Clinical trial results:
A randomized parallel-group, placebo-controlled, double-blind, multi-center trial to evaluate the efficacy and safety of the oral sGC stimulator vericiguat to improve physical functioning in activities of daily living in patients with heart failure and preserved ejection fraction (VITALITY-HFpEF)

Summary

EudraCT number	2018-000298-65
Trial protocol	BE PT AT ES HU BG GR PL IT
Global end of trial date	04 November 2019

Results information

Result version number	v1
This version publication date	15 October 2020
First version publication date	15 October 2020

Trial information

Trial identification

Sponsor protocol code	BAY1021189/19334

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03547583
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Patients suffering from Heart failure with preserved ejection fraction (HFpEF) are a large and growing population and HFpEF patients also have substantially reduced functional capacity and quality of life. Since patients with HFpEF are highly symptomatic with a poor quality of life, it is important to find new therapies that can alleviate symptoms and improve patient well-being.
Primary objectives:
• To evaluate the efficacy of vericiguat 10 mg in comparison to placebo on improving physical functioning from baseline to week 24.
• To evaluate the efficacy of vericiguat 15 mg in comparison to placebo on improving physical functioning from baseline to week 24.
• To evaluate the safety and tolerability of vericiguat.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2018
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	Argentina: 44
Country: Number of subjects enrolled	Austria: 35
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Bulgaria: 96
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Colombia: 12
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Greece: 48
Country: Number of subjects enrolled	Hungary: 43
Country: Number of subjects enrolled	Israel: 61
Country: Number of subjects enrolled	Italy: 44

Country: Number of subjects enrolled	Japan: 41
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Poland: 70
Country: Number of subjects enrolled	Portugal: 25
Country: Number of subjects enrolled	Russian Federation: 63
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	South Africa: 18
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	United States: 76
Worldwide total number of subjects	789
EEA total number of subjects	420

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)	155
From 65 to 84 years	558
85 years and over	76

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 178 study centers worldwide, between 15-Jun-2018 (first subject first visit) and 04-Nov-2019 (last subject last visit).

Pre-assignment

Screening details:

Overall, 979 subjects were screened, of whom 789 patients were randomized in the study. 788 of the randomized subjects were allocated to study treatment, of whom 672 subjects completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Vericiguat up to 10 mg

Arm description:

Subjects received vericiguat (BAY1021189) for 24 weeks, starting at 2.5 mg once daily at randomization and up-titrated to 5 mg at week 2, to 10 mg at week 4, with sham titration at week 6.

Arm type	Experimental
Investigational medicinal product name	vericiguat
Investigational medicinal product code	BAY1021189
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

vericiguat, which was started at 2.5 mg at randomization and up-titrated to 5 mg at week 2, and to 10 mg at week 4, with sham titration to 15 mg at week 6.

Arm title	Vericiguat up to 15 mg

Arm description:

Subjects received vericiguat (BAY1021189) for 24 weeks, starting at 2.5 mg once daily at randomization and up-titrated to 5 mg at week 2, to 10 mg at week 4, and to 15 mg at week 6.

Arm type	Experimental
Investigational medicinal product name	vericiguat
Investigational medicinal product code	BAY1021189
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

vericiguat, which was started at 2.5 mg at randomization and up-titrated to 5 mg at week 2, and to 10 mg at week 4, with up-titration to 15 mg at week 6.

Arm title	Placebo

Arm description:

Subject received placebo once daily and sham up-titration at weeks 2, 4, and 6.

Arm type	Placebo

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

Dosage and administration details:

placebo and sham up-titration at weeks 2, 4, and 6

Number of subjects in period 1	Vericiguat up to 10 mg	Vericiguat up to 15 mg	Placebo
Started	263	264	262
Treated	262	264	262
Completed	218	224	230
Not completed	45	40	32
Physician decision	1	-	3
Consent withdrawn by subject	12	19	10
Death	11	7	4
Adverse event	16	11	10
Non-compliance with study drug	-	-	1
Lost to follow-up	1	-	-
unspecified	2	2	3
Protocol deviation	2	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Vericiguat up to 10 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) for 24 weeks, starting at 2.5 mg once daily at randomization and up-titrated to 5 mg at week 2, to 10 mg at week 4, with sham titration at week 6.	
Reporting group title	Vericiguat up to 15 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) for 24 weeks, starting at 2.5 mg once daily at randomization and up-titrated to 5 mg at week 2, to 10 mg at week 4, and to 15 mg at week 6.	
Reporting group title	Placebo
Reporting group description:	
Subject received placebo once daily and sham up-titration at weeks 2, 4, and 6.	

Reporting group values	Vericiguat up to 10 mg	Vericiguat up to 15 mg	Placebo
Number of subjects	263	264	262
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	72.2	73.1	72.8
standard deviation	± 9.7	± 9.1	± 9.4
Gender Categorical Units: Subjects			
Female	124	140	121
Male	139	124	141
Race Units: Subjects			
White	228	224	222
Black or African American	5	7	9
Asian	24	26	25
American Indian or Alaska Native	3	4	4
Not reported	1	1	0
Multiple	2	2	2
Ethnicity Units: Subjects			
Not Hispanic or Latino	235	242	238
Hispanic or Latino	28	21	23
Not reported	0	1	1
Kansas City Cardiopathy Questionnaire Physical limitation score (KCCQ PLS)			
The KCCQ measures the impact of patients' heart failure, or its treatment, on 6 domains; Physical Limitation, Symptom (with subscores for frequency and burden), Quality of Life, Social Limitations, Symptom Stability and Self-Efficacy. Scores are calculated by summing domain responses and then transforming scores to a 0-100 unit scale with higher scores indicating better health status. The actual analyzed participants were 260 (3 missing) for Vericiguat up to 10 mg, 259 (5 missing) for Vericiguat up to 15 mg and 259 (3 missing) for placebo group.			
Units: Scores			
arithmetic mean	56.83	60.12	58.42

standard deviation	± 24.80	± 24.67	± 24.28
Six-minute walk test			
Six-minute walk test (6MWT) was conducted to test the physical limitations of the patient by assessing the patient's exercise capacity. The distance walked by the patient in 6 minutes was measured. Not all the randomized participants had a baseline measurement. The actual analyzed participants were 262 (1 missing) for Vericiguat up to 10 mg, 264 (0 missing) for Vericiguat up to 15 mg and 262 (0 missing) for placebo group.			
Units: Meters			
arithmetic mean	282.56	288.91	288.80
standard deviation	± 110.97	± 118.71	± 107.51

Reporting group values	Total		
Number of subjects	789		
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical			
Units: Subjects			
Female	385		
Male	404		
Race			
Units: Subjects			
White	674		
Black or African American	21		
Asian	75		
American Indian or Alaska Native	11		
Not reported	2		
Multiple	6		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	715		
Hispanic or Latino	72		
Not reported	2		
Kansas City Cardiopathy Questionnaire Physical limitation score (KCCQ PLS)			
The KCCQ measures the impact of patients' heart failure, or its treatment, on 6 domains; Physical Limitation, Symptom (with subscores for frequency and burden), Quality of Life, Social Limitations, Symptom Stability and Self-Efficacy. Scores are calculated by summing domain responses and then transforming scores to a 0-100 unit scale with higher scores indicating better health status. The actual analyzed participants were 260 (3 missing) for Vericiguat up to 10 mg, 259 (5 missing) for Vericiguat up to 15 mg and 259 (3 missing) for placebo group.			
Units: Scores			
arithmetic mean			
standard deviation	-		
Six-minute walk test			
Six-minute walk test (6MWT) was conducted to test the physical limitations of the patient by assessing the patient's exercise capacity. The distance walked by the patient in 6 minutes was measured. Not all the randomized participants had a baseline measurement. The actual analyzed participants were 262 (1 missing) for Vericiguat up to 10 mg, 264 (0 missing) for Vericiguat up to 15 mg and 262 (0 missing) for placebo group.			
Units: Meters			

arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Vericiguat up to 10 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) for 24 weeks, starting at 2.5 mg once daily at randomization and up-titrated to 5 mg at week 2, to 10 mg at week 4, with sham titration at week 6.	
Reporting group title	Vericiguat up to 15 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) for 24 weeks, starting at 2.5 mg once daily at randomization and up-titrated to 5 mg at week 2, to 10 mg at week 4, and to 15 mg at week 6.	
Reporting group title	Placebo
Reporting group description:	
Subject received placebo once daily and sham up-titration at weeks 2, 4, and 6.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects randomized were valid for the FAS.	

Primary: Change in KCCQ physical limitation score from baseline to week 24

End point title	Change in KCCQ physical limitation score from baseline to week 24
End point description:	
The City Cardiomyopathy Questionnaire (KCCQ) measures the impact of patients' heart failure, or its treatment, on 6 domains; Physical Limitation, Symptom (with subscores for frequency and burden), Quality of Life, Social Limitations, Symptom Stability and Self-Efficacy. Scores are calculated by summing domain responses and then transforming scores to a 0-100 unit scale with higher scores indicating better health status. The data were reported as arithmetic mean.	
End point type	Primary
End point timeframe:	
From baseline to Week 24	

End point values	Vericiguat up to 10 mg	Vericiguat up to 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	207	215	225	
Units: Score				
arithmetic mean (standard deviation)	9.24 (± 19.64)	6.40 (± 19.39)	7.27 (± 21.78)	

Statistical analyses

Statistical analysis title	Vericiguat 10 mg vs Placebo
Statistical analysis description:	
The analysis of each imputed dataset will be performed using mixed-effects model for repeated measures (MMRM), including treatment, region, heart rhythm, study visit as fixed effects, interaction between study visit and treatment group, and adjustment for the baseline PLS values as covariates.	
Comparison groups	Placebo v Vericiguat up to 10 mg

Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8008
Method	Mixed model repeated-measures
Parameter estimate	Difference of LS-means
Point estimate	-0.52
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-5.17
upper limit	4.13

Statistical analysis title	Vericiguat 15mg vs Placebo

Statistical analysis description:

The analysis of each imputed dataset will be performed using mixed-effects model for repeated measures (MMRM), including treatment, region, heart rhythm, study visit as fixed effects, interaction between study visit and treatment group, and adjustment for the baseline PLS values as covariates.

Comparison groups	Vericiguat up to 15 mg v Placebo
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4722
Method	Mixed model repeated-measures
Parameter estimate	Difference of LS-means
Point estimate	-1.46
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-6.02
upper limit	3.1

Secondary: Change in the Six-minute walk test (6MWT) from baseline to Week 24

End point title	Change in the Six-minute walk test (6MWT) from baseline to Week 24

End point description:

6MWT was conducted to test the physical limitations of the patient by assessing the patient's exercise capacity. The distance walked by the patient in 6 minutes was measured.

End point type	Secondary

End point timeframe:

From baseline to Week 24

End point values	Vericiguat up to 10 mg	Vericiguat up to 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	206	218	221	
Units: Meters				
arithmetic mean (standard deviation)	18.81 (± 67.41)	8.26 (± 78.79)	14.10 (± 74.13)	

Statistical analyses

Statistical analysis title	Vericiguat 10 mg vs Placebo

Statistical analysis description:

The analysis of each imputed dataset will be performed using mixed-effects model for repeated measures (MMRM), including treatment, region, heart rhythm, study visit as fixed effects, interaction between study visit and treatment group, and adjustment for the baseline 6MWT values as covariates.

Comparison groups	Vericiguat up to 10 mg v Placebo
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8054
Method	Mixed model repeated-measures
Parameter estimate	Difference of LS-means
Point estimate	-1.81
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-18.3
upper limit	14.67

Statistical analysis title	Vericiguat 15 mg vs Placebo

Statistical analysis description:

The analysis of each imputed dataset will be performed using mixed-effects model for repeated measures (MMRM), including treatment, region, heart rhythm, study visit as fixed effects, interaction between study visit and treatment group, and adjustment for the baseline 6MWT values as covariates.

Comparison groups	Vericiguat up to 15 mg v Placebo
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4502
Method	mixed model repeated measures
Parameter estimate	Difference of LS-means
Point estimate	-5.49
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-21.77
upper limit	10.8

Other pre-specified: Number of participants with treatment emergent adverse events

End point title	Number of participants with treatment emergent adverse events

End point description:

An AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Adverse events are considered to be treatment-emergent if they have started or worsened after first application of study medication up to 5 calendar days after end of treatment with study medication.

End point type	Other pre-specified

End point timeframe:

From first application of study drug up to 5 calendar days after end of treatment with study drug

End point values	Vericiguat up to 10 mg	Vericiguat up to 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	262	264	262	
Units: Subjects				
Any TEAE	163	172	172	
Any study drug related TEAE	38	42	24	
Any TESAE	46	54	48	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for reporting adverse events: From the first application of study medication up to 5 calendar days after end of treatment with study medication

Timeframe for number of death (all causes): After study medication start until last contact date

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Vericiguat up to 10 mg

Reporting group description:

Subjects received vericiguat (BAY1021189) for 24 weeks, starting at 2.5 mg once daily at randomization and up-titrated to 5 mg at week 2, to 10 mg at week 4, with sham titration at week 6.

Reporting group title	Vericiguat up to 15 mg

Reporting group description:

Subjects received vericiguat (BAY1021189) for 24 weeks, starting at 2.5 mg once daily at randomization and up-titrated to 5 mg at week 2, to 10 mg at week 4, and to 15 mg at week 6.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo for 24 weeks, once daily, starting sham up-titration at weeks 2, 4, and 6.

Serious adverse events	Vericiguat up to 10 mg	Vericiguat up to 15 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 262 (17.56%)	54 / 264 (20.45%)	48 / 262 (18.32%)
number of deaths (all causes)	15	10	7
number of deaths resulting from adverse events	8	5	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal cancer			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Oesophageal carcinoma			

subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phaeochromocytoma			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Aortic stenosis			
subjects affected / exposed	1 / 262 (0.38%)	1 / 264 (0.38%)	0 / 262 (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
Hypertension			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	2 / 262 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 262 (0.76%)	3 / 264 (1.14%)	4 / 262 (1.53%)
occurrences causally related to treatment / all	2 / 2	1 / 3	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Peripheral ischaemia			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Deep vein thrombosis			

subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Peripheral artery stenosis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Surgical and medical procedures			
Inguinal hernia repair			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Leg amputation			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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 pacemaker replacement			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
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			
Chest pain			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	2 / 262 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 262 (0.38%)	1 / 264 (0.38%)	0 / 262 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Pelvic mass			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Sudden death			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Sudden cardiac death			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 262 (0.00%)	2 / 264 (0.76%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 262 (0.38%)	4 / 264 (1.52%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 262 (0.38%)	1 / 264 (0.38%)	0 / 262 (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
Pleural effusion			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Pulmonary oedema			
subjects affected / exposed	1 / 262 (0.38%)	1 / 264 (0.38%)	0 / 262 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 262 (0.38%)	1 / 264 (0.38%)	0 / 262 (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
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Product issues			
Device malfunction			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Transaminases increased			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Angiocardiogram			

subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Fall			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	2 / 262 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Humerus fracture			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Radius fracture			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Rib fracture			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal haematoma			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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 compression fracture			

subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Tendon rupture			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Toxicity to various agents			
subjects affected / exposed	2 / 262 (0.76%)	0 / 264 (0.00%)	0 / 262 (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
Vulvovaginal injury			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Meniscus injury			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Atrial fibrillation			
subjects affected / exposed	4 / 262 (1.53%)	4 / 264 (1.52%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			

subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Cardiovascular disorder			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Coronary artery disease			
subjects affected / exposed	1 / 262 (0.38%)	2 / 264 (0.76%)	2 / 262 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	2 / 262 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Coronary artery insufficiency			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Sinus node dysfunction			
subjects affected / exposed	1 / 262 (0.38%)	1 / 264 (0.38%)	0 / 262 (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
Nervous system disorders			
Diabetic neuropathy			

subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Syncope			
subjects affected / exposed	1 / 262 (0.38%)	2 / 264 (0.76%)	0 / 262 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamus haemorrhage			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 262 (1.15%)	2 / 264 (0.76%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Macular oedema			

subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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 disorder			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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 haemorrhage			
subjects affected / exposed	0 / 262 (0.00%)	2 / 264 (0.76%)	0 / 262 (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
Ileus			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Intestinal obstruction			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Nausea			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Odynophagia			

subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Proctitis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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 haemorrhage			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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 gastrointestinal haemorrhage			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal incarcerated hernia			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Stevens-Johnson syndrome			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Diabetic foot			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	2 / 262 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	2 / 262 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	3 / 262 (1.15%)	3 / 264 (1.14%)	4 / 262 (1.53%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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	2 / 262 (0.76%)	0 / 264 (0.00%)	0 / 262 (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
Osteoarthritis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psoriatic arthropathy			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 262 (0.76%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 262 (0.00%)	3 / 264 (1.14%)	0 / 262 (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
Cellulitis staphylococcal			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Diverticulitis			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Gastroenteritis			
subjects affected / exposed	0 / 262 (0.00%)	2 / 264 (0.76%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			

subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Nasopharyngitis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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	3 / 262 (1.15%)	7 / 264 (2.65%)	4 / 262 (1.53%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	3 / 262 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site infection			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Respiratory tract infection viral			

subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
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	0 / 262 (0.00%)	1 / 264 (0.38%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia pyelonephritis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Medical device site joint infection			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	0 / 262 (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
Hyperglycaemia			
subjects affected / exposed	1 / 262 (0.38%)	0 / 264 (0.00%)	1 / 262 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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
Hyponatraemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 264 (0.38%)	0 / 262 (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

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Vericiguat up to 10 mg	Vericiguat up to 15 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 262 (46.18%)	134 / 264 (50.76%)	131 / 262 (50.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 262 (1.91%)	11 / 264 (4.17%)	10 / 262 (3.82%)
occurrences (all)	5	12	12
Hypotension			
subjects affected / exposed	16 / 262 (6.11%)	22 / 264 (8.33%)	12 / 262 (4.58%)
occurrences (all)	18	31	14
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 262 (0.38%)	2 / 264 (0.76%)	3 / 262 (1.15%)
occurrences (all)	2	2	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 262 (1.15%)	1 / 264 (0.38%)	3 / 262 (1.15%)
occurrences (all)	3	1	4
Chest pain			
subjects affected / exposed	2 / 262 (0.76%)	4 / 264 (1.52%)	3 / 262 (1.15%)
occurrences (all)	3	4	4
Fatigue			
subjects affected / exposed	3 / 262 (1.15%)	7 / 264 (2.65%)	3 / 262 (1.15%)
occurrences (all)	4	8	3
Oedema			
subjects affected / exposed	2 / 262 (0.76%)	3 / 264 (1.14%)	0 / 262 (0.00%)
occurrences (all)	2	3	0
Oedema peripheral			
subjects affected / exposed	16 / 262 (6.11%)	10 / 264 (3.79%)	8 / 262 (3.05%)
occurrences (all)	17	13	10
Pyrexia			
subjects affected / exposed	2 / 262 (0.76%)	4 / 264 (1.52%)	5 / 262 (1.91%)
occurrences (all)	2	4	5
Respiratory, thoracic and mediastinal			

disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 262 (1.15%)	3 / 264 (1.14%)	3 / 262 (1.15%)
occurrences (all)	3	4	3
Cough			
subjects affected / exposed	5 / 262 (1.91%)	5 / 264 (1.89%)	6 / 262 (2.29%)
occurrences (all)	5	6	6
Dyspnoea			
subjects affected / exposed	7 / 262 (2.67%)	5 / 264 (1.89%)	14 / 262 (5.34%)
occurrences (all)	8	5	15
Epistaxis			
subjects affected / exposed	3 / 262 (1.15%)	5 / 264 (1.89%)	3 / 262 (1.15%)
occurrences (all)	5	5	3
Rhinorrhoea			
subjects affected / exposed	2 / 262 (0.76%)	3 / 264 (1.14%)	0 / 262 (0.00%)
occurrences (all)	2	3	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 262 (1.15%)	2 / 264 (0.76%)	3 / 262 (1.15%)
occurrences (all)	4	2	4
Insomnia			
subjects affected / exposed	1 / 262 (0.38%)	3 / 264 (1.14%)	1 / 262 (0.38%)
occurrences (all)	1	3	1
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 262 (1.15%)	3 / 264 (1.14%)	0 / 262 (0.00%)
occurrences (all)	3	4	0
Blood uric acid increased			
subjects affected / exposed	3 / 262 (1.15%)	4 / 264 (1.52%)	2 / 262 (0.76%)
occurrences (all)	3	4	2
Weight decreased			
subjects affected / exposed	3 / 262 (1.15%)	3 / 264 (1.14%)	2 / 262 (0.76%)
occurrences (all)	3	3	2
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	2 / 262 (0.76%)	1 / 264 (0.38%)	4 / 262 (1.53%)
occurrences (all)	2	1	5

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 262 (1.53%)	3 / 264 (1.14%)	3 / 262 (1.15%)
occurrences (all)	4	4	3
Contusion			
subjects affected / exposed	2 / 262 (0.76%)	3 / 264 (1.14%)	1 / 262 (0.38%)
occurrences (all)	2	5	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	7 / 262 (2.67%)	7 / 264 (2.65%)	6 / 262 (2.29%)
occurrences (all)	8	9	6
Coronary artery disease			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	3 / 262 (1.15%)
occurrences (all)	0	0	3
Palpitations			
subjects affected / exposed	4 / 262 (1.53%)	0 / 264 (0.00%)	3 / 262 (1.15%)
occurrences (all)	5	0	3
Ventricular extrasystoles			
subjects affected / exposed	1 / 262 (0.38%)	4 / 264 (1.52%)	1 / 262 (0.38%)
occurrences (all)	1	4	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 262 (3.05%)	7 / 264 (2.65%)	11 / 262 (4.20%)
occurrences (all)	9	9	14
Headache			
subjects affected / exposed	5 / 262 (1.91%)	6 / 264 (2.27%)	11 / 262 (4.20%)
occurrences (all)	6	7	16
Tremor			
subjects affected / exposed	0 / 262 (0.00%)	0 / 264 (0.00%)	3 / 262 (1.15%)
occurrences (all)	0	0	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 262 (2.29%)	13 / 264 (4.92%)	9 / 262 (3.44%)
occurrences (all)	6	13	9
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 262 (0.38%)	3 / 264 (1.14%)	4 / 262 (1.53%)
occurrences (all)	1	3	4
Abdominal pain upper			
subjects affected / exposed	5 / 262 (1.91%)	1 / 264 (0.38%)	6 / 262 (2.29%)
occurrences (all)	5	1	6
Constipation			
subjects affected / exposed	2 / 262 (0.76%)	8 / 264 (3.03%)	4 / 262 (1.53%)
occurrences (all)	2	9	6
Diarrhoea			
subjects affected / exposed	3 / 262 (1.15%)	5 / 264 (1.89%)	5 / 262 (1.91%)
occurrences (all)	3	5	5
Dyspepsia			
subjects affected / exposed	4 / 262 (1.53%)	6 / 264 (2.27%)	3 / 262 (1.15%)
occurrences (all)	4	7	3
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 262 (1.15%)	4 / 264 (1.52%)	1 / 262 (0.38%)
occurrences (all)	3	4	1
Nausea			
subjects affected / exposed	8 / 262 (3.05%)	4 / 264 (1.52%)	2 / 262 (0.76%)
occurrences (all)	10	4	2
Vomiting			
subjects affected / exposed	3 / 262 (1.15%)	4 / 264 (1.52%)	0 / 262 (0.00%)
occurrences (all)	4	5	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 262 (1.15%)	3 / 264 (1.14%)	6 / 262 (2.29%)
occurrences (all)	4	5	8
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 262 (1.15%)	4 / 264 (1.52%)	2 / 262 (0.76%)
occurrences (all)	3	4	2
Renal impairment			
subjects affected / exposed	5 / 262 (1.91%)	4 / 264 (1.52%)	5 / 262 (1.91%)
occurrences (all)	6	7	7
Chronic kidney disease			

subjects affected / exposed	1 / 262 (0.38%)	1 / 264 (0.38%)	3 / 262 (1.15%)
occurrences (all)	1	1	3
Acute kidney injury			
subjects affected / exposed	3 / 262 (1.15%)	3 / 264 (1.14%)	7 / 262 (2.67%)
occurrences (all)	3	4	9
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 262 (0.38%)	5 / 264 (1.89%)	8 / 262 (3.05%)
occurrences (all)	1	6	10
Back pain			
subjects affected / exposed	5 / 262 (1.91%)	3 / 264 (1.14%)	5 / 262 (1.91%)
occurrences (all)	6	3	6
Muscle spasms			
subjects affected / exposed	1 / 262 (0.38%)	1 / 264 (0.38%)	3 / 262 (1.15%)
occurrences (all)	1	1	3
Myalgia			
subjects affected / exposed	2 / 262 (0.76%)	3 / 264 (1.14%)	2 / 262 (0.76%)
occurrences (all)	2	3	2
Osteoarthritis			
subjects affected / exposed	2 / 262 (0.76%)	2 / 264 (0.76%)	4 / 262 (1.53%)
occurrences (all)	2	2	4
Pain in extremity			
subjects affected / exposed	1 / 262 (0.38%)	4 / 264 (1.52%)	3 / 262 (1.15%)
occurrences (all)	2	4	4
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 262 (1.15%)	5 / 264 (1.89%)	7 / 262 (2.67%)
occurrences (all)	3	6	7
Gastroenteritis			
subjects affected / exposed	4 / 262 (1.53%)	5 / 264 (1.89%)	2 / 262 (0.76%)
occurrences (all)	5	5	2
Influenza			
subjects affected / exposed	3 / 262 (1.15%)	4 / 264 (1.52%)	3 / 262 (1.15%)
occurrences (all)	3	4	4
Nasopharyngitis			

subjects affected / exposed	8 / 262 (3.05%)	7 / 264 (2.65%)	7 / 262 (2.67%)
occurrences (all)	9	7	7
Pneumonia			
subjects affected / exposed	2 / 262 (0.76%)	2 / 264 (0.76%)	5 / 262 (1.91%)
occurrences (all)	2	2	5
Upper respiratory tract infection			
subjects affected / exposed	2 / 262 (0.76%)	4 / 264 (1.52%)	6 / 262 (2.29%)
occurrences (all)	2	4	6
Urinary tract infection			
subjects affected / exposed	1 / 262 (0.38%)	6 / 264 (2.27%)	4 / 262 (1.53%)
occurrences (all)	1	6	4
Respiratory tract infection viral			
subjects affected / exposed	3 / 262 (1.15%)	1 / 264 (0.38%)	2 / 262 (0.76%)
occurrences (all)	3	1	2
Respiratory tract infection			
subjects affected / exposed	5 / 262 (1.91%)	7 / 264 (2.65%)	4 / 262 (1.53%)
occurrences (all)	5	7	6
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	5 / 262 (1.91%)	7 / 264 (2.65%)	12 / 262 (4.58%)
occurrences (all)	5	7	13
Hyperuricaemia			
subjects affected / exposed	7 / 262 (2.67%)	8 / 264 (3.03%)	3 / 262 (1.15%)
occurrences (all)	7	9	3
Hypoglycaemia			
subjects affected / exposed	0 / 262 (0.00%)	2 / 264 (0.76%)	3 / 262 (1.15%)
occurrences (all)	0	2	3
Hypokalaemia			
subjects affected / exposed	5 / 262 (1.91%)	7 / 264 (2.65%)	8 / 262 (3.05%)
occurrences (all)	7	8	8
Decreased appetite			
subjects affected / exposed	0 / 262 (0.00%)	4 / 264 (1.52%)	1 / 262 (0.38%)
occurrences (all)	0	5	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported