

**Clinical trial results:**

A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with reduced Ejection Fraction (HFrEF)

Summary

EudraCT number	2016-002280-34
Trial protocol	DE NL FR ES HU CZ BE GB IT
Global end of trial date	28 May 2020

Results information

Result version number	v2 (current)
This version publication date	01 December 2021
First version publication date	12 June 2021
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	1245.121
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03057977
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Straße 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 001 18002430127, clintrriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 001 18002430127, clintrriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 July 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this event-driven trial was to demonstrate superiority of empagliflozin 10 mg versus placebo on top of guideline-directed medical therapy in patients with symptomatic, chronic HF and reduced left ventricular ejection fraction (LVEF \leq 40%).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 April 2017
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: 911
Country: Number of subjects enrolled	Australia: 56
Country: Number of subjects enrolled	Belgium: 78
Country: Number of subjects enrolled	Brazil: 1629
Country: Number of subjects enrolled	Canada: 344
Country: Number of subjects enrolled	China: 278
Country: Number of subjects enrolled	Czechia: 194
Country: Number of subjects enrolled	Germany: 231
Country: Number of subjects enrolled	Spain: 73
Country: Number of subjects enrolled	France: 95
Country: Number of subjects enrolled	United Kingdom: 100
Country: Number of subjects enrolled	Hungary: 200
Country: Number of subjects enrolled	India: 261
Country: Number of subjects enrolled	Italy: 176
Country: Number of subjects enrolled	Japan: 343
Country: Number of subjects enrolled	Korea, Republic of: 150
Country: Number of subjects enrolled	Mexico: 184
Country: Number of subjects enrolled	Netherlands: 338
Country: Number of subjects enrolled	Poland: 874

Country: Number of subjects enrolled	United States: 705
Worldwide total number of subjects	7220
EEA total number of subjects	2259

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)	3144
From 65 to 84 years	3909
85 years and over	167

Subject disposition

Recruitment

Recruitment details:

A randomised, double-blind trial to demonstrate superiority of empagliflozin versus placebo, in patients with chronic Heart Failure with reduced Ejection Fraction (HFrEF).

Pre-assignment

Screening details:

Patients were included in the trial after they had signed the informed consent form (ICF). All patients who met the all inclusion and none of the exclusion criteria during screening and at the randomisation approximately 1 to 4 weeks later were randomised to empagliflozin or placebo in a 1:1 ratio.

Period 1

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

Blinding implementation details:

Patients, investigators and everyone involved in the trial conduct or analysis or with any other interest in this double-blind trial remained blinded with regard to the randomised treatment assignments until after database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

1 film-coated tablet of matching placebo was administered orally once daily.

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

Dosage and administration details:

1 film-coated tablet of matching placebo was administered orally once daily.

Arm title	10 mg Empagliflozin
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Arm description:

Film-coated tablet of 10 milligram (mg) Empagliflozin was administered orally once daily.

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

Dosage and administration details:

Film-coated tablet of 10 milligram (mg) Empagliflozin was administered orally once daily.

Number of subjects in period 1^[1]	Placebo	10 mg Empagliflozin
Started	1867	1863
Treated	1863	1863
Completed	1352	1381
Not completed	515	482
Adverse Event	343	337
Principle Investigator Decision	2	-
Patient decision to stop/interrupt medication	8	6
Personal Reasons	1	1
Other medical condition (no Adverse Event)	2	4
Unblinded medication	1	-
Not treated	4	-
Consent withdrawn by subject	124	92
Unable to continue treatment	4	1
Reason Unknown	-	1
Patient received Empagliflozin for Diabetes	1	1
Lost to follow-up	11	17
Patient moved away/being abroad	4	3
Not attending study visit	3	10
Due to Covid-19 Pandemic	1	4
Protocol deviation	6	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 7220 patient were enrolled world wide, whereas 3730 patients actually started the trial.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: 1 film-coated tablet of matching placebo was administered orally once daily.	
Reporting group title	10 mg Empagliflozin
Reporting group description: Film-coated tablet of 10 milligram (mg) Empagliflozin was administered orally once daily.	

Reporting group values	Placebo	10 mg Empagliflozin	Total
Number of subjects	1867	1863	3730
Age categorical			
Randomised Set (RS): All randomised patients.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	740	675	1415
From 65-84 years	1086	1130	2216
85 years and over	41	58	99
Age Continuous			
Randomised Set (RS): All randomised patients.			
Units: years			
arithmetic mean	66.5	67.2	
standard deviation	± 11.2	± 10.8	-
Sex: Female, Male			
Randomised Set (RS): All randomised patients.			
Units: Subjects			
Female	456	437	893
Male	1411	1426	2837
Race (NIH/OMB)			
Randomised Set (RS): All randomised patients.			
Units: Subjects			
American Indian or Alaska Native	24	15	39
Asian	335	337	672
Native Hawaiian or Other Pacific Islander	6	8	14
Black or African American	134	123	257
White	1304	1325	2629
More than one race	33	28	61
Unknown or Not Reported	31	27	58
Ethnicity (NIH/OMB)			
Randomised Set (RS): All randomised patients.			
Units: Subjects			

Hispanic or Latino	613	616	1229
Not Hispanic or Latino	1178	1164	2342
Unknown or Not Reported	76	83	159

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
1 film-coated tablet of matching placebo was administered orally once daily.	
Reporting group title	10 mg Empagliflozin
Reporting group description:	
Film-coated tablet of 10 milligram (mg) Empagliflozin was administered orally once daily.	

Primary: Time to the first event of adjudicated cardiovascular (CV) death or adjudicated hospitalisation for heart failure (HHF)

End point title	Time to the first event of adjudicated cardiovascular (CV) death or adjudicated hospitalisation for heart failure (HHF)
End point description:	
Time to the first event of adjudicated cardiovascular (CV) death or adjudicated hospitalisation for heart failure (HHF). The incidence rate per 100 patient years ($100 * \text{number of patients with event} / \text{time at risk [years]}$) is presented. With time at risk [year] calculated as: $\text{Sum of time at risk [days]} / 365.25$. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Randomised Set (RS): All randomised patients. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.	
End point type	Primary
End point timeframe:	
From randomisation until completion of the planned treatment period, up to 1040 days.	

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1867 ^[1]	1863 ^[2]		
Units: Patients with events/ 100 pt-yrs at risk				
number (confidence interval 95%)	21.00 (19.13 to 22.96)	15.77 (14.19 to 17.44)		

Notes:

[1] - RS

[2] - RS

Statistical analyses

Statistical analysis title	Cox regression model
Statistical analysis description:	
Model with terms for age, baseline eGFR (CKD-EPK)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment. $\alpha = 0.0496$ (resulting from interim analysis) eGFR (CKP-EPI)cr: Glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement LVEF: Left ventricular ejection fraction.	
Comparison groups	Placebo v 10 mg Empagliflozin

Number of subjects included in analysis	3730
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95.04 %
sides	2-sided
lower limit	0.65
upper limit	0.86

Secondary: Occurrence of adjudicated Hospitalisation for Heart Failure (HHF) (first and recurrent)

End point title	Occurrence of adjudicated Hospitalisation for Heart Failure (HHF) (first and recurrent)
End point description:	
Reported is the total number of HHF events (first and recurrent) which occurred. All data up to the end of the planned treatment period (including the data after the end of treatment for patients not completing the treatment period as planned) from all randomised patients was used. Randomised Set (RS): All randomised patients.	
End point type	Secondary
End point timeframe:	
From randomisation until completion of the planned treatment phase, up to 1040 days.	

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1867 ^[3]	1863 ^[4]		
Units: HHF events	553	388		

Notes:

[3] - RS

[4] - RS

Statistical analyses

Statistical analysis title	Joint frailty model
Statistical analysis description:	
Model accounts for dependence between recurrent HHF and cardiovascular death, with terms for age, baseline eGFR (CKD-EPK)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment. eGFR (CKP-EPI)cr: Glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement LVEF: Left ventricular ejection fraction.	
Comparison groups	Placebo v 10 mg Empagliflozin

Number of subjects included in analysis	3730
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Joint frailty model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95.04 %
sides	2-sided
lower limit	0.58
upper limit	0.85

Secondary: eGFR (CKD-EPI) cr slope of change from baseline

End point title	eGFR (CKD-EPI) cr slope of change from baseline
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End point description:

Glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement (eGFR (CKD-EPI)cr) [mL/min/1.73m²] slope of change from baseline. Available on-treatment change-from-baseline data were to be used. Patients without on-treatment data after randomisation were not to be included in this analysis. Slope represents the long term effect on eGFR. Timepoints after baseline were included in calculation of slope of change from baseline. Descriptive statistic (mean(standard error)) is reported. Treated Set (TS): All patients treated with at least one dose of the study medication and at least one on-treatment measurement of eGFR.

End point type	Secondary
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End point timeframe:

Assessed at baseline, week 4, 12, 32, 52, 76, 100, 124, 148 and at end of treatment (EOT), up to 1040 days.

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1792 ^[5]	1799 ^[6]		
Units: Milliliter/minute/1.73 meters squared				
arithmetic mean (standard error)	-2.278 (± 0.229)	-0.546 (± 0.227)		

Notes:

[5] - TS

[6] - TS

Statistical analyses

Statistical analysis title	Random coefficient model
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Statistical analysis description:

Random coefficient model allowing for random intercept and random slope per patient, with the same factors used for the primary endpoint (age, baseline eGFR (CKD-EPI)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment) and additional factors "time", "treatment-by-time interaction", and "baseline eGFR (CKD-EPI)cr-by-time interaction". Only "on-treatment" data from treated patients were used. alpha=0.001

Comparison groups	Placebo v 10 mg Empagliflozin
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Number of subjects included in analysis	3591
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Random intercept random coef. model
Parameter estimate	Treatment by time interaction
Point estimate	1.733
Confidence interval	
level	Other: 99.9 %
sides	2-sided
lower limit	0.669
upper limit	2.796

Secondary: Time to first event in composite renal endpoint: chronic dialysis, renal transplant or sustained reduction of eGFR(CKD-EPI)cr

End point title	Time to first event in composite renal endpoint: chronic dialysis, renal transplant or sustained reduction of eGFR(CKD-EPI)cr
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End point description:

Time to the first event in the composite renal endpoint: chronic dialysis (with a frequency of twice per week or more for at least 90 days), renal transplant, or sustained reduction in Glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement (eGFR (CKD-EPI)cr). The incidence rate per 100 patient years (100 * number of patients with event /time at risk [years]) is presented. With time at risk [year] calculated as: Sum of time at risk [days] over all patients in a treatment group / 365.25. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Randomised Set (RS): All randomised patients. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.

End point type	Secondary
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End point timeframe:

From randomisation until completion of the planned treatment period, up to 1040 days.

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1867 ^[7]	1863 ^[8]		
Units: Patients with events/ 100 pt-yrs at risk				
number (confidence interval 95%)	3.07 (2.33 to 3.91)	1.56 (1.06 to 2.17)		

Notes:

[7] - RS

[8] - RS

Statistical analyses

Statistical analysis title	Cox regression model
Comparison groups	10 mg Empagliflozin v Placebo

Number of subjects included in analysis	3730
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0019
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.77

Secondary: Time to first adjudicated Hospitalisation for Heart Failure (HHF)

End point title	Time to first adjudicated Hospitalisation for Heart Failure (HHF)
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End point description:

Time to first adjudicated Hospitalisation for Heart Failure (HHF). The incidence rate per 100 patient years ($100 * \text{number of patients with event} / \text{time at risk [years]}$) is presented. With time at risk [year] calculated as: $\text{Sum of time at risk [days]} / 365.25$. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Randomised Set (RS): All randomised patients. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.

End point type	Secondary
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End point timeframe:

From randomisation until completion of the planned treatment period, up to 1040 days.

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1867 ^[9]	1863 ^[10]		
Units: Patients with events/ 100 pt-yrs at risk				
number (confidence interval 95%)	15.55 (13.94 to 17.24)	10.75 (9.45 to 12.13)		

Notes:

[9] - RS

[10] - RS

Statistical analyses

Statistical analysis title	Cox regression model
Comparison groups	10 mg Empagliflozin v Placebo
Number of subjects included in analysis	3730
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.81

Secondary: Time to adjudicated cardiovascular (CV) death

End point title	Time to adjudicated cardiovascular (CV) death
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End point description:

Time to adjudicated CV (Cardiovascular) death. The incidence rate (patients with events per 100 person years at risk) is reported. The incidence rate per 100 patient years (100 * number of patients with event /time at risk [years]) is presented. With time at risk [year] calculated as: Sum of time at risk [days] over all patients in a treatment group / 365.25. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Randomised Set (RS): All randomised patients. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.

End point type	Secondary
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End point timeframe:

From randomisation until completion of the planned treatment period, up to 1040 days.

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1867 ^[11]	1863 ^[12]		
Units: Patients with events/ 100 pt-yrs at risk				
number (confidence interval 95%)	8.13 (7.05 to 9.29)	7.55 (6.51 to 8.67)		

Notes:

[11] - RS

[12] - RS

Statistical analyses

Statistical analysis title	Cox regression model
Comparison groups	10 mg Empagliflozin v Placebo
Number of subjects included in analysis	3730
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4133
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.12

Secondary: Time to all-cause mortality

End point title	Time to all-cause mortality
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End point description:

Time to all-cause mortality. The incidence rate (patients with events per 100 person years at risk) is reported. The incidence rate per 100 patient years ($100 \times \text{number of patients with event} / \text{time at risk [years]}$) is presented. With time at risk [year] calculated as: Sum of time at risk [days] over all patients in a treatment group / 365.25. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Randomised Set (RS): All randomised patients. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.

End point type	Secondary
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End point timeframe:

From randomisation until completion of the planned treatment period, up to 1040 days.

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1867 ^[13]	1863 ^[14]		
Units: Patients with events/ 100 pt-yrs at risk				
number (confidence interval 95%)	10.71 (9.46 to 12.04)	10.06 (8.85 to 11.34)		

Notes:

[13] - RS

[14] - RS

Statistical analyses

Statistical analysis title	Cox regression model
Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	3730
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3536
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.1

Secondary: Time to onset of Diabetes Mellitus (DM)

End point title	Time to onset of Diabetes Mellitus (DM)
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End point description:

Time to onset of DM (Glycated haemoglobin (HbA1c) $\geq 6.5\%$ or as diagnosed by the investigator) in patients with pre-DM (no history of DM and no HbA1c $\geq 6.5\%$ before treatment, and a pre-treatment HbA1c value of 5.7 to $<6.5\%$). The incidence rate (patients with events per 100 person years at risk) is reported. The incidence rate per 100 patient years ($100 * \text{number of patients with event} / \text{time at risk} [\text{years}]$) is presented. With time at risk [year] calculated as: Sum of time at risk [days] over all patients in a treatment group / 365.25. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Patients in the randomised set with pre-DM. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.

End point type	Secondary
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End point timeframe:

From randomisation until completion of the planned treatment period, up to 1040 days.

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	636	632		
Units: Patients with events/ 100 pt-yrs at risk				
number (confidence interval 95%)	10.62 (8.42 to 13.07)	9.31 (7.27 to 11.60)		

Statistical analyses

Statistical analysis title	Cox regression model
Comparison groups	10 mg Empagliflozin v Placebo
Number of subjects included in analysis	1268
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3576
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.19

Secondary: Change from baseline in KCCQ (Kansas City cardiomyopathy questionnaire) clinical summary score at Week 52

End point title	Change from baseline in KCCQ (Kansas City cardiomyopathy questionnaire) clinical summary score at Week 52
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End point description:

The KCCQ is a 23-item self-administered questionnaire designed to evaluate physical limitations, symptoms (frequency, severity, and changes over time), social limitations, self efficacy, and quality of life in patients with Heart Failure. The KCCQ-clinical summary score comprises the following domains:

Symptom frequency, symptom burden and physical limitation. The score is calculated by summing domain responses and then transforming scores to a 0-100 unit scale with higher scores indicating better health status. For patients who died, a worst score (score of 0) is imputed at all subsequent scheduled visits after the date of death. Standard error is adjusted standard error. Change from baseline in KCCQ-score at week 52 was modeled using a MMRM with visit (week 12, 32 and 52) as repeated measures, adjusted mean (standard error) at week 52 is reported. Patients in the randomized set (RS) with available data for this endpoint, including values obtained on treatment or post-treatment.

End point type	Secondary
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End point timeframe:

Assessed at baseline, week 12, week 32 and week 52.

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1395	1401		
Units: Score on a scale				
least squares mean (standard error)	-3.36 (± 0.69)	-1.30 (± 0.69)		

Statistical analyses

Statistical analysis title	Mixed model
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Statistical analysis description:

Mixed model with age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, treatment by visit interaction, baseline KCCQ - Clinical Summary Score by Visit interaction as fixed effects. An unstructured covariance structure has been used.

Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	2796
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.034
Method	Mixed Model
Parameter estimate	Difference of adjusted means
Point estimate	2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	3.96
Variability estimate	Standard error of the mean
Dispersion value	0.97

Secondary: Number of all-cause hospitalizations (first and recurrent)

End point title	Number of all-cause hospitalizations (first and recurrent)
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End point description:

Number of all-cause hospitalizations (first and recurrent). Randomised Set (RS): All randomised patients.

End point type	Secondary
End point timeframe:	
From randomisation until completion of the planned treatment phase, up to 1040 days.	

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1867 ^[15]	1863 ^[16]		
Units: Hospitalizations for any cause	1570	1364		

Notes:

[15] - RS

[16] - RS

Statistical analyses

Statistical analysis title	Joint frailty model
Statistical analysis description:	
Joint frailty model with terms for age, baseline eGFR (CDK-EPI), region, sex, baseline diabetes status and baseline LVEF. Model accounts for dependence between recurrent all-cause hospitalizations and all-cause mortality.	
Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	3730
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0065
Method	Joint frailty model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	0.95

Adverse events

Adverse events information

Timeframe for reporting adverse events:

[All-Cause Mortality]: From randomization until end of planned treatment period, up to 1040 days.

[Serious/Other AE]: From first intake of study medication until end of planned treatment period + 7 days (Residual Effect Period), up to 1047 days.

Adverse event reporting additional description:

[All-Cause Mortality]: Randomised Set: All randomised patients. The actual number of participants at risk for all-cause deaths is 1867 for Placebo group. [Serious Adverse Events and Other Adverse Events]: Treated Set: All patients treated with at least one dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

1 film-coated tablet of matching placebo was administered orally once daily.

Reporting group title	10mg Empagliflozin
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Reporting group description:

Film-coated tablet of 10 milligram (mg) Empagliflozin was administered orally once daily.

Serious adverse events	Placebo	10mg Empagliflozin	
Total subjects affected by serious adverse events			
subjects affected / exposed	896 / 1863 (48.09%)	772 / 1863 (41.44%)	
number of deaths (all causes)	266	249	
number of deaths resulting from adverse events	181	181	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal neoplasm			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma gastric			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			

subjects affected / exposed	2 / 1863 (0.11%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Adenocarcinoma of the cervix		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Adenocarcinoma pancreas		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Adrenal adenoma		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Basal cell carcinoma		
subjects affected / exposed	4 / 1863 (0.21%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Bile duct adenocarcinoma		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Bladder cancer		
subjects affected / exposed	3 / 1863 (0.16%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bladder cancer stage IV		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bladder neoplasm		

subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bladder transitional cell carcinoma		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bowen's disease		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic lymphocytic leukaemia		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic myelomonocytic leukaemia		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Clear cell renal cell carcinoma		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colon adenoma		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colon cancer		
subjects affected / exposed	3 / 1863 (0.16%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cutaneous T-cell lymphoma		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diffuse large B-cell lymphoma recurrent			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal neoplasm			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypergammaglobulinaemia benign monoclonal			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung neoplasm malignant		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0
Malignant melanoma		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastases to spine		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Metastatic carcinoma of the bladder		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastatic neoplasm		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Myelodysplastic syndrome		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Non-Hodgkin's lymphoma		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal carcinoma		

subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ovarian adenoma		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic carcinoma		
subjects affected / exposed	3 / 1863 (0.16%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0
Pancreatic carcinoma metastatic		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Plasma cell myeloma		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Prostate cancer		
subjects affected / exposed	7 / 1863 (0.38%)	6 / 1863 (0.32%)
occurrences causally related to treatment / all	0 / 7	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Prostate cancer metastatic		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal adenocarcinoma		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal cancer		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer metastatic			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 1863 (0.05%)	6 / 1863 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Aortic dissection		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Aortic intramural haematoma		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Aortic stenosis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Arterial thrombosis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriosclerosis		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bleeding varicose vein		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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	5 / 1863 (0.27%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0
Deep vein thrombosis		

subjects affected / exposed	5 / 1863 (0.27%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic vascular disorder		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dry gangrene		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Embolism		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Extremity necrosis		
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Femoral artery embolism		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertension		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive crisis		
subjects affected / exposed	4 / 1863 (0.21%)	6 / 1863 (0.32%)
occurrences causally related to treatment / all	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive emergency		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive urgency		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypotension		
subjects affected / exposed	13 / 1863 (0.70%)	14 / 1863 (0.75%)
occurrences causally related to treatment / all	2 / 14	4 / 14
deaths causally related to treatment / all	0 / 0	0 / 0
Hypovolaemic shock		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Intermittent claudication		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Leriche syndrome		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Lymphocele		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Orthostatic hypotension		
subjects affected / exposed	1 / 1863 (0.05%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral arterial occlusive disease		

subjects affected / exposed	4 / 1863 (0.21%)	7 / 1863 (0.38%)
occurrences causally related to treatment / all	0 / 5	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral artery aneurysm		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral artery stenosis		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral artery thrombosis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral embolism		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Peripheral ischaemia		
subjects affected / exposed	4 / 1863 (0.21%)	5 / 1863 (0.27%)
occurrences causally related to treatment / all	0 / 4	1 / 5
deaths causally related to treatment / all	0 / 1	0 / 1
Peripheral vascular disorder		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Shock haemorrhagic		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Subclavian artery occlusion		

subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein occlusion			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subgaleal haemorrhage			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular insufficiency			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac resynchronisation therapy			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardioversion			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary arterial stent insertion			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			

subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implantable defibrillator insertion			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cardiac death			
subjects affected / exposed	8 / 1863 (0.43%)	4 / 1863 (0.21%)	
occurrences causally related to treatment / all	0 / 8	2 / 4	
deaths causally related to treatment / all	0 / 8	2 / 4	
Chest pain			
subjects affected / exposed	2 / 1863 (0.11%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	27 / 1863 (1.45%)	20 / 1863 (1.07%)	
occurrences causally related to treatment / all	1 / 27	1 / 20	
deaths causally related to treatment / all	1 / 27	1 / 20	
Discomfort			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body reaction			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Euthanasia			

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Gait disturbance		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Medical device site haematoma		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Implant site haematoma		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1
Non-cardiac chest pain		
subjects affected / exposed	7 / 1863 (0.38%)	5 / 1863 (0.27%)
occurrences causally related to treatment / all	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Oedema due to cardiac disease		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oedema peripheral		
subjects affected / exposed	2 / 1863 (0.11%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Stent-graft endoleak		

subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	10 / 1863 (0.54%)	8 / 1863 (0.43%)	
occurrences causally related to treatment / all	1 / 10	0 / 8	
deaths causally related to treatment / all	1 / 10	0 / 8	
Sudden death			
subjects affected / exposed	5 / 1863 (0.27%)	5 / 1863 (0.27%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 5	0 / 5	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device occlusion			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vessel puncture site phlebitis			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Heart transplant rejection			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Acquired hydrocele			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balanoposthitis			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrocystic breast disease			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterovaginal prolapse			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
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 / 1863 (0.11%)	3 / 1863 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	5 / 1863 (0.27%)	3 / 1863 (0.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Asthma			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	13 / 1863 (0.70%)	11 / 1863 (0.59%)	
occurrences causally related to treatment / all	0 / 17	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 1863 (0.21%)	7 / 1863 (0.38%)	
occurrences causally related to treatment / all	1 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	3 / 1863 (0.16%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemothorax		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Idiopathic pulmonary fibrosis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lung disorder		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Organising pneumonia		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Paranasal cyst		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pleural effusion		
subjects affected / exposed	5 / 1863 (0.27%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pleuritic pain		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
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	3 / 1863 (0.16%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonitis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Pneumothorax		
subjects affected / exposed	3 / 1863 (0.16%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary arterial hypertension		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary congestion		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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	4 / 1863 (0.21%)	5 / 1863 (0.27%)
occurrences causally related to treatment / all	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1
Pulmonary fibrosis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary hypertension		
subjects affected / exposed	3 / 1863 (0.16%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary oedema		

subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory acidosis			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	5 / 1863 (0.27%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord thickening			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Delirium			

subjects affected / exposed	4 / 1863 (0.21%)	8 / 1863 (0.43%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium tremens			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device inappropriate shock delivery			

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device lead damage			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device lead issue			
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	4 / 1863 (0.21%)	3 / 1863 (0.16%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device physical property issue			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac cirrhosis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis		
subjects affected / exposed	3 / 1863 (0.16%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis acute		
subjects affected / exposed	5 / 1863 (0.27%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	1 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis chronic		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cholelithiasis		
subjects affected / exposed	2 / 1863 (0.11%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Drug-induced liver injury		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatic cirrhosis		

subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 1863 (0.11%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	4 / 1863 (0.21%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	5 / 1863 (0.27%)	3 / 1863 (0.16%)	
occurrences causally related to treatment / all	1 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-alcoholic steatohepatitis			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac electrophysiologic study			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endoscopic retrograde cholangiopancreatography			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme abnormal			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Ankle fracture			
subjects affected / exposed	3 / 1863 (0.16%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Avulsion fracture			
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder injury			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbon monoxide poisoning			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery restenosis			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costal cartilage fracture			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
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	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Fall		
subjects affected / exposed	4 / 1863 (0.21%)	15 / 1863 (0.81%)
occurrences causally related to treatment / all	0 / 5	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 1
Femoral neck fracture		
subjects affected / exposed	2 / 1863 (0.11%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Femur fracture		
subjects affected / exposed	3 / 1863 (0.16%)	5 / 1863 (0.27%)
occurrences causally related to treatment / all	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Fibula fracture		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Fracture		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Head injury		
subjects affected / exposed	0 / 1863 (0.00%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1
Heat stroke		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
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	3 / 1863 (0.16%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Humerus fracture		
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Jaw fracture		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Joint dislocation		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Limb crushing injury		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Limb injury		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbar vertebral fracture		
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Multiple injuries		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Open globe injury		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Overdose		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pelvic fracture		
subjects affected / exposed	3 / 1863 (0.16%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural haemorrhage		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural swelling		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Post-traumatic pain		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative respiratory failure		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Procedural shock		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Rib fracture		

subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Road traffic accident		
subjects affected / exposed	2 / 1863 (0.11%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Skin laceration		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal compression fracture		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Splenic rupture		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Subdural haematoma		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Subdural haemorrhage		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Thermal burn		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tibia fracture		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tooth fracture		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Toxicity to various agents		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Traumatic fracture		
subjects affected / exposed	0 / 1863 (0.00%)	6 / 1863 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Traumatic haematoma		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Traumatic intracranial haemorrhage		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Upper limb fracture		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Vascular pseudoaneurysm		
subjects affected / exposed	2 / 1863 (0.11%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Wound dehiscence		

subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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			
Dermoid cyst			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal arteriovenous malformation			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phimosis			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type IV hyperlipidaemia			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	3 / 1863 (0.16%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	5 / 1863 (0.27%)	7 / 1863 (0.38%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	

Acute myocardial infarction		
subjects affected / exposed	18 / 1863 (0.97%)	24 / 1863 (1.29%)
occurrences causally related to treatment / all	0 / 20	0 / 24
deaths causally related to treatment / all	0 / 5	0 / 11
Angina pectoris		
subjects affected / exposed	10 / 1863 (0.54%)	6 / 1863 (0.32%)
occurrences causally related to treatment / all	0 / 12	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Angina unstable		
subjects affected / exposed	9 / 1863 (0.48%)	11 / 1863 (0.59%)
occurrences causally related to treatment / all	0 / 9	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 1
Aortic valve stenosis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Arrhythmia		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Arrhythmia supraventricular		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriosclerosis coronary artery		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Atrial fibrillation		
subjects affected / exposed	44 / 1863 (2.36%)	24 / 1863 (1.29%)
occurrences causally related to treatment / all	1 / 49	1 / 30
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial flutter		

subjects affected / exposed	11 / 1863 (0.59%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 12	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial tachycardia		
subjects affected / exposed	2 / 1863 (0.11%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial thrombosis		
subjects affected / exposed	2 / 1863 (0.11%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block complete		
subjects affected / exposed	1 / 1863 (0.05%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block second degree		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bradyarrhythmia		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Bradycardia		
subjects affected / exposed	4 / 1863 (0.21%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bundle branch block left		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac aneurysm		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac arrest		
subjects affected / exposed	10 / 1863 (0.54%)	9 / 1863 (0.48%)
occurrences causally related to treatment / all	0 / 11	0 / 9
deaths causally related to treatment / all	0 / 6	0 / 9
Cardiac asthma		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac disorder		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac dysfunction		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure		
subjects affected / exposed	444 / 1863 (23.83%)	332 / 1863 (17.82%)
occurrences causally related to treatment / all	9 / 687	7 / 494
deaths causally related to treatment / all	0 / 39	1 / 41
Cardiac failure acute		
subjects affected / exposed	29 / 1863 (1.56%)	19 / 1863 (1.02%)
occurrences causally related to treatment / all	2 / 46	0 / 32
deaths causally related to treatment / all	0 / 4	0 / 4
Cardiac failure chronic		
subjects affected / exposed	32 / 1863 (1.72%)	18 / 1863 (0.97%)
occurrences causally related to treatment / all	1 / 53	1 / 33
deaths causally related to treatment / all	0 / 2	0 / 2
Cardiac failure congestive		

subjects affected / exposed	41 / 1863 (2.20%)	26 / 1863 (1.40%)
occurrences causally related to treatment / all	3 / 62	1 / 38
deaths causally related to treatment / all	0 / 2	0 / 2
Cardiac tamponade		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Cardiac ventricular thrombosis		
subjects affected / exposed	2 / 1863 (0.11%)	5 / 1863 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Cardio-respiratory arrest		
subjects affected / exposed	4 / 1863 (0.21%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0
Cardiogenic shock		
subjects affected / exposed	11 / 1863 (0.59%)	8 / 1863 (0.43%)
occurrences causally related to treatment / all	1 / 11	0 / 8
deaths causally related to treatment / all	0 / 5	0 / 5
Cardiomegaly		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiomyopathy		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiopulmonary failure		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1
Cardiorenal syndrome		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiovascular disorder		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Chronic left ventricular failure		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Congestive cardiomyopathy		
subjects affected / exposed	6 / 1863 (0.32%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 1
Coronary artery disease		
subjects affected / exposed	16 / 1863 (0.86%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	1 / 16	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0
Coronary artery occlusion		
subjects affected / exposed	3 / 1863 (0.16%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery stenosis		
subjects affected / exposed	2 / 1863 (0.11%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary ostial stenosis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intracardiac thrombus		

subjects affected / exposed	2 / 1863 (0.11%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemic cardiomyopathy		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Left ventricular dysfunction		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Left ventricular failure		
subjects affected / exposed	3 / 1863 (0.16%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1
Low cardiac output syndrome		
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Mitral valve incompetence		
subjects affected / exposed	5 / 1863 (0.27%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Myocardial infarction		
subjects affected / exposed	16 / 1863 (0.86%)	16 / 1863 (0.86%)
occurrences causally related to treatment / all	0 / 17	1 / 17
deaths causally related to treatment / all	0 / 7	1 / 8
Myocardial ischaemia		
subjects affected / exposed	1 / 1863 (0.05%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Palpitations		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Paroxysmal atrioventricular block		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pericardial effusion		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Prinzmetal angina		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pulseless electrical activity		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Right ventricular failure		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Supraventricular tachycardia		
subjects affected / exposed	6 / 1863 (0.32%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Torsade de pointes		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Trifascicular block		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	5 / 1863 (0.27%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	2 / 1863 (0.11%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	8 / 1863 (0.43%)	10 / 1863 (0.54%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 3	
Ventricular flutter			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachyarrhythmia			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	37 / 1863 (1.99%)	55 / 1863 (2.95%)	
occurrences causally related to treatment / all	1 / 46	2 / 73	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Brain injury			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid arteriosclerosis			

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Carotid artery occlusion		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Carotid artery stenosis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebellar haemorrhage		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebellar infarction		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebellar stroke		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral haemorrhage		
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral hypoperfusion		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral infarction		
subjects affected / exposed	2 / 1863 (0.11%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1
Cerebral ischaemia		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebrovascular accident		
subjects affected / exposed	12 / 1863 (0.64%)	17 / 1863 (0.91%)
occurrences causally related to treatment / all	0 / 13	2 / 17
deaths causally related to treatment / all	0 / 3	1 / 4
Cerebrovascular insufficiency		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dementia		
subjects affected / exposed	3 / 1863 (0.16%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dizziness		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dysarthria		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Embolic stroke		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Epilepsy		
subjects affected / exposed	3 / 1863 (0.16%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Guillain-Barre syndrome		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhagic stroke		
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2
Headache		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hemiparesis		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hemiplegia		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperglycaemic seizure		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoxic-ischaemic encephalopathy		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intracranial aneurysm		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemic stroke		
subjects affected / exposed	20 / 1863 (1.07%)	19 / 1863 (1.02%)
occurrences causally related to treatment / all	0 / 20	0 / 21
deaths causally related to treatment / all	0 / 5	0 / 2
Lacunar infarction		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Loss of consciousness		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbar radiculopathy		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbosacral radiculopathy		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Migraine		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Myoclonus		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Paraplegia		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peroneal nerve palsy		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Postresuscitation encephalopathy		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Presyncope		
subjects affected / exposed	0 / 1863 (0.00%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Seizure		
subjects affected / exposed	3 / 1863 (0.16%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal cord compression		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Subarachnoid haemorrhage		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	8 / 1863 (0.43%)	17 / 1863 (0.91%)	
occurrences causally related to treatment / all	0 / 9	1 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	9 / 1863 (0.48%)	5 / 1863 (0.27%)	
occurrences causally related to treatment / all	0 / 9	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 1863 (0.32%)	10 / 1863 (0.54%)	
occurrences causally related to treatment / all	0 / 6	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haematoma			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness neurosensory			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness unilateral			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mixed deafness			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden hearing loss			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	3 / 1863 (0.16%)	5 / 1863 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract cortical			

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	5 / 1863 (0.27%)	3 / 1863 (0.16%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular degeneration			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open angle glaucoma			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 1863 (0.00%)	3 / 1863 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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	3 / 1863 (0.16%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal pain upper		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal wall haematoma		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Acute abdomen		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic gastritis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Coeliac disease		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colitis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colitis ischaemic		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Constipation		

subjects affected / exposed	1 / 1863 (0.05%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Diarrhoea		
subjects affected / exposed	2 / 1863 (0.11%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenal ulcer		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Enteritis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Erosive oesophagitis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric haemorrhage		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric mucosa erythema		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric perforation		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric ulcer		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis		
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis erosive		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal haemorrhage		
subjects affected / exposed	4 / 1863 (0.21%)	8 / 1863 (0.43%)
occurrences causally related to treatment / all	0 / 4	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 2
Gastrointestinal necrosis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal ulcer haemorrhage		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal vascular malformation haemorrhagic		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gingival bleeding		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haematochezia		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhoids		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Ileus		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Ileus paralytic		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Incarcerated inguinal hernia		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Inguinal hernia		
subjects affected / exposed	0 / 1863 (0.00%)	7 / 1863 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal ischaemia		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (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	2 / 1863 (0.11%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Intussusception		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Large intestine polyp		
subjects affected / exposed	2 / 1863 (0.11%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mallory-Weiss syndrome		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mechanical ileus		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mesenteric artery stenosis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nausea		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Obstructive pancreatitis		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal obstruction		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis		

subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis acute		
subjects affected / exposed	2 / 1863 (0.11%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1
Pancreatitis chronic		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Periodontal disease		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pharyngo-oesophageal diverticulum		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal haemorrhage		
subjects affected / exposed	3 / 1863 (0.16%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Small intestinal obstruction		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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	7 / 1863 (0.38%)	5 / 1863 (0.27%)
occurrences causally related to treatment / all	0 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1
Vomiting		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	3 / 1863 (0.16%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	2 / 1863 (0.11%)	6 / 1863 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eczema			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	3 / 1863 (0.16%)	4 / 1863 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stasis dermatitis			

subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	55 / 1863 (2.95%)	35 / 1863 (1.88%)	
occurrences causally related to treatment / all	8 / 59	6 / 40	
deaths causally related to treatment / all	0 / 3	0 / 1	
Azotaemia			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	6 / 1863 (0.32%)	3 / 1863 (0.16%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic nephropathy			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 1863 (0.11%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Nephrolithiasis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nephropathy		
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Nephropathy toxic		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Prerenal failure		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
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	14 / 1863 (0.75%)	9 / 1863 (0.48%)
occurrences causally related to treatment / all	0 / 14	2 / 9
deaths causally related to treatment / all	0 / 1	0 / 1
Renal impairment		
subjects affected / exposed	27 / 1863 (1.45%)	17 / 1863 (0.91%)
occurrences causally related to treatment / all	5 / 27	2 / 17
deaths causally related to treatment / all	0 / 1	0 / 0
Renal infarct		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Renal tubular necrosis		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 1863 (0.00%)	3 / 1863 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	2 / 1863 (0.11%)	3 / 1863 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crystal arthropathy			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint destruction			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Muscular weakness		
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal chest pain		
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Osteoarthritis		
subjects affected / exposed	7 / 1863 (0.38%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 8	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Osteochondrosis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pathological fracture		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Polymyalgia rheumatica		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rhabdomyolysis		
subjects affected / exposed	2 / 1863 (0.11%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Rotator cuff syndrome		

subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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 / 1863 (0.00%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Appendicitis			
subjects affected / exposed	3 / 1863 (0.16%)	3 / 1863 (0.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			

subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchitis		
subjects affected / exposed	5 / 1863 (0.27%)	5 / 1863 (0.27%)
occurrences causally related to treatment / all	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Bullous erysipelas		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
COVID-19		
subjects affected / exposed	3 / 1863 (0.16%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
COVID-19 pneumonia		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cellulitis		
subjects affected / exposed	3 / 1863 (0.16%)	8 / 1863 (0.43%)
occurrences causally related to treatment / all	0 / 3	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Clostridium difficile infection		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cystitis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dengue fever		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Device related infection		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Diabetic foot infection		
subjects affected / exposed	0 / 1863 (0.00%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Disseminated tuberculosis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulitis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Encephalitis viral		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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	3 / 1863 (0.16%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0
Erysipelas		
subjects affected / exposed	3 / 1863 (0.16%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Escherichia bacteraemia		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Eye abscess		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Fournier's gangrene		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gangrene		
subjects affected / exposed	1 / 1863 (0.05%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis viral		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis		
subjects affected / exposed	9 / 1863 (0.48%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 9	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal infection		
subjects affected / exposed	2 / 1863 (0.11%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhagic fever		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Human anaplasmosis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Implant site infection		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
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 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Infection		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infective spondylitis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Influenza		
subjects affected / exposed	5 / 1863 (0.27%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral discitis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Labyrinthitis		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Localised infection		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection		
subjects affected / exposed	2 / 1863 (0.11%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Medical device site infection		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nail infection		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Nocardiosis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis		
subjects affected / exposed	2 / 1863 (0.11%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis chronic		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pelvic abscess		

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Perineal abscess		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peritonitis		
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Peritonitis bacterial		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Pharyngitis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	62 / 1863 (3.33%)	53 / 1863 (2.84%)
occurrences causally related to treatment / all	0 / 63	2 / 56
deaths causally related to treatment / all	0 / 5	0 / 5
Pneumonia bacterial		
subjects affected / exposed	3 / 1863 (0.16%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia chlamydial		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia influenzal		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative wound infection		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary sepsis		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary tuberculosis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelitis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis acute		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory syncytial virus bronchitis		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory tract infection		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis		
subjects affected / exposed	8 / 1863 (0.43%)	8 / 1863 (0.43%)
occurrences causally related to treatment / all	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 2	0 / 2
Septic encephalopathy		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Septic shock		
subjects affected / exposed	5 / 1863 (0.27%)	9 / 1863 (0.48%)
occurrences causally related to treatment / all	0 / 5	0 / 9
deaths causally related to treatment / all	0 / 4	0 / 5
Sinobronchitis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal cord abscess		
subjects affected / exposed	0 / 1863 (0.00%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Staphylococcal bacteraemia		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Staphylococcal sepsis		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Streptococcal sepsis		

subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 1863 (0.05%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	10 / 1863 (0.54%)	14 / 1863 (0.75%)	
occurrences causally related to treatment / all	6 / 10	5 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 1863 (0.00%)	4 / 1863 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vessel puncture site cellulitis			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral diarrhoea			
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 1863 (0.05%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Decreased appetite			

subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dehydration		
subjects affected / exposed	4 / 1863 (0.21%)	8 / 1863 (0.43%)
occurrences causally related to treatment / all	0 / 4	4 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetes mellitus		
subjects affected / exposed	5 / 1863 (0.27%)	4 / 1863 (0.21%)
occurrences causally related to treatment / all	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetes mellitus inadequate control		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic complication		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic metabolic decompensation		
subjects affected / exposed	7 / 1863 (0.38%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	0 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gout		
subjects affected / exposed	3 / 1863 (0.16%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperglycaemia		
subjects affected / exposed	2 / 1863 (0.11%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome		

subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperkalaemia		
subjects affected / exposed	9 / 1863 (0.48%)	2 / 1863 (0.11%)
occurrences causally related to treatment / all	2 / 9	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hypernatraemia		
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoglycaemia		
subjects affected / exposed	5 / 1863 (0.27%)	6 / 1863 (0.32%)
occurrences causally related to treatment / all	4 / 7	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Hypokalaemia		
subjects affected / exposed	2 / 1863 (0.11%)	3 / 1863 (0.16%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hyponatraemia		
subjects affected / exposed	2 / 1863 (0.11%)	1 / 1863 (0.05%)
occurrences causally related to treatment / all	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypophagia		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypovolaemia		
subjects affected / exposed	1 / 1863 (0.05%)	0 / 1863 (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	0 / 1863 (0.00%)	2 / 1863 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	3 / 1863 (0.16%)	4 / 1863 (0.21%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 1863 (0.00%)	1 / 1863 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	10mg Empagliflozin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	369 / 1863 (19.81%)	328 / 1863 (17.61%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	109 / 1863 (5.85%)	120 / 1863 (6.44%)	
occurrences (all)	120	132	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	94 / 1863 (5.05%)	89 / 1863 (4.78%)	
occurrences (all)	109	125	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	109 / 1863 (5.85%)	99 / 1863 (5.31%)	
occurrences (all)	124	117	
Hyperuricaemia			
subjects affected / exposed	115 / 1863 (6.17%)	63 / 1863 (3.38%)	
occurrences (all)	120	66	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2017	The screening period was extended by 7 days. It was also clarified that screening procedures could be performed over multiple days; Additional criteria for N-terminal pro-brain natriuretic peptide (NT-proBNP) were added for patients with documented HHF in inclusion criterion 5; Implantable cardioverter defibrillator (ICD) and Cardiac resynchronisation therapy (CRT) (and intention to implant thereof) were added to exclusion criterion 29; The exploratory secondary endpoint "first occurrence of sustained reduction of $\geq 40\%$ Estimated glomerular filtration rate (eGFR)" was further specified; An Electrocardiogram (ECG) was to be performed at screening rather than the baseline visit; For laboratory analyses at screening, a haematology panel was added while urinalysis was removed; A national coordinator committee was set up to advise on the trial. An explanation was added to the protocol; The ketone monitoring strategy for patients with Type 1 diabetes mellitus (T1DM) was added; The guidance to sites on the consent process for patients with T1DM was added.
18 July 2018	No major changes to the protocol were introduced by this amendment. The changes involved logistical or administrative aspects only and did not require Independent ethics committee (IEC)/ Institutional review board (IRB) approval (unless required by local regulations).
20 November 2019	The use of any Sodium-dependent glucose co-transporter (SGLT)-2/1 inhibitors was allowed during the 30 day-period between the end-of-trial visit (EOT) and the follow-up visit occurring at study close-out; Changes to the planned analyses to be consistent with the changes introduced by the TSAP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported