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 Severe Renal Impairment who have Inadequate Glycemic Control

Summary

EudraCT number	2016-004906-32
Trial protocol	DE ES HU IT RO
Global end of trial date	11 December 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	EFC15166

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03242018
WHO universal trial number (UTN)	U1111-1190-7589

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	11 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of sotagliflozin 400 milligram (mg) versus placebo with respect to hemoglobin A1c (HbA1c) reduction at week 26 in subjects with Type 2 diabetes who have inadequate glycemic control and severe 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: 21
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Colombia: 14
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	Ukraine: 14
Country: Number of subjects enrolled	United States: 48
Country: Number of subjects enrolled	Brazil: 24
Worldwide total number of subjects	277
EEA total number of subjects	80

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)	102
From 65 to 84 years	170
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 106 investigative sites in the United States, Argentina, Brazil, Colombia, Germany, Hungary, Israel, Italy, Mexico, Poland, Romania, Russian Federation, South Africa, Spain, Ukraine from 16 August 2017 to 11 December 2019.

Pre-assignment

Screening details:

A total of 277 subjects with a diagnosis of Type 2 Diabetes Mellitus were randomised 1:1:1 to 1 of the 3 treatment groups: Placebo, Sotagliflozin 200 milligrams (mg) or Sotagliflozin 400 mg.

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, Monitor, Data analyst, 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 56.3 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 2 tablets (identical to the sotagliflozin 200 mg tablet in appearance), orally once daily.

Arm title	Sotagliflozin 200 mg

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 55.3 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.

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.

Arm title	Sotagliflozin 400 mg

Arm description:

Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as 2 sotagliflozin 200 mg tablets, orally once daily for up to 56.1 weeks.

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

Dosage and administration details:

Sotagliflozin 200 mg was administered as 2 tablets, orally once daily.

Number of subjects in period 1	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Started	93	92	92
Entered Follow-up Period	93	92	92
Completed	75	78	78
Not completed	18	14	14
At the subject’s own request	5	1	4
Adverse event	7	7	6
Study terminated by sponsor	1	-	1
Lost to follow-up	2	2	2
Reason not specified	3	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 56.3 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 55.3 weeks.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as 2 sotagliflozin 200 mg tablets, orally once daily for up to 56.1 weeks.	

Reporting group values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Number of subjects	93	92	92
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	68.0	66.8	67.3
standard deviation	± 8.3	± 10.0	± 9.6
Gender categorical Units: Subjects			
Female	51	48	43
Male	42	44	49
Race Units: Subjects			
White	76	73	78
Black or African American	6	7	3
Asian	1	2	2
American Indian or Alaska Native	7	8	7
Native Hawaiian or Other Pacific Islander	0	1	0
Multiple	3	1	2
Ethnicity Units: Subjects			
Hispanic or Latino	41	33	33
Not Hispanic or Latino	52	59	59
HbA1c Units: percentage of HbA1c			
arithmetic mean	8.38	8.28	8.25
standard deviation	± 1.06	± 1.03	± 0.87
Systolic Blood Pressure (SBP) Units: millimetre of mercury (mmHg)			
arithmetic mean	144.72	143.10	144.20

standard deviation	± 15.56	± 14.98	± 15.10

Reporting group values	Total		
Number of subjects	277		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	142		
Male	135		
Race Units: Subjects			
White	227		
Black or African American	16		
Asian	5		
American Indian or Alaska Native	22		
Native Hawaiian or Other Pacific Islander	1		
Multiple	6		
Ethnicity Units: Subjects			
Hispanic or Latino	107		
Not Hispanic or Latino	170		
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 56.3 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 55.3 weeks.

Reporting group title	Sotagliflozin 400 mg

Reporting group description:

Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as 2 sotagliflozin 200 mg tablets, orally once daily for up to 56.1 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 55.3 weeks. There were 2 subjects randomised to sotagliflozin 400 mg who were dosed with both sotagliflozin 200 mg and sotagliflozin 400 mg treatments during the study. The data for these subjects were summarised 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 2 sotagliflozin 200 mg tablets, orally once daily for up to 56.1 weeks. There were 2 subjects randomised to sotagliflozin 400 mg who were dosed with both sotagliflozin 200 mg and sotagliflozin 400 mg treatments during the study. The data for these subjects were summarized in the sotagliflozin 200 mg arm in the safety population.

Primary: Change from Baseline in HbA1c at Week 26 Comparing Sotagliflozin 400 mg Versus Placebo

End point title	Change from Baseline in HbA1c at Week 26 Comparing Sotagliflozin 400 mg Versus Placebo[1]

End point description:

Intent-to-treat (ITT) population included all randomised subjects, irrespective of compliance with the study protocol and procedures. Missing data was imputed using the retrieved dropouts & washout imputation method. An analysis of covariance (ANCOVA) model was used for the analysis.

End point type	Primary

End point timeframe:

Baseline to Week 26

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 Sotagliflozin 400 mg only.

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	92		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.11 (± 0.151)	-0.40 (± 0.131)		

Statistical analyses

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, and country as fixed effects, and baseline HbA1c as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0962
Method	ANCOVA
Parameter estimate	Difference in Least Square (LS) Means
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.628
upper limit	0.051
Variability estimate	Standard error of the mean
Dispersion value	0.173

Secondary: Change from Baseline in HbA1c at Week 26 Comparing Sotagliflozin 200 mg Versus Placebo

End point title	Change from Baseline in HbA1c at Week 26 Comparing Sotagliflozin 200 mg Versus Placebo[2]

End point description:

ITT population included all randomised subjects, irrespective of compliance with the study protocol and procedures. Missing data was imputed using the retrieved dropouts & washout imputation method. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 26

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 Sotagliflozin 200 mg only.

End point values	Placebo	Sotagliflozin 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	92		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.11 (± 0.151)	-0.07 (± 0.162)		

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, and country as fixed effects, and baseline HbA1c as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8124
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.338
upper limit	0.431
Variability estimate	Standard error of the mean
Dispersion value	0.196

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

End point description:

ITT population included all randomised subjects, irrespective of compliance with the study protocol and procedures. Missing data was imputed using the retrieved dropouts & washout imputation method. An ANCOVA model was used for the analysis.

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	93	92	92	
Units: millimole per liter (mmol/L)				
least squares mean (standard error)	0.069 (± 0.4482)	-0.291 (± 0.5056)	-0.644 (± 0.4348)	

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, and country as fixed effects, and baseline FPG as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5501
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.361
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5431
upper limit	0.822
Variability estimate	Standard error of the mean
Dispersion value	0.6033

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, and country as fixed effects, and baseline FPG as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1779
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.714
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7524
upper limit	0.3246

Variability estimate	Standard error of the mean
Dispersion value	0.5298

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:

ITT population included all randomised subjects, irrespective of compliance with the study protocol and procedures. Missing data was imputed using the retrieved dropouts & washout imputation method. An ANCOVA model was used for the analysis.

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	93	92	92	
Units: kilogram (kg)				
least squares mean (standard error)	0.39 (± 0.615)	-0.43 (± 0.480)	-1.02 (± 0.490)	

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, and country as fixed effects, and baseline body weight as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2432
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.197
upper limit	0.557
Variability estimate	Standard error of the mean
Dispersion value	0.703

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, and country as fixed effects, and baseline body weight as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0487
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.81
upper limit	-0.008
Variability estimate	Standard error of the mean
Dispersion value	0.715

Secondary: Change from Baseline in SBP at Week 12 in Subjects with Baseline SBP ≥130 mmHg

End point title	Change from Baseline in SBP at Week 12 in Subjects with Baseline SBP ≥130 mmHg

End point description:

Analysis population included all subjects with baseline SBP ≥130 mmHg in ITT population where, ITT population included all randomised subjects, irrespective of compliance with the study protocol and procedures. Missing data are imputed using control-based copy reference multiple imputation under the missing not at random framework. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and 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	73	68	73	
Units: mmHg				
least squares mean (standard error)	-2.70 (± 1.815)	-4.84 (± 1.882)	-7.10 (± 1.842)	

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, and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3954
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-2.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.066
upper limit	2.792
Variability estimate	Standard error of the mean
Dispersion value	2.515

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, and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0716
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.185
upper limit	0.386
Variability estimate	Standard error of the mean
Dispersion value	2.442

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

End point description:

ITT population included all randomised subjects, irrespective of compliance with the study protocol and

procedures. Missing data are imputed using control-based copy reference multiple imputation under the missing not at random framework. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and 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	93	92	92	
Units: mmHg				
least squares mean (standard error)	-2.50 (± 1.762)	-5.74 (± 1.752)	-7.86 (± 1.794)	

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, and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1232
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-3.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.365
upper limit	0.881
Variability estimate	Standard error of the mean
Dispersion value	2.103

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, and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg

Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0098
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-5.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.433
upper limit	-1.292
Variability estimate	Standard error of the mean
Dispersion value	2.077

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)

End point description:

Analysis population included all subjects with baseline UACR > 30 mg/g in ITT population where, ITT population included all randomised subjects, irrespective of compliance with the study protocol and procedures. Missing data was imputed using the retrieved dropouts & washout imputation method. An ANCOVA model was used for the analysis.

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	66	71	75	
Units: percent change				
number (not applicable)	-4.56	-26.99	-30.66	

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, and country as fixed effects, and log-transformed baseline UACR as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.222
Method	ANCOVA
Parameter estimate	Percent Difference
Point estimate	-20.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.75
upper limit	14.77

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, and country as fixed effects, and log-transformed baseline UACR as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1965
Method	ANCOVA
Parameter estimate	Percent Difference
Point estimate	-21.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.05
upper limit	13.1

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, irrespective of compliance with the study protocol and procedures.

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	93	92	92	
Units: percentage of subjects				
number (not applicable)	2.2	5.4	8.7	

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 metformin use at screening (Yes, No), and the randomisation strata of mean SBP (<130, ≥130 mmHg) at screening.

Comparison groups	Sotagliflozin 200 mg v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.242
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.17
upper limit	8.66

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 metformin use at screening (Yes, No), and the randomisation strata of mean SBP (<130, ≥130 mmHg) at screening.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0513
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	12.93

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, irrespective of compliance with the study protocol and procedures.	
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	93	92	92	
Units: percentage of subjects				
number (not applicable)	4.3	16.3	17.4	

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 metformin use at screening (Yes, No), and the randomisation strata of mean SBP (<130, ≥130 mmHg) at screening.	
Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0066
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	12
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.48
upper limit	20.61

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 metformin use at screening (Yes, No), and the randomisation strata of mean SBP (<130, ≥130 mmHg) at screening.	

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0043
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	13
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.28
upper limit	21.75

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

End point title	Percentage of Subjects with Treatment-emergent Adverse Events (TEAEs)[3]

End point description:

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the investigational medicinal product (IMP). Safety population included all randomised subjects who received at least one dose of double-blind IMP (regardless of the amount of treatment administered).

End point type	Secondary

End point timeframe:

First dose of study drug to last dose of study drug (up to 56.3 weeks) + 4 weeks

Notes:

[3] - 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	93	94	90	
Units: percentage of subjects				
number (not applicable)	82.8	86.2	81.1	

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[4]

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 ≤ 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 ≤ 70 mg/dL]. Safety population included all randomised subjects who received at least 1 dose of double-blind investigational medicinal product (IMP) (regardless of the amount of treatment administered).

End point type	Other pre-specified

End point timeframe:

up to 56.3 weeks

Notes:

[4] - 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	93	94	90	
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	40.9	40.4	38.9	
Documented symptomatic hypoglycemia	35.5	28.7	27.8	
Severe or documented symptomatic hypoglycemia	35.5	30.9	27.8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Deaths: Up to approximately 60 weeks; Adverse Events: First dose of study drug to last dose of study drug (up to 56.3 weeks) + 4 weeks

Adverse event reporting additional description:

Safety population included all randomised subjects who had received at least one dose of double-blind IMP. Hypoglycemia was captured and handled separately from other adverse events and is reported in the endpoint section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

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 56.3 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 55.3 weeks. There were 2 subjects randomised to sotagliflozin 400 mg who were dosed with both sotagliflozin 200 mg and sotagliflozin 400 mg treatments during the study. The data for these subjects were summarised in the sotagliflozin 200 mg arm in the safety population.

Reporting group title	Sotagliflozin 400 mg

Reporting group description:

Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as 2 sotagliflozin 200 mg tablets, orally once daily for up to 56.1 weeks. There were 2 subjects randomised to sotagliflozin 400 mg who were dosed with both sotagliflozin 200 mg and sotagliflozin 400 mg treatments during the study. The data for these subjects were summarized in the sotagliflozin 200 mg arm in the safety population.

Serious adverse events	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 93 (22.58%)	18 / 94 (19.15%)	20 / 90 (22.22%)
number of deaths (all causes)	6	6	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			

subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Papillary thyroid cancer			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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			
Hypertension			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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

Death			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Sudden cardiac death			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 93 (1.08%)	1 / 94 (1.06%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Painful respiration			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
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 congestion			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
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 hypertension			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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

Pulmonary oedema			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheomalacia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Hepatitis C antibody positive			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Femoral neck fracture			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Hip fracture			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Limb injury			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Radius fracture			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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 coronary syndrome			
subjects affected / exposed	2 / 93 (2.15%)	0 / 94 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	4 / 93 (4.30%)	1 / 94 (1.06%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Cardiac failure			
subjects affected / exposed	2 / 93 (2.15%)	1 / 94 (1.06%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	2 / 93 (2.15%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	2 / 93 (2.15%)	1 / 94 (1.06%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Coronary artery disease			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Diastolic dysfunction			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
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			
Ischaemic stroke			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Sciatica			

subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Syncope			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Blood loss anaemia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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

Inguinal hernia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Obstructive pancreatitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Cholelithiasis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 93 (6.45%)	1 / 94 (1.06%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
End stage renal disease			
subjects affected / exposed	1 / 93 (1.08%)	2 / 94 (2.13%)	3 / 90 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
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 colic			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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 failure			
subjects affected / exposed	0 / 93 (0.00%)	2 / 94 (2.13%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Renal impairment			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fistula			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Metatarsalgia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Cellulitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Escherichia urinary tract infection			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gangrene			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Herpes zoster			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Influenza			
subjects affected / exposed	0 / 93 (0.00%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Pneumonia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	4 / 90 (4.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 93 (0.00%)	1 / 94 (1.06%)	0 / 90 (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
Sepsis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	0 / 90 (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
Urinary tract infection			
subjects affected / exposed	0 / 93 (0.00%)	2 / 94 (2.13%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Fluid overload			
subjects affected / exposed	1 / 93 (1.08%)	0 / 94 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 93 (0.00%)	2 / 94 (2.13%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	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	44 / 93 (47.31%)	44 / 94 (46.81%)	29 / 90 (32.22%)
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	3 / 93 (3.23%)	10 / 94 (10.64%)	8 / 90 (8.89%)
occurrences (all)	3	11	8
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 93 (5.38%)	1 / 94 (1.06%)	3 / 90 (3.33%)
occurrences (all)	5	1	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 93 (3.23%)	5 / 94 (5.32%)	5 / 90 (5.56%)
occurrences (all)	3	5	8
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	7 / 93 (7.53%)	5 / 94 (5.32%)	3 / 90 (3.33%)
occurrences (all)	7	6	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 93 (5.38%)	3 / 94 (3.19%)	2 / 90 (2.22%)
occurrences (all)	6	4	2
Infections and infestations			

Influenza			
subjects affected / exposed	5 / 93 (5.38%)	5 / 94 (5.32%)	2 / 90 (2.22%)
occurrences (all)	5	5	2
Nasopharyngitis			
subjects affected / exposed	4 / 93 (4.30%)	8 / 94 (8.51%)	1 / 90 (1.11%)
occurrences (all)	4	9	1
Urinary tract infection			
subjects affected / exposed	16 / 93 (17.20%)	10 / 94 (10.64%)	6 / 90 (6.67%)
occurrences (all)	19	12	6
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 93 (2.15%)	9 / 94 (9.57%)	5 / 90 (5.56%)
occurrences (all)	2	12	5
Hyperuricaemia			
subjects affected / exposed	6 / 93 (6.45%)	2 / 94 (2.13%)	1 / 90 (1.11%)
occurrences (all)	6	2	1
Vitamin D deficiency			
subjects affected / exposed	6 / 93 (6.45%)	9 / 94 (9.57%)	3 / 90 (3.33%)
occurrences (all)	6	9	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2017	Amendment 1: 1. Change to the exclusion criteria. 2. Changes to guidance on contraceptive methods. 3. Change to the temporary IMP discontinuation. 4. Change to hepatitis serology test at screening and the related exclusion criterion. 5. Change to the exclusion criterion requiring stability of insulin dose. 6. Change to the general guidelines for reporting of AEs. 7. Remove urgent coronary revascularizations from the events subject to the Clinical Endpoint Committees (CECs) review. 8. Addition of a new section to describe the independent safety assessments for drug-induced liver injuries (DILI) and amputation. 9. Changes to the observation period for safety endpoints. 10. Change to code breaking related to Pharmacokinetic laboratory. 11. Change to the definition of one Event of Special Interest (EOSI), "volume depletion". 12. Change to definition of baseline for estimated glomerular filtration rate (eGFR). 13. Change to instruction for blood pressure measurement. 14. Change to rescue therapy. 15. Change to urine laboratory test. 16. Change in the order of secondary objectives and endpoints for the study. 17. 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