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

Summary

EudraCT number	2016-001800-49
Trial protocol	HU SK
Global end of trial date	22 March 2019

Results information

Result version number	v1 (current)
This version publication date	03 July 2020
First version publication date	03 July 2020

Trial information

Trial identification

Sponsor protocol code	EFC14834

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02926950
WHO universal trial number (UTN)	U1111-1181-6145

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	22 March 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of sotagliflozin versus placebo on hemoglobin A1c (HbA1c) reduction at week 26 in subjects with type 2 diabetes (T2D) who have inadequate glycemic control with metformin.

Protection of trial subjects:

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

Background therapy:

Subjects were taking metformin at a stable dosage >=1500 milligrams per day (mg/day) for at least 12 weeks before enrollment.

Evidence for comparator: -

Actual start date of recruitment	11 November 2016
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	Slovakia: 29
Country: Number of subjects enrolled	Hungary: 48
Country: Number of subjects enrolled	Canada: 52
Country: Number of subjects enrolled	United States: 389
Worldwide total number of subjects	518
EEA total number of subjects	77

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)	339
From 65 to 84 years	176

85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 87 investigative sites in Canada, Hungary, Slovakia and the United States from 11 November 2016 to 22 March 2019.

Pre-assignment

Screening details:

Subjects with a diagnosis of type 2 diabetes mellitus were enrolled in 1 of 2 treatment groups, Sotagliflozin 400 mg once daily (qd) + Metformin and Placebo + Metformin. Subjects were randomly assigned to the ratio of 1:1 to these reporting groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Metformin

Arm description:

Following a 2-week run-in period, matching placebo was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 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 tablet in appearance), 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.

Arm title	Sotagliflozin 400 mg + Metformin

Arm description:

Following a 2-week run-in period, sotagliflozin 400 mg was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks.

Arm type	Experimental

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

Dosage and administration details:

Sotagliflozin 400 mg was administered as 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.

Number of subjects in period 1	Placebo + Metformin	Sotagliflozin 400 mg + Metformin
Started	259	259
Completed	210	211
Not completed	49	48
Adverse event	4	6
At the patient’s own request	21	25
Lost to follow-up	7	8
Reason not Specified	17	9

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Metformin
Reporting group description:	
Following a 2-week run-in period, matching placebo was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks.	
Reporting group title	Sotagliflozin 400 mg + Metformin
Reporting group description:	
Following a 2-week run-in period, sotagliflozin 400 mg was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks.	

Reporting group values	Placebo + Metformin	Sotagliflozin 400 mg + Metformin	Total
Number of subjects	259	259	518
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.9	60.0	
standard deviation	± 9.4	± 10.1	-
Gender categorical Units: Subjects			
Female	113	117	230
Male	146	142	288
Race Units: Subjects			
American Indian or Alaska Native	1	2	3
Asian	19	6	25
Black or African American	40	28	68
Native Hawaiian or other Pacific Islander	1	0	1
White	197	223	420
Unknown	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	106	117	223
Not Hispanic or Latino	153	140	293
Not reported	0	2	2
Hemoglobin A1c (HbA1c) Units: percentage of HbA1c			
arithmetic mean	8.19	8.20	
standard deviation	± 0.82	± 0.78	-
Systolic Blood Pressure (SBP) Units: Millimetre of Mercury (mmHg)			
arithmetic mean	133.80	134.06	

standard deviation	± 13.95	± 13.95	-

End points

End points reporting groups

Reporting group title	Placebo + Metformin

Reporting group description:

Following a 2-week run-in period, matching placebo was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks.

Reporting group title	Sotagliflozin 400 mg + Metformin

Reporting group description:

Following a 2-week run-in period, sotagliflozin 400 mg was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks.

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 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 and Week 26

End point values	Placebo + Metformin	Sotagliflozin 400 mg + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.29 (± 0.079)	-0.77 (± 0.077)		

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.0, >8.0%) 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 + Metformin v Sotagliflozin 400 mg + Metformin

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in Least Square (LS) Means
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	-0.309
Variability estimate	Standard error of the mean
Dispersion value	0.084

Secondary: Change from Baseline in 2-hour Postprandial Glucose (PPG) following a Mixed Meal at Week 26

End point title	Change from Baseline in 2-hour Postprandial Glucose (PPG) following a Mixed Meal at Week 26

End point description:

ITT population included all randomised subjects. Missing data are imputed using control-based copy reference multiple imputation method. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo + Metformin	Sotagliflozin 400 mg + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: millimole per litre (mmol/L)				
least squares mean (standard error)	-0.930 (± 0.2353)	-2.502 (± 0.2292)		

Statistical analyses

Statistical analysis title	Sotagliflozin 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 (≤8.0, >8.0%) at screening, randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and country as fixed effects, and baseline 2-hour postprandial glucose as a covariate.

Comparison groups	Placebo + Metformin v Sotagliflozin 400 mg + Metformin

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.572
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.0538
upper limit	-1.0909
Variability estimate	Standard error of the mean
Dispersion value	0.2457

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 was imputed using retrieved dropouts and washout imputation method. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo + Metformin	Sotagliflozin 400 mg + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: mmol/L				
least squares mean (standard error)	-0.550 (± 0.1864)	-1.310 (± 0.2089)		

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.0, >8.0%) at screening, randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline fasting plasma glucose as a covariate.

Comparison groups	Placebo + Metformin v Sotagliflozin 400 mg + Metformin

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2006
upper limit	-0.3198
Variability estimate	Standard error of the mean
Dispersion value	0.2247

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 was imputed using retrieved dropouts and 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 + Metformin	Sotagliflozin 400 mg + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: kilogram (kg)				
least squares mean (standard error)	-0.69 (± 0.310)	-2.56 (± 0.331)		

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.0, >8.0%) at screening, randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and country as fixed effects, and baseline weight as a covariate.

Comparison groups	Placebo + Metformin v Sotagliflozin 400 mg + Metformin

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.591
upper limit	-1.144
Variability estimate	Standard error of the mean
Dispersion value	0.369

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 was performed on ITT population in subjects with baseline SBP ≥130 mmHg. Missing data was imputed using control-based copy reference multiple imputation method. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo + Metformin	Sotagliflozin 400 mg + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	137		
Units: millimetre of mercury (mmHg)				
least squares mean (standard error)	-6.92 (± 1.233)	-10.21 (± 1.270)		

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo

Statistical analysis description:

The change from baseline to Week 12 is analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.0, >8.0%) at screening, and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Placebo + Metformin v Sotagliflozin 400 mg + Metformin

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0209
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-3.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.07
upper limit	-0.497
Variability estimate	Standard error of the mean
Dispersion value	1.422

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 was imputed using control-based copy reference multiple imputation method. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo + Metformin	Sotagliflozin 400 mg + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: mmHg				
least squares mean (standard error)	-1.87 (± 0.949)	-5.41 (± 0.950)		

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo

Statistical analysis description:

The change from baseline to Week 12 is analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.0, >8.0%) 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 + Metformin v Sotagliflozin 400 mg + Metformin

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-3.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.479
upper limit	-1.592
Variability estimate	Standard error of the mean
Dispersion value	0.992

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 + Metformin	Sotagliflozin 400 mg + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: percentage of subjects				
number (not applicable)	5.4	10.8		

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 (≤8.0, >8.0%) at screening, randomisation strata of mean SBP (<130, ≥130 mmHg) at screening. Missing data at Week 26 were assigned a status of nonresponder in the analysis.	
Comparison groups	Placebo + Metformin v Sotagliflozin 400 mg + Metformin

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0238
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	10.06

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 + Metformin	Sotagliflozin 400 mg + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: percentage of subjects				
number (not applicable)	15.8	29.7		

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 (≤8.0, >8.0%) at screening, randomisation strata of mean SBP (<130, ≥130 mmHg) at screening. Missing data at Week 26 were assigned a status of nonresponder in the analysis.	
Comparison groups	Sotagliflozin 400 mg + Metformin v Placebo + Metformin
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	13.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.91
upper limit	20.89

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 + Metformin	Sotagliflozin 400 mg + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	11.6	6.6		
Documented symptomatic hypoglycemia	6.2	3.1		
Severe or documented symptomatic hypoglycemia	6.2	3.1		

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 79 weeks) + 4 weeks

Adverse event reporting additional description:

Safety population was defined as all randomised subjects who had received at least 1 dose of the double-blind investigational medicinal product (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 + Metformin

Reporting group description:

Following a 2-week run-in period, matching placebo was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks.

Reporting group title	Sotagliflozin 400 mg + Metformin

Reporting group description:

Following a 2-week run-in period, sotagliflozin 400 mg was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks.

Serious adverse events	Placebo + Metformin	Sotagliflozin 400 mg + Metformin	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 259 (8.88%)	19 / 259 (7.34%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Biliary neoplasm			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intraductal papillary mucinous neoplasm			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (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	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal oncocytoma			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland cancer recurrent			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (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			
Chest discomfort			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 259 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical polyp			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colpocele			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (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			
Acute respiratory failure			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (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			
Acetabulum fracture			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 259 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Coronary artery disease			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 259 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar stroke			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery thrombosis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (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	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic cerebral infarction			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial venous sinus thrombosis			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Neurodermatitis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urethral			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (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 / 259 (0.39%)	0 / 259 (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			
Arthritis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 259 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Abscess limb			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 259 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 259 (0.39%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Metformin	Sotagliflozin 400 mg + Metformin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 259 (42.08%)	85 / 259 (32.82%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 259 (5.02%)	3 / 259 (1.16%)	
occurrences (all)	13	3	
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 259 (5.79%)	6 / 259 (2.32%)	
occurrences (all)	17	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 259 (4.25%)	22 / 259 (8.49%)	
occurrences (all)	12	25	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	19 / 259 (7.34%)	8 / 259 (3.09%)	
occurrences (all)	21	9	
Infections and infestations			
Bronchitis			
subjects affected / exposed	17 / 259 (6.56%)	5 / 259 (1.93%)	
occurrences (all)	20	6	
Nasopharyngitis			

subjects affected / exposed	17 / 259 (6.56%)	14 / 259 (5.41%)	
occurrences (all)	20	20	
Upper respiratory tract infection			
subjects affected / exposed	20 / 259 (7.72%)	20 / 259 (7.72%)	
occurrences (all)	23	22	
Urinary tract infection			
subjects affected / exposed	15 / 259 (5.79%)	16 / 259 (6.18%)	
occurrences (all)	18	22	
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	19 / 259 (7.34%)	14 / 259 (5.41%)	
occurrences (all)	19	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2017	Amendment 1: 1. Addition of SBP endpoints at Week 26 and Week 79, addition of HbA1c, fasting plasma glucose and body weight endpoints at Week 79. 2. Addition of adverse event leading to an amputation as a new event of special interest. 3. Drug-induced liver injury removed as an event of special interest. 4. Addition of urine cultures in the event of abnormal urinalysis findings. 5. Addition of a Steering Committee to the study. 6. Addition of exclusion criteria at randomisation.
19 December 2017	Amendment 2: 1. Change to guidance on contraceptive methods. 2. Change to temporary IMP discontinuation. 3. Change to the general guidelines for reporting of adverse events (AEs). 4. Remove urgent coronary revascularizations from the events subject to the Clinical Endpoint Committees (CECs) review. 5. Addition of a new section to describe the independent safety assessments for drug-induced liver injuries (DILI) and amputation. 6. Changes to the observation period for safety endpoints. 7. Change to code breaking related to pharmacokinetic (PK) laboratory. 8. Change to the definition of one Event of Special Interest (EOSI), "volume depletion". 9. Change to definition of baseline for estimated glomerular filtration rate (eGFR). 10. Change to urine laboratory test. 11. Change in the order of secondary objectives and endpoints for the study. 11. 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