



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
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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
Protocol deviation	6	5
Patient moved away/being abroad	4	3
Reason Unknown	-	1
Patient decision to stop/interrupt medication	8	6
Due to Covid-19 Pandemic	1	4
Unable to continue treatment	4	1
Consent withdrawn by subject	124	92
Principle Investigator Decision	2	-
Not treated	4	-
Patient received Empagliflozin for Diabetes	1	1
Unblinded medication	1	-
Personal Reasons	1	1
Not attending study visit	3	10
Adverse Event	343	337
Other medical condition (no Adverse Event)	2	4
Lost to follow-up	11	17

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 ($100 \times \text{number of patients with event} / \text{time at risk [years]}$) 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	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-EPI)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment. $\alpha = 0.0496$ (resulting from interim analysis) eGFR (CKD-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-EPI)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment. eGFR (CKD-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
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/1.73m ²] 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
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
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
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 ($100 \times \text{number of patients with event} / \text{time at risk [years]}$) 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 ^[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 ($100 \times \text{number of patients with event} / \text{time at risk [years]}$) 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 ^[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 ($100 \times \text{number of patients with event} / \text{time at risk [years]}$) 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
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)
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 ($100 \times \text{number of patients with event} / \text{time at risk [years]}$) 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. 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
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 (\pm 0.69)	-1.30 (\pm 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
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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	
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	
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	
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	
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	
Phimosi			
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	
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	
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	
Embololic 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	
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	
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	
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	
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	
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	0 / 4	0 / 3	

treatment / all			
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	
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	
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	
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	
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	
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	
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	0 / 1	0 / 0	

treatment / all			
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	
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	0 / 1	0 / 0	

treatment / all			
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	
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	
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	
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	
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	
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	

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	
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	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	94 / 1863 (5.05%)	89 / 1863 (4.78%)	
occurrences (all)	109	125	

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