Clinical trial results:
A Randomized, Double-blind, Placebo-Controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin Added to a Sulfonylurea Alone or in Combination with Metformin in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on a Sulfonylurea Alone or with Metformin

Summary

EudraCT number	2016-002826-35
Trial protocol	EE SK HU GB PL BG
Global end of trial date	30 April 2019

Results information

Result version number	v1 (current)
This version publication date	31 July 2020
First version publication date	31 July 2020

Trial information

Trial identification

Sponsor protocol code	EFC14835

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03066830
WHO universal trial number (UTN)	U1111-1186-2612

Notes:

Sponsors

Sponsor organisation name	Lexicon Pharmaceuticals, Inc.
Sponsor organisation address	8800 Technology Forest Place, The Woodlands, United States, TX 77381, Texas, United States,
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	30 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 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 mg versus Placebo on Hemoglobin A1c (HbA1c) reduction at Week 26 in subjects with Type 2 Diabetes (T2D) who have inadequate glycemic control with a Sulfonylurea alone or in combination with Metformin.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 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: 57
Country: Number of subjects enrolled	Slovakia: 32
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Hungary: 100
Country: Number of subjects enrolled	Korea, Republic of: 57
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Ukraine: 37
Country: Number of subjects enrolled	United States: 173
Worldwide total number of subjects	507
EEA total number of subjects	240

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)	283
From 65 to 84 years	221
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 76 investigative sites in the United States, Bulgaria, Estonia, Hungary, Republic of Korea, Poland, Romania, Slovakia, Ukraine, United Kingdom from 24 February 2017 to 30 April 2019.

Pre-assignment

Screening details:

Subjects with a diagnosis of Diabetes Mellitus were enrolled equally in 1 of 2 treatment groups, Sotagliflozin 400 milligrams (mg) and Placebo.

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 period, subjects were randomised to matching placebo administered as 2 tablets, once daily, before the first meal of the day plus Metformin and Sulfonylurea as prescribed for up to 26 weeks in the Core Treatment Period. Eligible subjects continued treatment in the Extension Period which was planned for up to 79 weeks.

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

Dosage and administration details:

Placebo administered as 2 tablets, once daily, before the first meal of the day.

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

Dosage and administration details:

Metformin was administered orally as prescribed by the Principal Investigator.

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

Dosage and administration details:

Sulfonylurea was administered orally as prescribed by the Principal Investigator.

Arm title	Sotagliflozin 400 mg

Arm description:

Following a 2-week run-in phase, subjects received two Sotagliflozin tablets of 200 mg, orally once daily, before the first meal of the day plus Metformin and Sulfonylurea as prescribed for up to 26 weeks

in the Core Treatment Period. Eligible subjects continued treatment in the Extension Period which was planned for up to 79 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, once daily, before the first meal of the day.

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

Dosage and administration details:

Metformin was administered orally as prescribed by the Principal Investigator.

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

Dosage and administration details:

Sulfonylurea was administered orally as prescribed by the Principal Investigator.

Number of subjects in period 1	Placebo	Sotagliflozin 400 mg
Started	254	253
Completed	221	231
Not completed	33	22
Adverse Event	2	2
Other	3	-
At the Subject's Own Request	16	17
Poor Compliance to Protocol	1	-
Lost to follow-up	11	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Following a 2-week run-in period, subjects were randomised to matching placebo administered as 2 tablets, once daily, before the first meal of the day plus Metformin and Sulfonylurea as prescribed for up to 26 weeks in the Core Treatment Period. Eligible subjects continued treatment in the Extension Period which was planned for up to 79 weeks.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Following a 2-week run-in phase, subjects received two Sotagliflozin tablets of 200 mg, orally once daily, before the first meal of the day plus Metformin and Sulfonylurea as prescribed for up to 26 weeks in the Core Treatment Period. Eligible subjects continued treatment in the Extension Period which was planned for up to 79 weeks.	

Reporting group values	Placebo	Sotagliflozin 400 mg	Total
Number of subjects	254	253	507
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	63.0	63.3	
standard deviation	± 9.9	± 8.8	-
Gender categorical			
Units: Subjects			
Female	124	104	228
Male	130	149	279
Race			
Units: Subjects			
White	211	215	426
Black or African American	8	8	16
Asian	34	28	62
American Indian or Alaska native	0	0	0
Native Hawaiian or other Pacific Islander	0	1	1
Multiple	1	0	1
Not Reported	0	1	1
Unknown	0	0	0
Ethinicity			
Units: Subjects			
Hispanic or Latino	43	53	96
Not Hispanic or Latino	210	198	408
Not Reported	0	2	2
Unknown	1	0	1
Hemoglobin A1c (HbA1c)			
Units: percentage of HbA1c			
arithmetic mean	8.18	8.20	
standard deviation	± 0.83	± 0.83	-
Systolic Blood Pressure (SBP)			

Units: millimetre of mercury (mmHg)			
arithmetic mean	133.08	134.30	
standard deviation	± 14.21	± 13.01	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Following a 2-week run-in period, subjects were randomised to matching placebo administered as 2 tablets, once daily, before the first meal of the day plus Metformin and Sulfonylurea as prescribed for up to 26 weeks in the Core Treatment Period. Eligible subjects continued treatment in the Extension Period which was planned for up to 79 weeks.

Reporting group title	Sotagliflozin 400 mg

Reporting group description:

Following a 2-week run-in phase, subjects received two Sotagliflozin tablets of 200 mg, orally once daily, before the first meal of the day plus Metformin and Sulfonylurea as prescribed for up to 26 weeks in the Core Treatment Period. Eligible subjects continued treatment in the Extension Period which was planned for up to 79 weeks.

Subject analysis set title	Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Following a 2-week run-in period, subjects were randomised to matching placebo administered as 2 tablets, once daily, before the first meal of the day plus Metformin and Sulfonylurea as prescribed for up to 26 weeks in the Core Treatment Period. Eligible subjects continued treatment in the Extension Period which was planned for up to 79 weeks. One subject randomised to Placebo who was dosed with Sotagliflozin 400 mg treatment during the study is included in the Sotagliflozin 400 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 two Sotagliflozin tablets of 200 mg, orally once daily, before the first meal of the day plus Metformin and Sulfonylurea as prescribed for up to 26 weeks in the Core Treatment Period. Eligible subjects continued treatment in the Extension Period which was planned for up to 79 weeks. One subject randomised to Placebo who was dosed with Sotagliflozin 400 mg treatment during the study is included in the Sotagliflozin 400 mg arm in the safety population.

Primary: Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26

End point title	Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26

End point description:

Intent-to-treat (ITT) population included all randomised subjects. Missing data are imputed using the retrieved dropouts imputation method. An analysis of covariance (ANCOVA) model was used for the analysis.

End point type	Primary

End point timeframe:

Baseline to Week 26

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	253		
Units: percentage of HbA1c				
least squares mean (standard error)	0.06 (± 0.082)	-0.70 (± 0.068)		

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo

Statistical analysis description:

The change from baseline to Week 26 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use 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	507
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in Least Square (LS) Mean
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.946
upper limit	-0.574
Variability estimate	Standard error of the mean
Dispersion value	0.095

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. Missing data are imputed using the retrieved dropouts 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 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	253		
Units: millimole per litre (mmol/L)				
least squares mean (standard error)	0.277 (± 0.2691)	-1.331 (± 0.1844)		

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo

Statistical analysis description:

The change from baseline to Week 26 is analysed using ANCOVA model with treatment groups randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening, randomization strata of mean SBP (< 130, ≥ 130 mmHg) at screening, and country as fixed effects, and baseline fasting plasma glucose as a covariate.

Comparison groups	Sotagliflozin 400 mg v Placebo
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.608
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1685
upper limit	-1.0471
Variability estimate	Standard error of the mean
Dispersion value	0.286

Secondary: Change from Baseline in Systolic Blood Pressure (SBP) at Week 12 in Subjects with Baseline SBP ≥130 mmHg

End point title	Change from Baseline in Systolic Blood Pressure (SBP) at Week 12 in Subjects with Baseline SBP ≥130 mmHg

End point description:

Analysis was performed on ITT population in subjects with baseline SBP ≥130 mmHg. Missing data are imputed using the washout imputation method under the missing, not at random framework. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	146		
Units: mmHg				
least squares mean (standard error)	-3.58 (± 1.052)	-4.41 (± 1.061)		

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo
Statistical analysis description:	
The change from baseline to Week 12 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening and country as fixed effects, and baseline SBP as a covariate.	
Comparison groups	Sotagliflozin 400 mg v Placebo
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5172
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.316
upper limit	1.669
Variability estimate	Standard error of the mean
Dispersion value	1.272

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. Missing data are imputed using washout imputation method under the missing not at random framework. An ANCOVA model was used for the analysis.	
End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	253		
Units: mmHg				
least squares mean (standard error)	-0.69 (± 0.826)	-1.71 (± 0.830)		

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo

Statistical analysis description:

The change from baseline to Week 12 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening, randomization 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	507
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2994
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.946
upper limit	0.907
Variability estimate	Standard error of the mean
Dispersion value	0.983

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. Missing data are imputed using the retrieved dropouts 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 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	253		
Units: kilogram (kg)				
least squares mean (standard error)	-0.29 (± 0.206)	-1.70 (± 0.215)		

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo

Statistical analysis description:

The change from baseline to Week 26 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of Metformin use at screening, randomisation strata of mean SBP (< 130, ≥ 130 mmHg) at screening, and country as fixed effects, and baseline weight as a covariate.

Comparison groups	Sotagliflozin 400 mg v Placebo
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.932
upper limit	-0.884
Variability estimate	Standard error of the mean
Dispersion value	0.267

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.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	253		
Units: percentage of subjects				
number (not applicable)	1.6	8.3		

Statistical analyses

Statistical analysis title	Sotagliflozin 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, randomization strata of mean SBP (< 130, ≥ 130 mmHg) at screening, randomization strata of metformin use at the screening. Missing data at Week 26 were assigned a status of nonresponder in the analysis.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.03
upper limit	10.47

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.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	253		
Units: percentage of subjects				
number (not applicable)	8.7	26.1		

Statistical analyses

Statistical analysis title	Sotagliflozin 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, randomisation strata of metformin use at screening. Missing data at Week 26 were assigned a status of nonresponder in the analysis.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	17.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.16
upper limit	23.73

Other pre-specified: Percentage of Subjects with Hypoglycemic Events

End point title	Percentage of Subjects with Hypoglycemic Events

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]. Subjects may be reported in more than one category. Safety population was defined as all randomised subjects who had received at least 1 dose of the double-blind investigational medicinal product.

End point type	Other pre-specified

End point timeframe:

Up to 79 weeks in the treatment period

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	253	254		
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	22.1	19.7		
Documented symptomatic hypoglycemia	13.0	11.4		
Severe or documented symptomatic hypoglycemia	13.0	11.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug to last dose of study drug (up to 82.9 weeks) + 2 weeks

Adverse event reporting additional description:

Safety population included all randomised subjects who received at least one dose of double-blind IMP. One subject randomised to Placebo who was dosed with Sotagliflozin 400 mg treatment during the study is included in the Sotagliflozin 400 mg arm in the safety population.

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 period, subjects were randomised to matching placebo administered as 2 tablets, once daily, before the first meal of the day plus Metformin and Sulfonylurea as prescribed for up to 26 weeks in the Core Treatment Period. Eligible subjects continued treatment in the Extension Period which was planned for up to 79 weeks. One subject randomised to Placebo who was dosed with Sotagliflozin 400 mg treatment during the study is included in the Sotagliflozin 400 mg arm in the safety population.

Reporting group title	Sotagliflozin 400 mg

Reporting group description:

Following a 2-week run-in phase, subjects received two Sotagliflozin tablets of 200 mg, orally once daily, before the first meal of the day plus Metformin and Sulfonylurea as prescribed for up to 26 weeks in the Core Treatment Period. Eligible subjects continued treatment in the Extension Period which was planned for up to 79 weeks. One subject randomised to Placebo who was dosed with Sotagliflozin 400 mg treatment during the study is included in the Sotagliflozin 400 mg arm in the safety population.

Serious adverse events	Placebo	Sotagliflozin 400 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 253 (15.81%)	32 / 254 (12.60%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 253 (0.79%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malignant melanoma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer recurrent			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 253 (0.79%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 253 (0.40%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	1 / 253 (0.40%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 253 (0.00%)	2 / 254 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 253 (0.40%)	2 / 254 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 253 (0.40%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	3 / 253 (1.19%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal arrhythmia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Silent myocardial infarction			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 253 (0.79%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	1 / 253 (0.40%)	2 / 254 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve compression			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures with secondary generalisation			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post stroke epilepsy			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			

subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			

subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 253 (0.40%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 253 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			

subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 253 (0.40%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 253 (1.19%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 253 (0.40%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Sotagliflozin 400 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 253 (35.57%)	71 / 254 (27.95%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 253 (4.35%)	22 / 254 (8.66%)	
occurrences (all)	12	48	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	23 / 253 (9.09%)	21 / 254 (8.27%)	
occurrences (all)	27	23	
Upper respiratory tract infection			
subjects affected / exposed	19 / 253 (7.51%)	9 / 254 (3.54%)	
occurrences (all)	23	11	
Urinary tract infection			
subjects affected / exposed	8 / 253 (3.16%)	19 / 254 (7.48%)	
occurrences (all)	9	26	

Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	 48 / 253 (18.97%) 61	 14 / 254 (5.51%) 24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported