Clinical trial results:
A double blind placebo controlled study to evaluate the effects of bexagliflozin on hemoglobin A1c in patients with type 2 diabetes and increased risk of cardiovascular adverse events

Summary

EudraCT number	2015-001760-19
Trial protocol	CZ DE PL DK NL
Global end of trial date	06 November 2019

Results information

Result version number	v1 (current)
This version publication date	26 May 2021
First version publication date	26 May 2021

Trial information

Trial identification

Sponsor protocol code	THR-1442-C-476

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02558296
WHO universal trial number (UTN)	-
Other trial identifiers	EMA UPI number: 498543

Notes:

Sponsors

Sponsor organisation name	Theracos Sub, LLC
Sponsor organisation address	225 Cedar Hill St #200, Marlborough, United States, 01752
Public contact	Albert Collinson, Theracos Sub, LLC, +1 5086884221, acollinson@theracos.com
Scientific contact	Albert Collinson, Theracos Sub, LLC, +1 5086884221, acollinson@theracos.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of this trial is to evaluate the placebo-adjusted change in HbA1c from baseline after 24 weeks of exposure to bexagliflozin in type 2 diabetic subjects with increased risk of cardiovascular adverse events.

The primary safety objective of this study is the contribution of at least 134 major adverse cardiovascular events (MACE+) to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to placebo. MACE+ is defined as cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina.

An additional objective is the evaluation of the safety of exposure to bexagliflozin for a minimum of 52 weeks in a treatment population that is at elevated risk for major adverse cardiovascular events.

Protection of trial subjects:

Safety information was drawn from review of adverse events (AEs), concomitant medications, vital signs, electrocardiograpms (ECGs), results from physical examinations, and blood and urine specimen collections. At every visit, subjects were to be queried regarding AEs and information on all events potentially represent major adverse cardiovascular events will be forwarded to a cardiovascular endpoint committee for blinded adjudication of the event. During the first 24 weeks of the treatment period, persistent hyperglycemia despite diet and exercise counseling was managed with intensification of the antidiabetic regimen based on the guideline in the protocol. After 24 weeks, medical therapy for hyperglycemia was to be adjusted at the discretion of the investigator based on self-monitored blood glucose (SMBG), FPG, and HbA1c using local standards of care for subjects with T2DM. Blood pressure and lipid values were to be managed according to standards of care for the management of hypertension and dyslipidemia. Following the end of study visit, subjects are advised to see their primary physician for treatment of their diabetes and cardiovascular conditions.

Background therapy:

Standard of Care

Evidence for comparator:

N/A

Actual start date of recruitment	23 October 2015
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	Netherlands: 54
Country: Number of subjects enrolled	Poland: 293
Country: Number of subjects enrolled	Czech Republic: 170
Country: Number of subjects enrolled	Denmark: 27

Country: Number of subjects enrolled	Russian Federation: 140
Country: Number of subjects enrolled	United States: 602
Country: Number of subjects enrolled	Canada: 91
Country: Number of subjects enrolled	Mexico: 183
Country: Number of subjects enrolled	Korea, Republic of: 74
Country: Number of subjects enrolled	Taiwan: 66
Worldwide total number of subjects	1700
EEA total number of subjects	544

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)	838
From 65 to 84 years	850
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

A total of 1701 patients were recruited from 10 countries: Canada, Czech Republic, Demark, Republic of Korea, Mexico, the Netherlands, Poland, Russian Federation, Taiwan, and the United States.

Pre-assignment

Screening details:

Subjects ≥ 40 years old with inadequately controlled T2DM with HbA1c between 7.5% (7.0% since protocol version 8) and 11% on stable medications and elevated risk for CV adverse events were enrolled. All subjects must belong to 1 of 3 CV risk groups to be eligible. All eligible subjects took placebo during 13 ± 2 days run-in period.

Period 1

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

Blinding implementation details:

Bexagliflozin tablets, 20 mg and placebo tablets were not distinguishable in appearance. Eligible subjects were randomly assigned to the bexagliflozin or the placebo arm in 2:1 proportion by an interactive web response system. The results of urinary glucose testing were not made available to any study personnel or subjects to prevent accidental unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bexagliflozin

Arm description:

The subjects received Bexagliflozin tablets, 20 mg, once daily.

Arm type	Experimental
Investigational medicinal product name	Bexagliflozin tablets, 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The subjects received Bexagliflozin tablets, 20 mg, orally once daily.

Arm title	Placebo

Arm description:

The subjects received placebo tablets once daily.

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

Dosage and administration details:

Placebo tablet, orally, once daily

Number of subjects in period 1	Bexagliflozin	Placebo
Started	1133	567
completed through week 24	1089	542
Completed	987	482
Not completed	146	85
Adverse event, serious fatal	39	25
Physician decision	6	-
Consent withdrawn by subject	53	31
Adverse event, non-fatal	14	5
Unknown	1	-
Lost to follow-up	31	23
Protocol deviation	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Bexagliflozin
Reporting group description:	
The subjects received Bexagliflozin tablets, 20 mg, once daily.	
Reporting group title	Placebo
Reporting group description:	
The subjects received placebo tablets once daily.	

Reporting group values	Bexagliflozin	Placebo	Total
Number of subjects	1133	567	1700
Age categorical			
Age is the age at informed consent, automatically computed in the case report form.			
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)	562	276	838
From 65-84 years	561	289	850
85 years and over	10	2	12
Age continuous			
Age is the age at informed consent, automatically computed in the case report form.			
Units: years			
arithmetic mean	64.4	64.6	
standard deviation	± 7.94	± 8.01	-
Gender categorical			
Units: Subjects			
Female	341	177	518
Male	792	390	1182
Age Group			
Units: Subjects			
< 65 years	562	276	838
>= 65 years	571	291	862
Race			
Units: Subjects			
American Indian or Alaskan Native	98	54	152
White	879	430	1309
Black or African American	46	28	74
Asian	108	55	163
Native Hawaiian/Other Pacific Islander	2	0	2
Other	0	0	0
Ethnicity			
Units: Subjects			

Hispanic or Latino	166	93	259
Not Hispanic or Latino	967	474	1441
Not Applicable	0	0	0
Unknown	0	0	0
Country Units: Subjects			
Czech Republic	118	52	170
Denmark	17	10	27
Netherlands	36	18	54
Poland	196	97	293
Russian Federation	87	53	140
USA	397	205	602
Canada	67	24	91
Mexico	121	62	183
Republic of Korea	48	26	74
Taiwan, Province of China	46	20	66
Region Units: Subjects			
North America	585	291	876
Europe	454	230	684
Asia	94	46	140
Cardiovascular Risk Groups			
1: History of atherosclerotic vascular disease with > 1 of the following: i) MI/ischemic stroke > 3 months but < 5 years prior to screening ii) Documented history of coronary, carotid or peripheral arterial revascularization (CABG must have occurred > 5 years prior to screening) 2: History of heart failure 3: Age >= 55 with > 2 of the following: i) Diabetes duration of > 10 years ii) Uncontrolled hypertension defined as SBP > 140 mmHg despite > 3 anti-hypertensive medications iii) current smoker iv) Urine albumin: creatinine ratio > 30 mg/g v) eGFR 45-60 mL/min/1.73 m2 vi) HDL < 1 mmol/L			
Units: Subjects			
Group 1	703	362	1065
Group 2	166	80	246
Group 3	264	125	389
Body Mass Index Categories			
BMI is calculated from Height at Screening and Body Weight at Baseline (BMI = weight (kg/)/height (m)^2).			
Units: Subjects			
BMI < 25	86	45	131
BMI >= 25	1047	522	1569
Systolic Blood Pressure Groups Units: Subjects			
< 140 mmHg	685	352	1037
>= 140 mmHg	448	215	663
eGFR group at Baseline Units: Subjects			
< 60 mL/min/1.73 m^2	225	109	334
>= 60 mL/min/1.73 m^2	908	458	1366
HbA1c Group at Baseline Units: Subjects			
<= 8.5%	716	362	1078
> 8.5%	417	205	622
Insulin Use at Baseline Units: Subjects			

Yes	610	292	902
No	523	275	798
Use Anti-Diabetic Treatment at Baseline			
Units: Subjects			
Yes	1125	564	1689
No	8	3	11
Body Weight at Baseline			
Units: kg			
arithmetic mean	94.59	92.62	
standard deviation	± 21.087	± 19.999	-
Body Mass Index at Baseline			
BMI is calculated from Height at Screening and Body Weight at Baseline (BMI = weight (kg/)/height (m)^2).			
Units: kg/m2			
arithmetic mean	32.80	32.24	
standard deviation	± 6.068	± 5.751	-
Systolic Blood Pressure at Baseline			
Units: mmHg			
arithmetic mean	134.2	133.7	
standard deviation	± 16.24	± 16.18	-
Diastolic Blood Pressure at Baseline			
Units: mmHg			
arithmetic mean	77.1	76.8	
standard deviation	± 9.94	± 10.16	-
eGFR at Screening			
Units: mL/min/1.73 m^2			
arithmetic mean	77.93	77.76	
standard deviation	± 19.475	± 19.653	-
HbA1c at Screening			
Units: Percentage			
arithmetic mean	8.49	8.49	
standard deviation	± 0.913	± 0.903	-
Duration of Diabetes from Diagnosis to the date of informed consent			
Units: Years			
arithmetic mean	14.87	15.23	
standard deviation	± 8.635	± 9.253	-

Subject analysis sets	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who are randomized regardless of treatment adherence or availability of follow up data will be included in the intention-to-treat analysis set (ITT). All analyses of the ITT will be based on each subject's randomized assigned treatment by the IWRS.

Reporting group values	Intention-to-treat		
Number of subjects	1700		
Age categorical			
Age is the age at informed consent, automatically computed in the case report form.			
Units: Subjects			

In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	837		
From 65-84 years	850		
85 years and over	12		
Age continuous			
Age is the age at informed consent, automatically computed in the case report form.			
Units: years			
arithmetic mean	64.4		
standard deviation	± 7.96		
Gender categorical			
Units: Subjects			
Female	518		
Male	1382		
Age Group			
Units: Subjects			
< 65 years	838		
>= 65 years	862		
Race			
Units: Subjects			
American Indian or Alaskan Native	152		
White	1309		
Black or African American	74		
Asian	163		
Native Hawaiian/Other Pacific Islander	2		
Other	0		
Ethnicity			
Units: Subjects			
Hispanic or Latino	259		
Not Hispanic or Latino	1441		
Not Applicable	0		
Unknown	0		
Country			
Units: Subjects			
Czech Republic	170		
Denmark	27		
Netherlands	54		
Poland	293		
Russian Federation	140		
USA	602		
Canada	91		
Mexico	183		
Republic of Korea	74		
Taiwan, Province of China	66		
Region			

Units: Subjects			
North America	876		
Europe	684		
Asia	140		
Cardiovascular Risk Groups			
1: History of atherosclerotic vascular disease with > 1 of the following: i) MI/ischemic stroke > 3 months but < 5 years prior to screening ii) Documented history of coronary, carotid or peripheral arterial revascularization (CABG must have occurred > 5 years prior to screening) 2: History of heart failure 3: Age >= 55 with > 2 of the following: i) Diabetes duration of > 10 years ii) Uncontrolled hypertension defined as SBP > 140 mmHg despite > 3 anti-hypertensive medications iii) current smoker iv) Urine albumin: creatinine ratio > 30 mg/g v) eGFR 45-60 mL/min/1.73 m2 vi) HDL < 1 mmol/L			
Units: Subjects			
Group 1	1065		
Group 2	246		
Group 3	389		
Body Mass Index Categories			
BMI is calculated from Height at Screening and Body Weight at Baseline (BMI = weight (kg/)/height (m)^2).			
Units: Subjects			
BMI < 25	131		
BMI >= 25	1569		
Systolic Blood Pressure Groups Units: Subjects			
< 140 mmHg	1037		
>= 140 mmHg	663		
eGFR group at Baseline Units: Subjects			
< 60 mL/min/1.73 m^2	334		
>= 60 mL/min/1.73 m^2	1366		
HbA1c Group at Baseline Units: Subjects			
<= 8.5%	1078		
> 8.5%	622		
Insulin Use at Baseline Units: Subjects			
Yes	902		
No	798		
Use Anti-Diabetic Treatment at Baseline Units: Subjects			
Yes	1689		
No	11		
Body Weight at Baseline Units: kg			
arithmetic mean	93.94		
standard deviation	± 20.745		
Body Mass Index at Baseline			
BMI is calculated from Height at Screening and Body Weight at Baseline (BMI = weight (kg/)/height (m)^2).			
Units: kg/m2			
arithmetic mean	32.62		
standard deviation	± 5.968		
Systolic Blood Pressure at Baseline			

Units: mmHg			
arithmetic mean	134.0		
standard deviation	± 16.21		
Diastolic Blood Pressure at Baseline			
Units: mmHg			
arithmetic mean	77.0		
standard deviation	± 10.01		
eGFR at Screening			
Units: mL/min/1.73 m^2			
arithmetic mean	77.88		
standard deviation	± 19.529		
HbA1c at Screening			
Units: Percentage			
arithmetic mean	8.49		
standard deviation	± 0.910		
Duration of Diabetes from Diagnosis to the date of informed consent			
Units: Years			
arithmetic mean	14.99		
standard deviation	± 8.845		

End points

End points reporting groups

Reporting group title	Bexagliflozin
Reporting group description:	
The subjects received Bexagliflozin tablets, 20 mg, once daily.	
Reporting group title	Placebo
Reporting group description:	
The subjects received placebo tablets once daily.	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who are randomized regardless of treatment adherence or availability of follow up data will be included in the intention-to-treat analysis set (ITT). All analyses of the ITT will be based on each subject's randomized assigned treatment by the IWRS.	

Primary: Analysis of Change From Baseline in HbA1c (%) at Week 24

End point title	Analysis of Change From Baseline in HbA1c (%) at Week 24
End point description:	
The null hypothesis is that the mean change in HbA1c from baseline to Week 24 in the bexagliflozin cohort would be equal to or greater than the mean change from baseline to Week 24 in the placebo cohort. Rejection of the null hypothesis would imply that the mean change in baseline HbA1c from baseline to Week 24 was less than that in the placebo cohort by a value that could not not be attributed to chance alone.	
End point type	Primary
End point timeframe:	
Data from Week 6, 12, and 24 are used in the model.	

End point values	Bexagliflozin	Placebo	Intention-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1046[1]	531[2]	1577	
Units: Percentage				
least squares mean (confidence interval 95%)	-0.85 (-0.90 to -0.80)	-0.37 (-0.44 to -0.30)	-0.48 (-0.56 to -0.39)	

Notes:

[1] - Number corresponds to subjects with a value at baseline and at the specified visit.

[2] - Number corresponds to subjects with a value at baseline and at the specified visit.

Statistical analyses

Statistical analysis title	Difference from Placebo
Statistical analysis description:	
The full model is a mixed-effects repeated measures analysis that includes region, baseline eGFR categories (<60 or >=60 mL/min/1.73 m2), baseline BMI (< or >=25 kg/m2), history of heart failure (yes or no), insulin use or not, treatment, visit, treatment-by-visit interaction and the baseline HbA1c value as a fixed effect covariate. An unstructured covariance matrix is used.	
Comparison groups	Bexagliflozin v Placebo

Number of subjects included in analysis	1577
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean
Point estimate	-0.48
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	-0.39
Variability estimate	Standard error of the mean

Notes:

[3] - The null hypothesis for the primary endpoint was that the mean change in HbA1c from baseline to Week 24 in the bexagliflozin arm would be equal to or greater than the mean change in the placebo arm. Rejection of the null hypothesis would imply that the mean change in baseline HbA1c from baseline to Week 24 was less than that in the placebo arm by a value that could not be attributed to chance alone.

[4] - p-value is presented based on one-sided statistical tests using a 0.025 level of significance.

Secondary: Change in HbA1c from baseline to Week 24 in randomized subjects who had been prescribed insulin

End point title	Change in HbA1c from baseline to Week 24 in randomized subjects who had been prescribed insulin

End point description:

End point type	Secondary

End point timeframe:

Data from Week 6, 12, and 24 are used.

End point values	Bexagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	561[5]	292		
Units: Percentage				
least squares mean (confidence interval 95%)	-0.84 (-0.92 to -0.77)	-0.32 (-0.43 to -0.22)		

Notes:

[5] - Subjects prescribed insulin at baseline with a value at baseline and at week 24 were included.

Statistical analyses

Statistical analysis title	Difference from Placebo

Statistical analysis description:

In the population prescribed insulin at baseline, the placebo-adjusted change in HbA1c from baseline to Week 24 was analyzed using an MMRM ANCOVA model with unstructured covariance. The model was to include terms for treatment, baseline eGFR categories, baseline BMI, and history of heart failure, visit, treatment-by-visit interaction, and region as fixed effects and the baseline HbA1c value as an additional fixed effect covariate.

Comparison groups	Placebo v Bexagliflozin

Number of subjects included in analysis	853
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.52
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	-0.4

Notes:

[6] - The p-value is presented based on one-sided statistical tests using a 0.025 level of significance.

Secondary: Change in Body Mass from Baseline to Week 48 in Subjects with BMI >= 25 kg/m2

End point title	Change in Body Mass from Baseline to Week 48 in Subjects with BMI >= 25 kg/m2

End point description:

The change in body mass was to be tested if the null hypothesis was rejected for the first secondary point (Change in HbA1c from baseline to Week 24 in randomized subjects who had been prescribed insulin).

End point type	Secondary

End point timeframe:

Data from Weeks 6, 12, 36 and 48 are used.

End point values	Bexagliflozin	Placebo	Intention-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	922[7]	456[8]	1569[9]	
Units: kg				
least squares mean (confidence interval 95%)	-3.03 (-3.27 to -2.80)	-0.38 (-0.72 to -0.04)	-2.65 (-3.07 to -2.24)	

Notes:

[7] - Number of subjects with a value at baseline and at the specified visits

[8] - Number of subjects with a value at baseline and at the specified visit.

[9] - Subjects in the ITT analysis set with a baseline BMI >= 25 mg/m2 are included.

Statistical analyses

Statistical analysis title	Difference from Placebo

Statistical analysis description:

The placebo-adjusted change in body weight from baseline to Week 48 was analyzed using an MMRM ANCOVA model with unstructured covariance. The model included treatment, visit, treatment-by-visit interaction, baseline HbA1c, geographical region, baseline eGFR categories, baseline BMI, history of heart failure and insulin prescription category as fixed effects and the corresponding baseline body weight value as an additional fixed effect covariate.

Comparison groups	Placebo v Bexagliflozin

Number of subjects included in analysis	1378
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.65
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	-2.24

Notes:

[10] - p-value is presented based on one-sided statistical tests using a 0.025 level of significance

Secondary: Change in SBP from Baseline to Week 24 in subjects with Baseline SBP >= 140 mmHg

End point title	Change in SBP from Baseline to Week 24 in subjects with Baseline SBP >= 140 mmHg

End point description:

The change in SBP was to be tested if the null hypothesis was rejected for the second key secondary endpoint (Change in Body Mass from Baseline to Week 48 in subjects with BMI >= 25 kg/m2).

End point type	Secondary

End point timeframe:

Data from Week 6, 12 and 24 are used.

End point values	Bexagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	417[11]	204[12]		
Units: mmHg				
least squares mean (confidence interval 95%)	-9.83 (-11.28 to -8.38)	-6.87 (-8.95 to -4.78)		

Notes:

[11] - Number of subjects with a value at baseline and at the specified visit.

[12] - Number of subjects with a value at baseline and at the specified visit.

Statistical analyses

Statistical analysis title	Difference from Placebo

Statistical analysis description:

The placebo-adjusted change in seated SBP from baseline to Week 24 was analyzed using an MMRM ANCOVA model with unstructured covariance. The model included treatment, visit, treatment-by-visit interaction, baseline HbA1c, geographical region, baseline eGFR categories, baseline BMI, history of heart failure and insulin prescription category as fixed effects and the corresponding baseline SBP value as an additional fixed effect covariate. Only subjects with baseline SBP >= 140 mmHg are included.

Comparison groups	Bexagliflozin v Placebo

Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0112 [13]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.96
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	-0.42

Notes:

[13] - p-value is presented based on one-sided statistical tests using a 0.025 level of significance

Adverse events

Adverse events information

Timeframe for reporting adverse events:

December 2015 to November 2019

Adverse event reporting additional description:

All treatment-emergent serious adverse events were reported by System Organ Class and Preferred Terms. For non-serious treatment-emergent adverse events, those occurred in > 5% of the subjects in either of the treatment groups were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Bexagliflozin
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Bexagliflozin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	373 / 1132 (32.95%)	208 / 567 (36.68%)	
number of deaths (all causes)	40	27	
number of deaths resulting from adverse events	40	27	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	0 / 1132 (0.00%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Prostate cancer			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	3 / 1132 (0.27%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
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	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal adenoma			

subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary cancer metastatic			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Carcinoid tumor of the appendix			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer recurrent			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric adenoma			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive papillary breast carcinoma			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of ampulla of Vater			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic renal cell carcinoma			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
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	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloproliferative disorder			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian cancer			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary cystadenoma lymphomatosum			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumor benign			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia vera			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer metastatic			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	11 / 1132 (0.97%)	7 / 567 (1.23%)	
occurrences causally related to treatment / all	0 / 12	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	8 / 1132 (0.71%)	6 / 567 (1.06%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	5 / 1132 (0.44%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 1132 (0.18%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	3 / 1132 (0.27%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			

subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Femoral artery occlusion			
subjects affected / exposed	3 / 1132 (0.27%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leriche syndrome			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrosis ischaemic			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			

subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac pacemaker battery replacement			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker replacement			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implantable defibrillator insertion			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prophylaxis			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitrectomy			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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			
Non-cardiac chest pain			
subjects affected / exposed	6 / 1132 (0.53%)	5 / 567 (0.88%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	6 / 1132 (0.53%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Necrosis			
subjects affected / exposed	3 / 1132 (0.27%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adverse drug reaction			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 1132 (0.27%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erectile dysfunction			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix disorder			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema genital			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatism			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			

subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	10 / 1132 (0.88%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	0 / 11	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	9 / 1132 (0.80%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	0 / 10	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory failure			
subjects affected / exposed	6 / 1132 (0.53%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pleural effusion			
subjects affected / exposed	4 / 1132 (0.35%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 1132 (0.00%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			

subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Troponin increased			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	3 / 1132 (0.27%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	3 / 1132 (0.27%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Foot fracture			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 1132 (0.00%)	2 / 567 (0.35%)	
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 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic ulcer			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
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 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
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 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoconiosis			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary contusion			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
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	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			

subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial septal defect			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phimosis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	31 / 1132 (2.74%)	19 / 567 (3.35%)	
occurrences causally related to treatment / all	0 / 39	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	31 / 1132 (2.74%)	14 / 567 (2.47%)	
occurrences causally related to treatment / all	0 / 33	0 / 15	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	18 / 1132 (1.59%)	15 / 567 (2.65%)	
occurrences causally related to treatment / all	0 / 21	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac failure			
subjects affected / exposed	21 / 1132 (1.86%)	7 / 567 (1.23%)	
occurrences causally related to treatment / all	0 / 27	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Angina pectoris			
subjects affected / exposed	16 / 1132 (1.41%)	11 / 567 (1.94%)	
occurrences causally related to treatment / all	0 / 20	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	21 / 1132 (1.86%)	6 / 567 (1.06%)	
occurrences causally related to treatment / all	0 / 21	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Atrial fibrillation			
subjects affected / exposed	15 / 1132 (1.33%)	9 / 567 (1.59%)	
occurrences causally related to treatment / all	0 / 21	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	11 / 1132 (0.97%)	13 / 567 (2.29%)	
occurrences causally related to treatment / all	0 / 11	1 / 13	
deaths causally related to treatment / all	0 / 2	1 / 2	
Cardiac arrest			
subjects affected / exposed	12 / 1132 (1.06%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 12	0 / 2	
deaths causally related to treatment / all	0 / 11	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	5 / 1132 (0.44%)	4 / 567 (0.71%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischemia			
subjects affected / exposed	8 / 1132 (0.71%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	3 / 1132 (0.27%)	6 / 567 (1.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	3 / 1132 (0.27%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	3 / 1132 (0.27%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	3 / 1132 (0.27%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorder			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sinus node dysfunction			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 1132 (0.00%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			

subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 1132 (0.00%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anginal equivalent			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac asthma			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiorenal syndrome			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve incompetence			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemic cardiomyopathy			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
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	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	15 / 1132 (1.33%)	7 / 567 (1.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	10 / 1132 (0.88%)	4 / 567 (0.71%)	
occurrences causally related to treatment / all	0 / 11	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	6 / 1132 (0.53%)	5 / 567 (0.88%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			

subjects affected / exposed	7 / 1132 (0.62%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 1132 (0.35%)	4 / 567 (0.71%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subarachnoid haemorrhage			
subjects affected / exposed	3 / 1132 (0.27%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem infarction			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral artery stenosis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery thrombosis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical myelopathy			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Miller Fisher syndrome			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			

subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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	0 / 1132 (0.00%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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 / 1132 (0.27%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal lesion			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratopathy			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lens dislocation			

subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 1132 (0.18%)	4 / 567 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 1132 (0.35%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 1132 (0.27%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Barrett's oesophagus			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			

subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal incontinence			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascending Cholangitis			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 1132 (0.00%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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			
Skin ulcer			
subjects affected / exposed	2 / 1132 (0.18%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			

subjects affected / exposed	3 / 1132 (0.27%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis contact			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Excessive granulation tissue			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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	9 / 1132 (0.80%)	4 / 567 (0.71%)	
occurrences causally related to treatment / all	4 / 10	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	3 / 1132 (0.27%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	15 / 1132 (1.33%)	4 / 567 (0.71%)	
occurrences causally related to treatment / all	0 / 17	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 1132 (0.18%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervetebral disc protrusion			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			

subjects affected / exposed	3 / 1132 (0.27%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dupuytren's contracture			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunoglobulin G4 related sclerosing disease			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint instability			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle instability			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic arthropathy			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scoliosis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			

subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	11 / 1132 (0.97%)	10 / 567 (1.76%)	
occurrences causally related to treatment / all	0 / 11	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	9 / 1132 (0.80%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 11	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Osteomyelitis			
subjects affected / exposed	10 / 1132 (0.88%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 13	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	9 / 1132 (0.80%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	1 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	6 / 1132 (0.53%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	2 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	4 / 1132 (0.35%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diverticulitis			
subjects affected / exposed	3 / 1132 (0.27%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	2 / 1132 (0.18%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	4 / 1132 (0.35%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	3 / 1132 (0.27%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	3 / 1132 (0.27%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	3 / 1132 (0.27%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 1132 (0.18%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 1132 (0.09%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysematous cholecystitis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			

subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gas gangrene			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site joint infection			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
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	0 / 1132 (0.00%)	1 / 567 (0.18%)	
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	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Muscle spasms			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	14 / 1132 (1.24%)	8 / 567 (1.41%)	
occurrences causally related to treatment / all	6 / 15	4 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 1132 (0.09%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	3 / 1132 (0.27%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 1132 (0.00%)	3 / 567 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 1132 (0.09%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic mellitus inadequate control			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 1132 (0.00%)	2 / 567 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	2 / 1132 (0.18%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic complication			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Latent autoimmune diabetes in adults			
subjects affected / exposed	0 / 1132 (0.00%)	1 / 567 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	1 / 1132 (0.09%)	0 / 567 (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	Bexagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	981 / 1132 (86.66%)	506 / 567 (89.24%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	45 / 1132 (3.98%)	36 / 567 (6.35%)	
occurrences (all)	46	38	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	72 / 1132 (6.36%)	31 / 567 (5.47%)	
occurrences (all)	90	40	
Nausea			
subjects affected / exposed	54 / 1132 (4.77%)	37 / 567 (6.53%)	
occurrences (all)	64	45	
Musculoskeletal and connective tissue disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	49 / 1132 (4.33%)	29 / 567 (5.11%)	
occurrences (all)	53	37	
Back pain			
subjects affected / exposed	66 / 1132 (5.83%)	33 / 567 (5.82%)	
occurrences (all)	72	36	
Arthralgia			
subjects affected / exposed	49 / 1132 (4.33%)	30 / 567 (5.29%)	
occurrences (all)	56	37	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	128 / 1132 (11.31%)	60 / 567 (10.58%)	
occurrences (all)	190	96	
Upper respiratory tract infection			
subjects affected / exposed	112 / 1132 (9.89%)	53 / 567 (9.35%)	
occurrences (all)	147	82	
Nasopharyngitis			
subjects affected / exposed	96 / 1132 (8.48%)	39 / 567 (6.88%)	
occurrences (all)	115	46	
Bronchitis			
subjects affected / exposed	52 / 1132 (4.59%)	34 / 567 (6.00%)	
occurrences (all)	65	40	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	475 / 1132 (41.96%)	246 / 567 (43.39%)	
occurrences (all)	3743	1857	
Hyperglycaemia			

subjects affected / exposed occurrences (all)	68 / 1132 (6.01%) 181	41 / 567 (7.23%) 80	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2015	The figure delineating the cardiovascular risk groups under Synopsis (page 10) and Section 3.2.1 (page 18) was revised to ensure consistency with the text of the protocol.
07 July 2015	The figure delineating the cardiovascular risk groups under Synopsis (page 10) and Section 3.2.1 (page 18) was revised to ensure consistency with the text of the protocol. Changes include: Inclusion of equal-to sign for History of HF & LVEF <= 40%, inclusion of equal-to sign for NYHA class II (N <= 200) and correction of age to 40 from 20 (this error was accidentally introduced into version 2.0).
08 September 2015	(Continued) Include instructions for subjects to contact the clinic in case of hypoglycaemia or symptoms suggestive of ketoacidosis. Rescue medications cannot be an SGLT2 inhibitor. Removal of the 10mg dose for dose selection. Clarified treatment for hyperglycemia with antidiabetic regimen for SMBG >= 200 mg/dL to include a set timeline between week 12 and week 24. Rescue medication is defined as antidiabetic therapy for treating hyperglycemia persisting for more than 2 weeks. Modified exclusion criteria to state that patient cannot be currently participating in another interventional trial. Replaced IRAE form with CRF AE form. Added clarification that INR to be assessed at the investigator's clinical judgement and discretion. Monitoring for potential signs of hypoglycemia to include hyperglycemia/symptoms suggestive of ketoacidosis. End of treatment period is re-defined as: i) all randomized subjects have either completed at least 52 weeks of treatment/withdrawn from the study and ii) at least 134 subjects have an adjudicated MACE+ event confirmed by the CEC. Inclusion of: The sample size is determined based on the required number of MACE+ for the program-wide meta-analysis of bexagliflozin cardiovascular safety assessment. Non-inferiority of bexagliflozin to placebo is assessed from a hazard ratio perspective. Inclusion of assumptions that randomization ratio is 2:1 bexagliflozin vs. placebo and the actual hazard ratio is an equivalence hazard ratio of 1.00 and the reference group hazard rate is 0.00308. Included justification that the sample size was based on the SAVOR cardiovascular study. Inclusion of ITT analysis set, which is to be based on each subject's randomized assigned treatment regardless of treatment adherence/availability to follow up. Inclusion of Safety Analysis Set, in case of randomization error. The analysis for SAS population will be performed based on the actual treatment received by the subjects.

08 September 2015	Primary Objectives changed to Primary Efficacy Objective and safety objective moved to separate heading. Modification of secondary efficacy objectives: a. Evaluating the effect of bexagliflozin on the change in body weight from baseline to week 48 in randomized subjects b. Evaluating the effect of bexagliflozin on systolic blood pressure from baseline to week 24 c. Removal of the evaluation of mycotic genital infections compared to placebo. Revised Safety Objectives: a. Primary safety objective is the contribution of at least 134 major adverse cardiovascular events (MACE+) to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to those exposed to placebo. b. Inclusion of additional safety objective to evaluate the safety exposure of bexagliflozin for a minimum of 52 weeks in high risk MACE population. Inclusion of Other Objective: Measurement of bexagliflozin plasma concentration as a function of time from dosing, to be conducted at 30 sites and include approximately 240 subjects. Inclusion of instructions specifying management of hyperglycemia. Removal of planned blinded interim event rate evaluation. Change to the inclusion criteria of Group 2 subjects: Subjects with NYHA II/III heart failure at screening with LVEF <=40% and no subsequent LVEF>40% within 6 months will be eligible. Duration of treatment modified to completion of at least 52 weeks of treatment and at least 134 subjects have experienced a MACE+. Statistical methods: Addition of ITT population to include all randomized subjects. Secondary efficacy endpoints will be tested for comparison using MMRM ANCOVA if there is a statistically significant benefit effect on the primary endpoint. Specified sample size of 1650 patients. Subjects will be included in Group 1 if they don't have heart failure history and history of atherosclerotic vascular disease.
02 February 2016	Addition of cardiovascular biomarkers relevant in the CV disease diagnosis and prognosis at baseline and week 12. Biomarker analysis will be performed separately. Modified study qualification: Subjects will be randomized only if they met the compliance by missing no more than 1 dose during run-in period. Addition of symptom assessment for possible DKA at every visit; Potential DKA assessments were added to the schedule for V2-V10 and every visit to the end of treatment. DKA adjudication committee to review all suspected DKA cases. Addition of detailed procedures for suspected DKA events. Removal of MACE+ endpoints. Incorporated recent published data from empagliflozin study. Addition of language to clarify that blood pressure to be measured in seated position. Clarification of criteria to include any surgical procedure. Addition of language to clarify that the investigational product is to be taken at the clinic on V2 and V3. DKA adjudication committee was added following recommendations by FDA. Height will be measured only at screening. P-wave axis and QRS-axis were removed and not to be analyzed. Blood volume for chemistry and electrolytes were changed to 5 mL from 10 mL. Deletion of urine drug screen from laboratory tests and removal of footnote regarding drug abuse screening. HIV testing to be added in Canada per requirement from Health Canada. The sample volume for Infectious Disease Testing was increased from 6 mL to 9 mL per central laboratory procedures. Language added to clarify when the urine culture should be performed. Microscopic urine study is to be performed by the central laboratory. Addition of instruction to allow investigators to obtain lab testing locally if clinically indicated. Clarification of AE assessment to begin after a subject consents to the study.

02 February 2016	Deleted language relating to treatment effect of 0.22% HbA1c as the sample size was not determined based on the required power to detect treatment effect in HbA1c reduction. Removed paragraph for the full analysis set, as the primary efficacy analysis was to be performed using the ITT population. Protocol was modified to clarify efficacy and safety analyses: 1. All observed data to be analyzed and data obtained after rescue will not be excluded and considered as missing; 2. Missing primary efficacy endpoint information will be imputed via multiple imputation linear regression approach; 3. Analyses on safety endpoint (MACE+) data to be analyzed in the meta-analyses only. Instead of BMI, body weight was considered as an analysis variable in the study. For exploratory efficacy endpoint, either hospitalization for heart failure or time to hospitalization for heart failure were examined and not both. Addition of sensitivity analysis of time-to-event data for the primary MACE+ endpoint. DKA events will be included in AESI under acid-base disorders. Addition of AE and potential DKA under Schedule of Events. Addition of language to describe glycemic control diary to be dispensed at V3 to reflect the change in protocol visit schedule.
04 October 2016	Medical monitor changed to Dr. J. Paul Lock. Addition of a secondary endpoint to perform an analysis of bexagliflozin treatment effect (change in HbA1c) on those who are taking insulin. The eligibility criteria was modified to include subjects with baseline HbA1c between 7.0 % (instead of 7.5 %) and 11 %. The eligibility criteria was modified to include subjects with FPG <= 300 mg/dL (instead of 250 mg/dL) at screening. The heart failure definition for Group 2 subjects was modified to allow more heart failure patients to be included. A cutoff for NT-proBNP was added to the criteria to confirm heart failure diagnosis. Rationale for the cut point based on arrhythmia is also included. Addition of sensitivity analyses for a key secondary efficacy endpoint; effect of bexagliflozin on the change in HbA1c from baseline to week 24 in subjects taking insulin at baseline, using MMRM ANCOVA. Clarified that subjects can continue in the study after randomization even if they omit the run-in drug due to acute illness. Addition of sensitivity analyses to evaluate potential impact on the population enrolled before or after the amendment. Clarified that the anticipated subjects to be included in the analysis should have sufficient power to demonstrate treatment effect. Safety profile for subjects in the insulin sub-population to be separately analyzed. Modified statement to clarify that a complete physical examination to be performed at V3 prior to randomization and at the follow up visit (instead of end of treatment visit).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported