Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Effects of Sotagliflozin on Clinical Outcomes in Hemodynamically Stable Patients with Type 2 Diabetes POST Worsening Heart Failure

Summary

EudraCT number	2017-003510-16
Trial protocol	SE NL ES LV LT GB BE DK FR AT CZ DE SK HU FI PT GR PL IE IT RO
Global end of trial date	05 June 2020

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	EFC15156

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03521934
WHO universal trial number (UTN)	U1111-1190-7891

Notes:

Sponsors

Sponsor organisation name	Lexicon Pharmaceuticals, Inc.
Sponsor organisation address	8800 Technology Forest Place, The Woodlands, United States, TX 77381
Public contact	Medical Affairs, Lexicon Pharmaceuticals, Inc., medical-information@lexpharma.com
Scientific contact	Medical Affairs, Lexicon Pharmaceuticals, Inc., medical-information@lexpharma.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	05 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of sotagliflozin to placebo on the total occurrences of cardiovascular (CV) death, hospitalization for heart failure (HHF), and urgent visit for heart failure (HF) in hemodynamically stable subjects after admission for worsening heart failure (WHF).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

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	Russian Federation: 168
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Turkey: 65
Country: Number of subjects enrolled	Israel: 49
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	New Zealand: 11
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Poland: 52
Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Slovakia: 18
Country: Number of subjects enrolled	Spain: 87
Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Czechia: 26
Country: Number of subjects enrolled	Denmark: 25
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 14

Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Greece: 29
Country: Number of subjects enrolled	Hungary: 81
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	Latvia: 30
Country: Number of subjects enrolled	Lithuania: 36
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	United States: 72
Country: Number of subjects enrolled	Argentina: 166
Country: Number of subjects enrolled	Brazil: 59
Country: Number of subjects enrolled	Chile: 41
Worldwide total number of subjects	1222
EEA total number of subjects	549

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)	364
From 65 to 84 years	843
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 306 investigative sites in North America, Latin America, Western Europe, Eastern Europe, and the Rest of the World from 15 June 2018 to 05 June 2020.

Pre-assignment

Screening details:

Subjects with a diagnosis of Type 2 Diabetes post Worsening Heart Failure were enrolled equally in 1 of 2 treatment groups, sotagliflozin or placebo.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sotagliflozin

Arm description:

Sotagliflozin 200 mg tablet once daily, with possible up-titration in the first 8 months to 400 mg, for up to 21.2 months.

Arm type	Experimental
Investigational medicinal product name	Sotagliflozin
Investigational medicinal product code	
Other name	SAR439954
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sotagliflozin was administered as a tablet(s), orally once daily.

Arm title	Placebo

Arm description:

Matching placebo to sotagliflozin 200 mg once daily, with possible up-titration in the first 8 months to matching placebo to sotagliflozin 400 mg, for up to 21.6 months.

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

Dosage and administration details:

Placebo was administered as a tablet(s) (identical to the sotagliflozin tablet in appearance), orally once daily.

Number of subjects in period 1	Sotagliflozin	Placebo
Started	608	614
Randomized and Treated	605	611
Completed	0	0
Not completed	608	614
Death	65	73
Site terminated by sponsor	39	35
Study terminated by sponsor	483	477
Reason not specified	3	6
Withdrawal by subject	18	23

Baseline characteristics

Reporting groups	
Reporting group title	Sotagliflozin
Reporting group description:	
Sotagliflozin 200 mg tablet once daily, with possible up-titration in the first 8 months to 400 mg, for up to 21.2 months.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to sotagliflozin 200 mg once daily, with possible up-titration in the first 8 months to matching placebo to sotagliflozin 400 mg, for up to 21.6 months.	

Reporting group values	Sotagliflozin	Placebo	Total
Number of subjects	608	614	1222
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	68.6	69.3	
standard deviation	± 9.5	± 8.8	-
Gender categorical Units: Subjects			
Female	198	214	412
Male	410	400	810
Race Units: Subjects			
White	567	572	1139
Black or African American	25	25	50
Asian	8	7	15
Native Hawaiian or other Pacific Islander	1	3	4
Multiple	1	1	2
Not Reported	6	5	11
Unknown	0	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	163	157	320
Not Hispanic or Latino	438	455	893
Not Reported	7	2	9

End points

End points reporting groups

Reporting group title	Sotagliflozin
Reporting group description:	
Sotagliflozin 200 mg tablet once daily, with possible up-titration in the first 8 months to 400 mg, for up to 21.2 months.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to sotagliflozin 200 mg once daily, with possible up-titration in the first 8 months to matching placebo to sotagliflozin 400 mg, for up to 21.6 months.	

Primary: Number of Total Occurrences of Cardiovascular (CV) Death, Hospitalizations for Heart Failure (HHF) and Urgent Visits for Heart Failure (HF)

End point title	Number of Total Occurrences of Cardiovascular (CV) Death, Hospitalizations for Heart Failure (HHF) and Urgent Visits for Heart Failure (HF)
End point description:	
Combined endpoint of the total number of occurrences (first and potentially subsequent) of CV death, HHF, and urgent HF visits after randomisation. Events that occurred during the study were calculated as the total number of events per 100 person-years of follow-up. Intent-to-treat (ITT) population includes all randomised subjects.	
End point type	Primary
End point timeframe:	
Up to 21.9 months	

End point values	Sotagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608	614		
Units: events per 100-person years				
number (not applicable)	51	76.3		

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo
Statistical analysis description:	
The estimates of the hazard ratio (HR) and corresponding 2-sided 95% confidence interval (CI) was to be provided by a marginal Cox proportional hazard model stratified by region and ejection fraction, with non-cardiovascular (non-CV) death treated as a competing event.	
Comparison groups	Sotagliflozin v Placebo

Number of subjects included in analysis	1222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.85

Secondary: Total Number of Occurrences of HHF and Urgent HF Visits

End point title	Total Number of Occurrences of HHF and Urgent HF Visits

End point description:

Combined endpoint of the total occurrences (first and potentially subsequent) of HHF and urgent HF visits after randomization. Events that occurred during the study were calculated as the total number of events per 100 person-years of follow-up. ITT population includes all randomised subjects.

End point type	Secondary

End point timeframe:

Up to 21.9 months

End point values	Sotagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608	614		
Units: events per 100-person years				
number (not applicable)	40.4	63.9		

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The estimates of the HR and corresponding 2-sided 95% CI was to be provided by a marginal Cox proportional hazard model stratified by region and ejection fraction, with non-CV death treated as a competing event.

Comparison groups	Sotagliflozin v Placebo
Number of subjects included in analysis	1222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.83

Secondary: Total Number of Deaths from Cardiovascular Causes

End point title	Total Number of Deaths from Cardiovascular Causes

End point description:

Number of events that occurred during the study were calculated as the total number of events per 100 person-years of follow-up. ITT population includes all randomised subjects.

End point type	Secondary

End point timeframe:

Up to 21.9 months

End point values	Sotagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608	614		
Units: events per 100-person years				
number (not applicable)	10.6	12.5		

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The estimates of the HR and corresponding 2-sided 95% CI was to be provided by a marginal Cox proportional hazard model stratified by region and ejection fraction, with non-CV death treated as a competing event.

Comparison groups	Sotagliflozin v Placebo
Number of subjects included in analysis	1222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.22

Secondary: Total Number of Occurrences of CV Death, HHF, Non-fatal Myocardial Infarction and Non-fatal Stroke

End point title	Total Number of Occurrences of CV Death, HHF, Non-fatal Myocardial Infarction and Non-fatal Stroke

End point description:

Combined endpoint of the total number of occurrences (first and potentially subsequent) of CV death, HHF, non-fatal stroke, and non-fatal myocardial infarction after randomisation. Events that occurred during the study were calculated as the total number of events per 100 person-years of follow-up. ITT population includes all randomised subjects.

End point type	Secondary

End point timeframe:

Up to 21.9 months

End point values	Sotagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608	614		
Units: events per 100-person years				
number (not applicable)	51.4	71.0		

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The estimates of the HR and corresponding 2-sided 95% CI was to be provided by a marginal Cox proportional hazard model stratified by region and ejection fraction, with non-CV death treated as a competing event.

Comparison groups	Sotagliflozin v Placebo
Number of subjects included in analysis	1222
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.92

Secondary: Total Number of Occurrences of HHF, Urgent HF Visit, CV Death, and HF While Hospitalized

End point title	Total Number of Occurrences of HHF, Urgent HF Visit, CV Death, and HF While Hospitalized

End point description:

Combined endpoint of the total number of occurrences (first and potentially subsequent) after randomisation of HHF, urgent HF visits, CV Death and HF while hospitalised. Events that occurred during the study were calculated as the total number of events per 100 person-years of follow-up. ITT population includes all randomised subjects.

End point type	Secondary

End point timeframe:

Up to 21.9 months

End point values	Sotagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608	614		
Units: events per 100-person years				
number (not applicable)	54.7	80.6		

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The estimates of the HR and corresponding 2-sided 95% CI was to be provided by a marginal Cox proportional hazard model stratified by region and ejection fraction, with non-CV death treated as a competing event.

Comparison groups	Sotagliflozin v Placebo
Number of subjects included in analysis	1222
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.86

Secondary: Total Number of Deaths from Any Cause

End point title	Total Number of Deaths from Any Cause

End point description:

Number of events that occurred during the study were calculated as the total number of events per 100 person-years of follow-up. ITT population includes all randomised subjects.

End point type	Secondary

End point timeframe:

Up to 21.9 months

End point values	Sotagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608	614		
Units: events per 100-person years				
number (not applicable)	13.5	16.3		

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The estimates of the HR and corresponding 2-sided 95% CI was to be provided by a marginal Cox proportional hazard model stratified by region and ejection fraction, with non-CV death treated as a competing event.

Comparison groups	Sotagliflozin v Placebo
Number of subjects included in analysis	1222
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.14

Secondary: Change from Baseline in Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) Scores at Month 4

End point title	Change from Baseline in Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) Scores at Month 4

End point description:

KCCQ-12 is a 12 question, subject completed questionnaire about how heart failure affected their life over the past 2 weeks. The scale has 4 domains: symptom frequency, physical limitation, social limitations and quality of life for a total possible transformed score of 0 to 100 where 100 denotes the highest health status. A positive change from baseline indicates improvement. An analysis of covariance (ANCOVA) model was used for analysis. ITT population includes all randomised subjects.

End point type	Secondary

End point timeframe:

Baseline to Month 4

End point values	Sotagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608	614		
Units: score on a scale				
least squares mean (standard error)	17.7 (± 0.41)	13.6 (± 0.41)		

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The change from baseline to Month 4 was analysed using an ANCOVA model with treatment groups as factor and baseline KCCQ-12 score and randomisation stratification factors as covariates.

Comparison groups	Sotagliflozin v Placebo
Number of subjects included in analysis	1222
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	7

Secondary: Change from Baseline in Estimated Glomerular Filtration Rate (eGFR)

End point title	Change from Baseline in Estimated Glomerular Filtration Rate (eGFR)

End point description:

eGFR is a test for renal function. A blood sample was collected and was sent to a central laboratory. eGFR was calculated by the Modification of Diet in Renal Disease (MDRD) equation reported as milliliters/minute/1.73 meter squared (mL/min/1.73 m^2). A mixed model for repeated measures (MMRM) was used for analysis. ITT population includes all randomised subjects.

End point type	Secondary

End point timeframe:

Baseline up to 21.9 months

End point values	Sotagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608	614		
Units: mL/min/1.73 m^2				
least squares mean (standard error)	-0.34 (± 1.33)	-0.18 (± 1.33)		

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

Rate of decline in eGFR observed over time was analysed by MMRM with absolute change in eGFR from baseline as the outcome, a random effect for intercept, and fixed effects for treatment, baseline value, and time.

Comparison groups	Placebo v Sotagliflozin
Number of subjects included in analysis	1222
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Least Squares Means
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.98

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug up to 10 days after the last dose of study drug (Up to 21.9 months)

Adverse event reporting additional description:

Number of Deaths (All causes) is based on all randomised subjects (n=608,614). Adverse Events are based on the Safety population that included all randomised subjects who received at least one dose of study drug (n=605,611).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Sotagliflozin

Reporting group description:

Sotagliflozin 200 mg tablet once daily, with possible up-titration in the first 8 months to 400 mg, for up to 21.2 months.

Reporting group title	Placebo

Reporting group description:

Matching placebo to sotagliflozin 200 mg once daily, once daily with possible up-titration in the first 8 months to matching placebo to sotagliflozin 400 mg, for up to 21.6 months.

Serious adverse events	Sotagliflozin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	235 / 605 (38.84%)	251 / 611 (41.08%)	
number of deaths (all causes)	65	76	
number of deaths resulting from adverse events	51	54	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kaposi's sarcoma			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pancreatic carcinoma			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Papillary renal cell carcinoma			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic rupture			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriosclerosis			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 605 (0.00%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 605 (0.00%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	6 / 605 (0.99%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 605 (0.17%)	5 / 611 (0.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Aortic valve replacement			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac rehabilitation therapy			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac resynchronisation therapy			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Percutaneous coronary intervention			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapeutic procedure			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac death			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 2	
Chest pain			
subjects affected / exposed	3 / 605 (0.50%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 605 (0.33%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 4	
Fatigue			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Generalised oedema			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nodule			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 605 (0.17%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 605 (0.00%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 605 (0.00%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	7 / 605 (1.16%)	9 / 611 (1.47%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 8	0 / 9	
Sudden death			
subjects affected / exposed	2 / 605 (0.33%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Vascular stent thrombosis			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	2 / 605 (0.33%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 605 (0.50%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 605 (0.33%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea exertional			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			

subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 605 (0.50%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 605 (0.00%)	6 / 611 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 605 (0.33%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory arrest			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 605 (0.50%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anxiety			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 605 (0.00%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lead dislodgement			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biopsy prostate			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation cardiac			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant evaluation			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cardiac valve replacement complication			
subjects affected / exposed	0 / 605 (0.00%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fall			

subjects affected / exposed	4 / 605 (0.66%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body in gastrointestinal tract			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Humerus fracture			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	2 / 605 (0.33%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	4 / 605 (0.66%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	4 / 605 (0.66%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	8 / 605 (1.32%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aortic valve stenosis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	8 / 605 (1.32%)	8 / 611 (1.31%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	80 / 605 (13.22%)	121 / 611 (19.80%)	
occurrences causally related to treatment / all	0 / 114	1 / 194	
deaths causally related to treatment / all	0 / 11	0 / 15	
Cardiac failure acute			
subjects affected / exposed	12 / 605 (1.98%)	11 / 611 (1.80%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 4	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 605 (0.17%)	8 / 611 (1.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 3	
Cardiac failure congestive			
subjects affected / exposed	11 / 605 (1.82%)	16 / 611 (2.62%)	
occurrences causally related to treatment / all	0 / 17	0 / 29	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			

subjects affected / exposed	2 / 605 (0.33%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Chronic left ventricular failure			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	6 / 605 (0.99%)	9 / 611 (1.47%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	2 / 605 (0.33%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 605 (0.00%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinoatrial block			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 605 (0.17%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	4 / 605 (0.66%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Brain oedema			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	5 / 605 (0.83%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cognitive disorder			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhagic stroke			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	9 / 605 (1.49%)	9 / 611 (1.47%)	
occurrences causally related to treatment / all	0 / 10	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Loss of consciousness			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postresuscitation encephalopathy			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal claudication			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord ischaemia			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 605 (0.33%)	12 / 611 (1.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 605 (0.83%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 605 (0.00%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis ulcerative			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 605 (0.17%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal perforation			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic artery aneurysm			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative gastritis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 605 (0.00%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 605 (0.17%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	2 / 605 (0.33%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	11 / 605 (1.82%)	16 / 611 (2.62%)	
occurrences causally related to treatment / all	3 / 14	1 / 16	
deaths causally related to treatment / all	0 / 1	0 / 2	
Calculus urinary			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	3 / 605 (0.50%)	6 / 611 (0.98%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 605 (0.50%)	6 / 611 (0.98%)	
occurrences causally related to treatment / all	1 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	0 / 605 (0.00%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 605 (0.00%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	3 / 605 (0.50%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 605 (0.33%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			

subjects affected / exposed	1 / 605 (0.17%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	4 / 605 (0.66%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Erysipelas			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	2 / 605 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 605 (0.00%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 605 (0.00%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective thrombosis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 605 (0.17%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	19 / 605 (3.14%)	26 / 611 (4.26%)	
occurrences causally related to treatment / all	0 / 21	0 / 28	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pneumonia bacterial			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	2 / 605 (0.33%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 605 (0.17%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 605 (0.00%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	2 / 605 (0.33%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
Skin infection			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 605 (0.33%)	6 / 611 (0.98%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	3 / 605 (0.50%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 605 (0.50%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic complication			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			

subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 605 (0.33%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperinsulinaemic hypoglycaemia			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 605 (0.17%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	8 / 605 (1.32%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	4 / 8	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 605 (0.17%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	2 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	1 / 605 (0.17%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sotagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 605 (16.69%)	90 / 611 (14.73%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	33 / 605 (5.45%)	27 / 611 (4.42%)	
occurrences (all)	37	29	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	41 / 605 (6.78%)	57 / 611 (9.33%)	
occurrences (all)	54	77	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	36 / 605 (5.95%)	18 / 611 (2.95%)	
occurrences (all)	42	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2018	Amendment 1: 1. Re-ordered secondary objectives and endpoints. 2. New endpoint was added which provides scientific and clinical leadership 3. Deleted other objective to compare sotagliflozin versus placebo on the occurrence of premature ventricular complexes. 4. Deleted information regarding mechanistic substudy. 5. Changed fixed sequence approach to an alpha passing concept. 6. Deleted sentence on open-ended questions within KCCQ-12 questionnaire. 7. Deleted renal adverse events from AEs waived from expedited reporting. 8. Revised to include additional tests on pregnancy. 9. Added the measurement of HbA1c to be performed at month 16. 10. Added the measurement of eGFR. 11. Added potential benefits of sotagliflozin outweigh potential risks for subjects with T1D and T2D. 12. Modified to include all diagnostic imaging to document historical LVEF at Screening. 13. Time point specified for changes from baseline in loop diuretics. 14. Modified to clarify urinalysis will be performed at the local laboratory at Visit 1 and subsequently at the central laboratory. If the urinalysis is positive for nitrite and leukocyte esterase or blood, reflexive testing will be performed at the local laboratory at Visit 1, and at the central laboratory for subsequent visits. 15. Clarified that blood samples for BNP or NT-proBNP collected at Screening to assess the subject's eligibility would be analysed by the local laboratory. 16. Separated IMP accounting and compliance in the study flow chart and deleted the accountability of IMP at Visit 3, 4, and 5. 17. Minor editorial, typographical error corrections, and document formatting revisions have been made throughout the document.
22 August 2019	Amendment 2: 1. Updated protocol title, number and date. 2. Extended randomisation window after hospital discharge. 3. Added secondary endpoint, "CV death and HHF in subjects with LVEF <50% with and without T2D". 4. Moved secondary endpoints to "Other" endpoints. 5. Updated a few Inclusion criteria. 6. Added stratification for subjects with T2D. 7. Added requirement for the same laboratory for consistency in testing results. 8. Updated Exclusion criteria. 9. Removed Serum potassium >5.5 mEq/L as laboratory finding exclusion criteria. 10. Added Type 1 diabetes to exclusion criteria. 11. Added exclusion criteria, Heart Failure with Preserved Ejection Fraction in subjects without T2D. 12. Reworded primary and secondary hypotheses and renumbering the hypotheses in the graph. Removed "final" from αFinal. Provided clearer language on the relationship between sotagliflozin and diabetic ketoacidosis. 13. Laboratory tests for chemistry clarified. 14. Delated asymptomatic overdose as a standard AE. 15. Deleted neutropenia, thrombocytopenia, and increased creatinine phosphokinase from the list of laboratory abnormalities. 16. Deleted Three decision trees in appendix D. 17. Removed redundant/unnecessary liver test analysis. 18. Minor editorial, typographical error corrections, and document formatting revisions were made throughout the document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was terminated prematurely due to financial reasons and Covid-19 pandemic.

Notes: