / 231 (19.91%)	8 / 56 (14.29%)	26 / 109 (23.85%)
occurrences (all)	63	10	41
Vomiting			

subjects affected / exposed	36 / 231 (15.58%)	9 / 56 (16.07%)	23 / 109 (21.10%)
occurrences (all)	47	19	34
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 231 (2.16%)	3 / 56 (5.36%)	3 / 109 (2.75%)
occurrences (all)	5	3	4
Erythema			
subjects affected / exposed	1 / 231 (0.43%)	4 / 56 (7.14%)	0 / 109 (0.00%)
occurrences (all)	1	4	0
Hyperhidrosis			
subjects affected / exposed	4 / 231 (1.73%)	4 / 56 (7.14%)	1 / 109 (0.92%)
occurrences (all)	4	5	1
Pruritus			
subjects affected / exposed	10 / 231 (4.33%)	3 / 56 (5.36%)	3 / 109 (2.75%)
occurrences (all)	16	3	3
Rash			
subjects affected / exposed	13 / 231 (5.63%)	3 / 56 (5.36%)	3 / 109 (2.75%)
occurrences (all)	18	3	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	28 / 231 (12.12%)	6 / 56 (10.71%)	10 / 109 (9.17%)
occurrences (all)	34	7	15
Arthritis			
subjects affected / exposed	2 / 231 (0.87%)	4 / 56 (7.14%)	3 / 109 (2.75%)
occurrences (all)	2	5	4
Back pain			
subjects affected / exposed	36 / 231 (15.58%)	5 / 56 (8.93%)	11 / 109 (10.09%)
occurrences (all)	48	7	17
Joint swelling			
subjects affected / exposed	4 / 231 (1.73%)	3 / 56 (5.36%)	2 / 109 (1.83%)
occurrences (all)	5	4	2
Muscle spasms			
subjects affected / exposed	6 / 231 (2.60%)	3 / 56 (5.36%)	9 / 109 (8.26%)
occurrences (all)	8	4	11
Musculoskeletal pain			

subjects affected / exposed	10 / 231 (4.33%)	4 / 56 (7.14%)	6 / 109 (5.50%)
occurrences (all)	16	4	6
Myalgia			
subjects affected / exposed	5 / 231 (2.16%)	4 / 56 (7.14%)	7 / 109 (6.42%)
occurrences (all)	6	4	10
Pain in extremity			
subjects affected / exposed	27 / 231 (11.69%)	7 / 56 (12.50%)	12 / 109 (11.01%)
occurrences (all)	35	7	15
Systemic lupus erythematosus			
subjects affected / exposed	4 / 231 (1.73%)	4 / 56 (7.14%)	0 / 109 (0.00%)
occurrences (all)	4	4	0
Spinal pain			
subjects affected / exposed	5 / 231 (2.16%)	3 / 56 (5.36%)	1 / 109 (0.92%)
occurrences (all)	5	3	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	24 / 231 (10.39%)	11 / 56 (19.64%)	14 / 109 (12.84%)
occurrences (all)	35	13	19
Conjunctivitis			
subjects affected / exposed	8 / 231 (3.46%)	3 / 56 (5.36%)	4 / 109 (3.67%)
occurrences (all)	10	5	4
Gastroenteritis			
subjects affected / exposed	14 / 231 (6.06%)	6 / 56 (10.71%)	6 / 109 (5.50%)
occurrences (all)	15	6	7
Gastrointestinal infection			
subjects affected / exposed	9 / 231 (3.90%)	3 / 56 (5.36%)	3 / 109 (2.75%)
occurrences (all)	11	5	3
Influenza			
subjects affected / exposed	14 / 231 (6.06%)	7 / 56 (12.50%)	4 / 109 (3.67%)
occurrences (all)	21	7	5
Lower respiratory tract infection			
subjects affected / exposed	8 / 231 (3.46%)	3 / 56 (5.36%)	6 / 109 (5.50%)
occurrences (all)	11	5	17
Nasopharyngitis			
subjects affected / exposed	76 / 231 (32.90%)	21 / 56 (37.50%)	31 / 109 (28.44%)
occurrences (all)	160	44	81

Oral candidiasis			
subjects affected / exposed	2 / 231 (0.87%)	3 / 56 (5.36%)	0 / 109 (0.00%)
occurrences (all)	2	3	0
Pharyngitis			
subjects affected / exposed	9 / 231 (3.90%)	4 / 56 (7.14%)	4 / 109 (3.67%)
occurrences (all)	13	8	4
Pneumonia			
subjects affected / exposed	9 / 231 (3.90%)	7 / 56 (12.50%)	8 / 109 (7.34%)
occurrences (all)	9	7	10
Sinusitis			
subjects affected / exposed	13 / 231 (5.63%)	1 / 56 (1.79%)	9 / 109 (8.26%)
occurrences (all)	25	1	11
Upper respiratory tract infection			
subjects affected / exposed	39 / 231 (16.88%)	10 / 56 (17.86%)	24 / 109 (22.02%)
occurrences (all)	64	20	49
Urinary tract infection			
subjects affected / exposed	12 / 231 (5.19%)	9 / 56 (16.07%)	12 / 109 (11.01%)
occurrences (all)	21	12	17
Lung infection			
subjects affected / exposed	4 / 231 (1.73%)	3 / 56 (5.36%)	4 / 109 (3.67%)
occurrences (all)	5	4	4
Respiratory tract infection			
subjects affected / exposed	24 / 231 (10.39%)	5 / 56 (8.93%)	13 / 109 (11.93%)
occurrences (all)	53	10	19
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	26 / 231 (11.26%)	9 / 56 (16.07%)	12 / 109 (11.01%)
occurrences (all)	34	14	16
Iron deficiency			
subjects affected / exposed	11 / 231 (4.76%)	4 / 56 (7.14%)	7 / 109 (6.42%)
occurrences (all)	13	4	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2009	Amendment 5:This amendment was implemented in response to recommendations from a series of investigator meetings conducted on a global level. The major changes concerned: - Change of initial dose for subjects from the PATENT-1 study's 1.5mg dose group to remain at 1.5mg riociguat for the first 2weeks of the titration phase of PATENT-2. - Clarifications and additions of exclusion criteria, including mandatory withdrawal from the trial if a subject misses study medication for longer than 3days at a stretch (9 missing doses) during the titration phase - Specification of 6-minute walking distance (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 andsyncope as undesirable effects - Visit window from Vn onextendedto 14days - Addition of role of SC and DMC
21 March 2010	Amendment 6: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: - Abolishment 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 PATENT-1 study protocol amendment4in 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 8:This amendment modified the protocol to correct some typographical errors and to add laboratory measurements for calcium and phosphate for subjects included under study protocol amendment8 of the PATENT-1 study.
12 December 2012	This amendment was primarily prepared to update the PATENT-2 protocol to consider status and the results of the of the PATENT-1 studyand the overall riociguat development program. Changes of the protocol by the amendment focused on operational aspects of the study execution and facilitated some of the study related activities. - Amongst others central laboratory and ECG collection were stopped and instead performed locally upon decision of the investigator. - Visit procedures at individual visits were reduced, but all other aspects of safety monitoring were mostly unchanged.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported