



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled, 3-arm, Parallel-group 52-week Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment who have Inadequate Glycemic Control

Summary

EudraCT number	2016-004889-26
Trial protocol	ES DE HU IT RO
Global end of trial date	25 October 2019

Results information

Result version number	v1 (current)
This version publication date	20 September 2020
First version publication date	20 September 2020

Trial information

Trial identification

Sponsor protocol code	EFC14837
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03242252
WHO universal trial number (UTN)	U1111-1187-8662

Notes:

Sponsors

Sponsor organisation name	Lexicon Pharmaceuticals, Inc.
Sponsor organisation address	8800 Technology Forest Place, The Woodlands, United States, TX 77381
Public contact	Medical Affairs, Lexicon Pharmaceuticals, Inc., medical-information@lexpharma.com
Scientific contact	Medical Affairs, Lexicon Pharmaceuticals, Inc., medical-information@lexpharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 October 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of sotagliflozin 200 milligrams (mg) and sotagliflozin 400 mg versus placebo on hemoglobin A1c (HbA1c) reduction at Week 26 in subjects with Type 2 diabetes who have inadequate glycemic control and moderate renal impairment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 August 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 84
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Hungary: 57
Country: Number of subjects enrolled	Argentina: 24
Country: Number of subjects enrolled	Brazil: 66
Country: Number of subjects enrolled	Canada: 41
Country: Number of subjects enrolled	Colombia: 32
Country: Number of subjects enrolled	Israel: 56
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Mexico: 34
Country: Number of subjects enrolled	Romania: 33
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	South Africa: 22
Country: Number of subjects enrolled	Ukraine: 39
Country: Number of subjects enrolled	United States: 200
Worldwide total number of subjects	787
EEA total number of subjects	234

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)	197
From 65 to 84 years	576
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 166 investigative sites in the United States, Argentina, Brazil, Canada, Colombia, Germany, Hungary, Israel, Italy, Mexico, Poland, Romania, Russian Federation, South Africa, Spain, and Ukraine from 16 August 2017 to 25 October 2019.

Pre-assignment

Screening details:

Subjects with a diagnosis of Type 2 Diabetes Mellitus were enrolled in 1 of 3 treatment groups: Placebo or Sotagliflozin 200 mg or Sotagliflozin 400 mg. Subjects were randomly assigned in the ratio of 1:1:1 to these reporting groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Following a 2-week run-in phase, subjects received two placebo tablets (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 54 weeks.

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

Dosage and administration details:

Placebo was administered as two tablets (identical to sotagliflozin in appearance), once daily before the first meal of the day.

Arm title	Sotagliflozin 200 mg
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Arm description:

Following a 2-week run-in phase, subjects received two tablets, one sotagliflozin 200 mg tablet and one placebo tablet (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 58 weeks.

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

Dosage and administration details:

Placebo was administered as one tablet (identical to the sotagliflozin 200 mg tablet in appearance), orally, once daily before the first meal of the day.

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

Dosage and administration details:

Sotagliflozin 200 mg was administered as one tablet, orally once daily before the first meal of the day.

Arm title	Sotagliflozin 400 mg
Arm description: Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as two sotagliflozin 200 mg tablets, orally once daily for up to 60 weeks.	
Arm type	Experimental
Investigational medicinal product name	Sotagliflozin
Investigational medicinal product code	
Other name	SAR439954
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sotagliflozin 400 mg was administered as two sotagliflozin 200 mg tablets, orally once daily before the first meal of the day.

Number of subjects in period 1	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Started	260	263	264
Completed	224	240	232
Not completed	36	23	32
At the subject's own request	18	10	15
Adverse event	8	6	9
Study terminated by sponsor	1	-	-
Poor compliance to protocol	-	2	3
Lost to follow-up	5	1	4
Reason not specified	4	4	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Following a 2-week run-in phase, subjects received two placebo tablets (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 54 weeks.	
Reporting group title	Sotagliflozin 200 mg
Reporting group description:	
Following a 2-week run-in phase, subjects received two tablets, one sotagliflozin 200 mg tablet and one placebo tablet (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 58 weeks.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as two sotagliflozin 200 mg tablets, orally once daily for up to 60 weeks.	

Reporting group values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Number of subjects	260	263	264
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	69.3	69.6	69.5
standard deviation	± 8.1	± 7.5	± 8.2
Gender categorical			
Units: Subjects			
Female	111	120	112
Male	149	143	152
Race			
Units: Subjects			
White	220	231	215
Black or African American	12	14	15
Asian	5	7	8
American Indian or Alaska Native	15	9	20
Native Hawaiian or Other Pacific Islander	1	1	0
Multiple	3	0	3
Not Reported	2	0	3
Unknown	2	1	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	67	67	64
Not Hispanic or Latino	193	196	200
HbA1c			
Units: percentage of HbA1c			
arithmetic mean	8.33	8.33	8.31
standard deviation	± 1.00	± 0.90	± 0.94
Systolic Blood Pressure (SBP)			
Units: millimetre of mercury (mmHg)			

arithmetic mean	140.59	140.31	141.71
standard deviation	± 14.59	± 15.15	± 15.01

Reporting group values	Total		
Number of subjects	787		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	343		
Male	444		
Race			
Units: Subjects			
White	666		
Black or African American	41		
Asian	20		
American Indian or Alaska Native	44		
Native Hawaiian or Other Pacific Islander	2		
Multiple	6		
Not Reported	5		
Unknown	3		
Ethnicity			
Units: Subjects			
Hispanic or Latino	198		
Not Hispanic or Latino	589		
HbA1c			
Units: percentage of HbA1c			
arithmetic mean			
standard deviation	-		
Systolic Blood Pressure (SBP)			
Units: millimetre of mercury (mmHg)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Following a 2-week run-in phase, subjects received two placebo tablets (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 54 weeks.	
Reporting group title	Sotagliflozin 200 mg
Reporting group description: Following a 2-week run-in phase, subjects received two tablets, one sotagliflozin 200 mg tablet and one placebo tablet (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 58 weeks.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description: Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as two sotagliflozin 200 mg tablets, orally once daily for up to 60 weeks.	
Subject analysis set title	Sotagliflozin 200 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Following a 2-week run-in phase, subjects received two tablets, one sotagliflozin 200 mg tablet and one placebo tablet (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 58 weeks. Four subjects randomised to sotagliflozin 400 mg were dosed with both sotagliflozin 200 mg and sotagliflozin 400 mg were included in the sotagliflozin 200 mg arm in the safety population.	
Subject analysis set title	Sotagliflozin 400 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as two sotagliflozin 200 mg tablets, orally once daily for up to 60 weeks. Four subjects randomised to sotagliflozin 400 mg were dosed with both sotagliflozin 200 mg and sotagliflozin 400 mg were included in the sotagliflozin 200 mg arm in the safety population.	

Primary: Change From Baseline in HbA1c % at Week 26

End point title	Change From Baseline in HbA1c % at Week 26
End point description: An Analysis of covariance (ANCOVA) model was used for analysis. Intent-to-treat (ITT) population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using control-based copy reference multiple imputation under the missing not at random framework.	
End point type	Primary
End point timeframe: Baseline to Week 26	

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	260	263	264	
Units: percentage of HbA1c				
least squares mean (standard error)	-0.22 (± 0.061)	-0.32 (± 0.060)	-0.46 (± 0.060)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description:	
The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of Chronic Kidney Disease (CKD) stage (3A, 3B) at screening, and country as fixed effects, and baseline HbA1c as a covariate.	
Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2095
Method	ANCOVA
Parameter estimate	Difference in Least Square (LS) Means
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.245
upper limit	0.054
Variability estimate	Standard error of the mean
Dispersion value	0.076

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
Statistical analysis description:	
The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, and country as fixed effects, and baseline HbA1c as a covariate.	
Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.386
upper limit	-0.085
Variability estimate	Standard error of the mean
Dispersion value	0.077

Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) at Week 26

End point title	Change From Baseline in Fasting Plasma Glucose (FPG) at Week 26
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End point description:

An ANCOVA model was used for analysis. ITT population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using the retrieved dropouts & washout imputation method.

End point type	Secondary
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End point timeframe:

Baseline to Week 26

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	260	263	264	
Units: millimole per litre (mmol/L)				
least squares mean (standard error)	-0.374 (\pm 0.1949)	-0.961 (\pm 0.1715)	-0.852 (\pm 0.1668)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, and country as fixed effects, and baseline FPG as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0144
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.587
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.0564
upper limit	-0.1169
Variability estimate	Standard error of the mean
Dispersion value	0.2397

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, and country as fixed effects, and baseline FPG as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
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Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0436
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.478
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.942
upper limit	-0.0136
Variability estimate	Standard error of the mean
Dispersion value	0.2368

Secondary: Change From Baseline in SBP for Subjects With Baseline SBP ≥ 130 mmHg at Week 12

End point title	Change From Baseline in SBP for Subjects With Baseline SBP ≥ 130 mmHg at Week 12
End point description:	An ANCOVA model was used for analysis. Analysis population included subjects with baseline SBP ≥ 130 mmHg in ITT population where, ITT population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using the retrieved dropouts & washout imputation method.
End point type	Secondary
End point timeframe:	Baseline to Week 12

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	162	182	
Units: millimetre of mercury (mmHg)				
least squares mean (standard error)	-5.18 (\pm 1.462)	-7.46 (\pm 1.597)	-7.71 (\pm 1.247)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description:	The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, and country as fixed effects, and baseline SBP as a covariate.
Comparison groups	Placebo v Sotagliflozin 200 mg

Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2627
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-2.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.265
upper limit	1.709
Variability estimate	Standard error of the mean
Dispersion value	2.034

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1602
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-2.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.052
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	1.799

Secondary: Change From Baseline in SBP at Week 12 for All Subjects

End point title	Change From Baseline in SBP at Week 12 for All Subjects
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End point description:

An ANCOVA model was used for analysis. ITT population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using the retrieved dropouts & washout imputation method.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	260	263	264	
Units: mmHg				
least squares mean (standard error)	-3.31 (\pm 1.037)	-4.91 (\pm 1.010)	-4.94 (\pm 0.983)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description:	
The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and baseline SBP as a covariate.	
Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2212
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.142
upper limit	0.958
Variability estimate	Standard error of the mean
Dispersion value	1.301

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
Statistical analysis description:	
The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and baseline SBP as a covariate.	
Comparison groups	Placebo v Sotagliflozin 400 mg

Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2089
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.171
upper limit	0.912
Variability estimate	Standard error of the mean
Dispersion value	1.297

Secondary: Change From Baseline in Body Weight at Week 26

End point title	Change From Baseline in Body Weight at Week 26
End point description: An ANCOVA model was used for analysis. ITT population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using the retrieved dropouts & washout imputation method.	
End point type	Secondary
End point timeframe: Baseline to Week 26	

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	260	263	264	
Units: kilogram (kg)				
least squares mean (standard error)	-0.38 (± 0.262)	-1.66 (± 0.246)	-1.20 (± 0.257)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description: The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and baseline body weight as a covariate.	
Comparison groups	Placebo v Sotagliflozin 200 mg

Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.92
upper limit	-0.644
Variability estimate	Standard error of the mean
Dispersion value	0.326

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and baseline body weight as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0155
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.487
upper limit	-0.156
Variability estimate	Standard error of the mean
Dispersion value	0.339

Secondary: Percentage Change from Baseline in the Urine Albumin: Creatinine Ratio (UACR) at Week 26 in Subjects with Baseline UACR >30 milligrams per gram (mg/g)

End point title	Percentage Change from Baseline in the Urine Albumin: Creatinine Ratio (UACR) at Week 26 in Subjects with Baseline UACR >30 milligrams per gram (mg/g)
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End point description:

An ANCOVA model was used for analysis. Analysis population included subjects with baseline UACR > 30 mg/g in ITT population where, ITT population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using control-based copy reference multiple imputation under the missing not at random framework.

End point type	Secondary
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End point timeframe:

Baseline to Week 26

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	260	263	264	
Units: percent change				
number (not applicable)	-18.71	-43.68	-48.12	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and and log-transformed baseline UACR as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	ANCOVA
Parameter estimate	Percent Difference
Point estimate	-30.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.78
upper limit	-13.07

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and and log-transformed baseline UACR as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	ANCOVA
Parameter estimate	Percent Difference
Point estimate	-36.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.91
upper limit	-18.68

Secondary: Percentage of Subjects With HbA1c < 6.5% at Week 26

End point title	Percentage of Subjects With HbA1c < 6.5% at Week 26
End point description: ITT population included all randomised subjects or subjects analysed according to their randomised treatment.	
End point type	Secondary
End point timeframe: Week 26	

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	260	263	264	
Units: percentage of subjects				
number (not applicable)	4.2	5.7	5.7	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description: Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening and randomisation strata of CKD stage (3A, 3B) at screening.	
Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4328
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	5.21

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
Statistical analysis description: Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening and randomisation strata of CKD stage (3A, 3B) at screening.	
Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4328
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	5.17

Secondary: Percentage of Subjects with HbA1c < 7.0% at Week 26

End point title	Percentage of Subjects with HbA1c < 7.0% at Week 26
End point description: ITT population included all randomised subjects or subjects analysed according to their randomised treatment.	
End point type	Secondary
End point timeframe: Week 26	

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	260	263	264	
Units: percentage of subjects				
number (not applicable)	13.5	19.4	20.8	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description: Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening and randomisation strata of CKD stage (3A, 3B) at screening.	
Comparison groups	Placebo v Sotagliflozin 200 mg

Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0614
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	12.21

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
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Statistical analysis description:

Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening and randomisation strata of CKD stage (3A, 3B) at screening.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	13.65

Secondary: Percentage of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects With Treatment-emergent Adverse Events (TEAEs) ^[1]
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End point description:

Safety population included all subjects who received at least 1 dose of study drug analysed according to the treatment actually received.

End point type	Secondary
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End point timeframe:

Up to 60 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was planned to be reported for the following reporting arms Placebo and subject analysis sets Sotagliflozin 200 mg and Sotagliflozin 400 mg.

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	260	267	260	
Units: percentage of subjects				
number (not applicable)	78.1	76.8	74.2	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects with Hypoglycemic Events

End point title	Percentage of Subjects with Hypoglycemic Events ^[2]
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End point description:

Percentage of subjects with hypoglycemic events are reported for the following 3 categories: Any hypoglycemia (as reported in the Electronic Case Report Form); Documented symptomatic hypoglycemia [typical symptoms of hypoglycemia (increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, and/or coma) and plasma glucose \leq 70 mg/dL (3.9 mmol/L)]; Severe [an event requiring assistance of another person to actively administer carbohydrate, glucagon, intravenous glucose or other resuscitative actions] or documented symptomatic hypoglycemia [typical symptoms of hypoglycemia and plasma glucose \leq 70 mg/dL]. Safety population included all subjects who received at least 1 dose of study drug analysed according to the treatment actually received.

End point type	Other pre-specified
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End point timeframe:

Up to 60 weeks

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was planned to be reported for the following reporting arms Placebo and subject analysis sets Sotagliflozin 200 mg and Sotagliflozin 400 mg.

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	260	267	260	
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	38.1	41.9	35.4	
Documented symptomatic hypoglycemia	26.9	29.6	22.3	
Severe or documented symptomatic hypoglycemia	26.9	29.6	22.3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 60 weeks

Adverse event reporting additional description:

Safety population included all subjects who received at least 1 dose of study drug analysed according to the treatment actually received. Hypoglycemia was captured and handled separately from other adverse events and is reported in the endpoint section.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Following a 2-week run-in phase, subjects received two placebo tablets (identical to sotagliflozin 200 mg in appearance) orally once daily for up to 54 weeks.

Reporting group title	Sotagliflozin 200 mg
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Reporting group description:

Following a 2-week run-in phase, subjects received two tablets, one sotagliflozin 200 mg tablet and one placebo tablet (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 58 weeks. Four subjects randomised to sotagliflozin 400 mg were dosed with both sotagliflozin 200 mg and sotagliflozin 400 mg were included in the sotagliflozin 200 mg arm in the safety population.

Reporting group title	Sotagliflozin 400 mg
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Reporting group description:

Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as two sotagliflozin 200 mg tablets, orally once daily for up to 60 weeks.

Serious adverse events	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 260 (18.46%)	43 / 267 (16.10%)	44 / 260 (16.92%)
number of deaths (all causes)	3	2	5
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	3 / 260 (1.15%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Breast cancer			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer female			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipoma			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma of eyelid			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			

subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine neoplasm			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery aneurysm			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			

subjects affected / exposed	0 / 260 (0.00%)	2 / 267 (0.75%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Cardiac death			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord polyp			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Blood creatinine increased			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cranio-cerebral injury			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural shock			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Rib fracture			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 260 (0.77%)	2 / 267 (0.75%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Angina pectoris			
subjects affected / exposed	1 / 260 (0.38%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 260 (0.00%)	4 / 267 (1.50%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery insufficiency			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 260 (0.38%)	1 / 267 (0.37%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			

subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Basal ganglia infarction			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 260 (0.38%)	3 / 267 (1.12%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic neuropathy			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic unconsciousness			

subjects affected / exposed	0 / 260 (0.00%)	2 / 267 (0.75%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	2 / 260 (0.77%)	2 / 267 (0.75%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iris neovascularisation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal hernia			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 260 (0.00%)	2 / 267 (0.75%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss syndrome			

subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver injury			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ingrowing nail			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chronic kidney disease			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
End stage renal disease			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteoarthritis			
subjects affected / exposed	2 / 260 (0.77%)	1 / 267 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenosynovitis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 260 (0.00%)	2 / 267 (0.75%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 260 (0.38%)	1 / 267 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal abscess			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal infection			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Funguria			

subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective periostitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 260 (0.38%)	2 / 267 (0.75%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis pasteurella			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tick-borne viral encephalitis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 267 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 260 (0.00%)	3 / 267 (1.12%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 260 (0.38%)	1 / 267 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 260 (0.38%)	1 / 267 (0.37%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 260 (30.77%)	72 / 267 (26.97%)	77 / 260 (29.62%)
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 260 (5.00%)	15 / 267 (5.62%)	22 / 260 (8.46%)
occurrences (all)	14	16	28
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 260 (5.00%)	7 / 267 (2.62%)	12 / 260 (4.62%)
occurrences (all)	15	8	13
Upper respiratory tract infection			
subjects affected / exposed	18 / 260 (6.92%)	16 / 267 (5.99%)	13 / 260 (5.00%)
occurrences (all)	21	22	15
Urinary tract infection			
subjects affected / exposed	21 / 260 (8.08%)	19 / 267 (7.12%)	21 / 260 (8.08%)
occurrences (all)	32	21	24
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	30 / 260 (11.54%)	24 / 267 (8.99%)	24 / 260 (9.23%)
occurrences (all)	31	24	25

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2017	Amendment 1: 1. Change to exclusion criterion and guidance on contraceptive methods. 2. Change to exclusion criterion and temporary IMP discontinuation. 3. Change to exclusion criterion to clarify that subjects should not be enrolled in case of any concomitant condition or major systemic disorder that in investigator's opinion could affect their safety during the study. 4. Change to hepatitis serology test at screening. 5. Change to exclusion criterion to clarify that subjects should not be enrolled if currently enrolled in other investigational studies. 6. Change to the exclusion criterion requiring stability of insulin dose. 7. Change to the general guidelines for reporting of AEs. 8. Remove urgent coronary revascularizations from the events subject to the Clinical Endpoint Committees (CECs) review. 9. Addition of a new section to describe the independent safety assessments for drug-induced liver injuries (DILI) and amputation. 10. Changes to the observation period for safety endpoints. 11. Change to code breaking related to pharmacokinetic (PK) laboratory. 12. Change to the definition of one Event of Special Interest (EOSI), "volume depletion". 13. Change to definition of baseline for estimated glomerular filtration rate (eGFR). 14. Change to instruction for blood pressure measurement. 15. Change to rescue therapy. 16. Change to urine laboratory test. 17. Change in the order of secondary objectives and endpoints for the study. 18. Addition of femoral neck as a region for the bone mineral density (BMD) assessments. 19. Other minor changes for corrections of inconsistency, editorial changes, or administration clarification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported