Clinical trial results:
A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Net Clinical Benefit of Sotagliflozin as Adjunct to Insulin Therapy in Type 1 Diabetes

Summary

EudraCT number	2015-001709-15
Trial protocol	DE HU CZ BE SK GB ES BG PL IT
Global end of trial date	18 April 2017

Results information

Result version number	v1 (current)
This version publication date	02 May 2018
First version publication date	02 May 2018

Trial information

Trial identification

Sponsor protocol code	LX4211.1-312-T1DM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02531035
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lexicon Pharmaceuticals, Inc.
Sponsor organisation address	8800 Technology Forest Place, The Woodlands, United States, 77381-1160
Public contact	Sangeeta Sawhney, Executive Medical Director, Lexicon Pharmaceuticals, Inc., +01 832 702 6527, ssawhney@lexpharma.com
Scientific contact	Sangeeta Sawhney, Executive Medical Director, Lexicon Pharmaceuticals, Inc., +01 832 702 6527, ssawhney@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	18 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 April 2017
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 in the proportion of patients with glycosylated A1C <7.0% at Week 24 and no episode of severe hypoglycemia and no episode of diabetic ketoacidosis (DKA) after randomization.

Protection of trial subjects:

All subjects were required to read and sign an informed consent.

Background therapy:

All subjects received insulin therapy adjusted consistent with standard of care.

Evidence for comparator: -

Actual start date of recruitment	18 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 88
Country: Number of subjects enrolled	Slovakia: 26
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Bulgaria: 61
Country: Number of subjects enrolled	Czech Republic: 70
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Hungary: 62
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Argentina: 23
Country: Number of subjects enrolled	Australia: 79
Country: Number of subjects enrolled	Canada: 172
Country: Number of subjects enrolled	Colombia: 33
Country: Number of subjects enrolled	Israel: 39
Country: Number of subjects enrolled	New Zealand: 53
Country: Number of subjects enrolled	South Africa: 98
Country: Number of subjects enrolled	United States: 409

Worldwide total number of subjects	1405
EEA total number of subjects	499

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)	1304
From 65 to 84 years	101
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 133 investigative sites in Poland, Slovakia, Spain, United Kingdom, Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Argentina, Australia, Canada, Colombia, Israel, New Zealand, South Africa and United States from 18 September 2015 to 18 April 2017.

Pre-assignment

Screening details:

1755 subjects were screened and 1490 entered the Single-blind Placebo run-in Period. 1405 subjects with a diagnosis of Type 1 Diabetes were enrolled equally in 1 of 2 treatment groups: placebo or sotagliflozin 400 mg.

Pre-assignment period milestones

Number of subjects started	1405
Number of subjects completed	1402

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Lost to follow up: 1
Reason: Number of subjects	Withdrawal by subject: 2

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Two placebo-matching sotagliflozin tablets daily, orally, before the first meal of the day for 24 weeks.

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

Dosage and administration details:

Two tablets daily, by mouth, before the first meal of the day for 24 weeks.

Arm title	Sotagliflozin 400 mg

Arm description:

Sotagliflozin 400 mg (two 200 mg tablets) once daily, orally, before the first meal of the day for 24 weeks.

Arm type	Experimental

Investigational medicinal product name	Sotagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Two 200 mg tablets once daily, by mouth, before the first meal of the day for 24 weeks

Number of subjects in period 1[1]	Placebo	Sotagliflozin 400 mg
Started	703	699
Completed	624	605
Not completed	79	94
Physician decision	1	-
Adverse event, non-fatal	16	45
Other, unspecified	3	2
Death	-	1
Noncompliance with study drug	8	3
Lost to follow-up	8	10
Protocol deviation	1	1
Withdrawal by subject	42	32

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Three participants did not receive study drug and are not included in the modified Intent-to-treat (mITT) population that is used for the Baseline Period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Two placebo-matching sotagliflozin tablets daily, orally, before the first meal of the day for 24 weeks.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Sotagliflozin 400 mg (two 200 mg tablets) once daily, orally, before the first meal of the day for 24 weeks.	

Reporting group values	Placebo	Sotagliflozin 400 mg	Total
Number of subjects	703	699	1402
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	42.4	43.3	
standard deviation	± 14.04	± 14.17	-
Gender categorical			
Units: Subjects			
Female	364	341	705
Male	339	358	697
Race			
Units: Subjects			
American Indian or Alaska Native	5	1	6
Asian	5	7	12
Black or African American	22	24	46
Native Hawaiian or Other Pacific Islander	0	1	1
White	621	619	1240
Other	37	31	68
Not Applicable	13	16	29
Body weight			
Units: kg (kilograms)			
arithmetic mean	81.55	82.40	
standard deviation	± 17.032	± 17.131	-
A1C			
A1C is the measurement of hemoglobin A1C. Data is available for 701 participants in the Placebo arm and 699 participants in the Sotagliflozin arm.			
Units: percent of A1C			
arithmetic mean	8.21	8.26	
standard deviation	± 0.921	± 0.965	-
Body Mass Index			
Units: kg/m^2 (kilogram(s)/square meter)			
arithmetic mean	28.1	28.29	
standard deviation	± 5.183	± 5.128	-
Duration of Diabetes			

Units: years			
arithmetic mean	19.6	20.5	
standard deviation	± 12.07	± 12.37	-
Baseline Total Daily Insulin			
Units: International Units/kilogram (IU/kg)			
arithmetic mean	0.71	0.69	
standard deviation	± 0.291	± 0.276	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Two placebo-matching sotagliflozin tablets daily, orally, before the first meal of the day for 24 weeks.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Sotagliflozin 400 mg (two 200 mg tablets) once daily, orally, before the first meal of the day for 24 weeks.	
Subject analysis set title	Placebo (Baseline SBP >=130 mm Hg)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Two placebo-matching sotagliflozin tablets daily, orally, before the first meal of the day for 24 weeks. Includes participants with Baseline Systolic Blood Pressure (SBP) >=130 mm Hg.	
Subject analysis set title	Sotagliflozin 400 mg (Baseline SBP >=130 mm Hg)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Sotagliflozin 400 mg (two 200 mg tablets) once daily, orally, before the first meal of the day for 24 weeks. Includes participants with SBP >= 130 mm Hg.	

Primary: Percentage of Participants with A1C <7.0% at Week 24 and No Episode of Severe Hypoglycemia and No Episode of DKA after Randomization

End point title	Percentage of Participants with A1C <7.0% at Week 24 and No Episode of Severe Hypoglycemia and No Episode of DKA after Randomization
End point description:	
The Primary composite endpoint included fasting blood samples for the assessment of Hemoglobin A1C to determine the participants with a value <7.0%. A central blinded adjudication process determined whether participants experienced either DKA or Severe Hypoglycemia. The primary efficacy analyses were based on the modified Intent-to-Treat (mITT) population, defined as all randomly assigned patients who had taken at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Baseline to end of treatment (Week 24)	

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	703	699		
Units: percentage of participants				
number (not applicable)	15.2	28.6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	1402
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	13.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.97
upper limit	17.81

Notes:

[1] - P-values from a CMH test stratified by the different levels of the stratification factors of BMI at Screening (<25 kg/m^2, ≥25 kg/m^2), Week -2 A1C (≤9.0%, >9.0%), and use of continuous subcutaneous insulin infusion (CSII) at Screening (yes, no).

Secondary: Change from Baseline in A1C

End point title	Change from Baseline in A1C

End point description:

Baseline value was defined as the last value collected prior to the first dose of double-blind study medication. LS means were obtained from a MMRM model including all available post baseline data. A negative change from Baseline (a lower AIC value at Week 24) indicates an improvement. Analyses included participants from the mITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	627		
Units: percent change in A1C				
least squares mean (standard error)	-0.33 (± 0.031)	-0.79 (± 0.032)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing according to hierarchical procedure. Post-Baseline LS means and p-values were obtained from MMRM model with treatment, randomization stratum of BMI at Screening (<25 kg/m^2, ≥25 kg/m^2), randomization stratum of Week -2 A1C (≤9.0%, >9.0%), randomization stratum of use of CSII at Screening (yes, no), time (study week), and a treatment-by-time interaction as fixed categorical effects, and Baseline A1C-by-time interaction as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg

Number of subjects included in analysis	1255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	-0.38

Secondary: Absolute Change from Baseline in Body Weight

End point title	Absolute Change from Baseline in Body Weight

End point description:

Baseline value was defined as the last value collected prior to the first dose of double-blind study medication. LS means were obtained from MMRM model. A negative change from Baseline indicates a loss in body weight from Baseline to Week 24. Analyses included participants from the mITT population, including all available post baseline values.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	633	630		
Units: kg (kilograms)				
least squares mean (standard error)	0.77 (± 0.122)	-2.21 (± 0.122)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing according to hierarchical procedure. Post-Baseline LS means and p-values were obtained from MMRM model with treatment, randomization stratum of BMI at Screening (<25 kg/m^2, >=25 kg/m^2), randomization stratum of Week -2 A1C (<=9%, >9%), randomization stratum of Use of CSII at Screening (Yes, No), time (study week), and a treatment-by-time interaction as fixed categorical effects, and Baseline weight-by-time interaction as a covariate.

Comparison groups	Sotagliflozin 400 mg v Placebo

Number of subjects included in analysis	1263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.31
upper limit	-2.66

Secondary: Change from Baseline in Systolic Blood Pressure (SBP) in the Subset of Participants with Baseline SBP >=130 mm Hg

End point title	Change from Baseline in Systolic Blood Pressure (SBP) in the Subset of Participants with Baseline SBP >=130 mm Hg

End point description:

An automatic sphygmomanometer was used with instructions on blood pressure measurements to allow for standardization. Week 16 was used because the protocol required Investigators to keep participant's hypertensive medications stable between Baseline and Week 16, unless a change was required for safety reasons. Baseline was defined as the last value collected prior to the first does of double-blind study medication. LS means were obtained from MMRM model including all available post baseline values. A negative change indicates a decrease in SBP between Baseline and Week 16. Participants from mITT population, all randomly assigned participants who had a Baseline SBP ≥130 mm Hg.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo (Baseline SBP >=130 mm Hg)	Sotagliflozin 400 mg (Baseline SBP >=130 mm Hg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	192	186		
Units: mm Hg				
least squares mean (standard error)	-5.7 (± 0.90)	-9.2 (± 0.92)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing according to the hierarchical procedure. Post-Baseline LS means and p-values were obtained from MMRM model with treatment, randomization stratum of BMI at Screening (<25 kg/m2, ≥25 kg/m2), randomization stratum of Week -2 A1C (≤9.0%, >9.0%), randomization stratum of use of CSII at Screening (yes, no), time (study week), and a treatment-by- time interaction as fixed categorical effects, and Baseline SBP-by-time interaction as a covariate.

Comparison groups	Sotagliflozin 400 mg (Baseline SBP >=130 mm Hg) v Placebo (Baseline SBP >=130 mm Hg)
Number of subjects included in analysis	378
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	-1.3

Secondary: Percent Change from Baseline in Mean Daily Bolus Insulin Dose

End point title	Percent Change from Baseline in Mean Daily Bolus Insulin Dose

End point description:

The mean bolus insulin dose in international units/day (IU/day) for Week 24 was the average over the 3 to 5 days prior to the Week 24 visit. The Baseline value was defined as the last value collected prior to the first dose of double-blind study medication. LS means were obtained from MMRM model including all available post Baseline values. A negative percent change from Baseline indicated a reduction in the amount of bolus insulin used and a positive percent change from Baseline indicated an increase in the amount of bolus insulin used between Baseline and Week 24. Analyses included participants from the mITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	Sotagliflozin 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	617		
Units: percent change in IU/day				
least squares mean (standard error)	6.62 (± 2.272)	-5.71 (± 2.289)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing according to hierarchical procedure. Post-Baseline LS means and p-values were obtained from MMRM model with treatment, randomization stratum of BMI at Screening (<25 kg/m2, ≥25 kg/m2), randomization stratum of Week -2 A1C (≤9.0%, >9.0%), randomization stratum of use of CSII at Screening (yes, no), time (study week), a treatment-by-time interaction as fixed categorical effects, and Baseline mean daily bolus insulin dose-by-time interaction as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg

Number of subjects included in analysis	1240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-12.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.17
upper limit	-6.48

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline (Day 1) of the Double-blind Period to 30 days after end of treatment (Up to 28 Weeks)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Two placebo-matching sotagliflozin tablets daily, orally, before the first meal of the day for 24 weeks.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Sotagliflozin 400 mg (two 200 mg tablets) once daily, orally, before the first meal of the day for 24 weeks.	

Serious adverse events	Placebo	Sotagliflozin 400 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 703 (3.27%)	48 / 699 (6.87%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Suicidal ideation			

subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood ketone body increased			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine ketone body present			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 703 (0.00%)	2 / 699 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericarditis			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoglycaemic unconsciousness			
subjects affected / exposed	4 / 703 (0.57%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalomalacia			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic seizure			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Aural polyp			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric panniculitis			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
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 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 703 (0.14%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (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 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	5 / 703 (0.71%)	22 / 699 (3.15%)	
occurrences causally related to treatment / all	3 / 5	12 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 703 (0.14%)	3 / 699 (0.43%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 703 (0.14%)	0 / 699 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolic acidosis			
subjects affected / exposed	0 / 703 (0.00%)	1 / 699 (0.14%)	
occurrences causally related to treatment / all	0 / 0	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	70 / 703 (9.96%)	70 / 699 (10.01%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 703 (2.42%)	35 / 699 (5.01%)	
occurrences (all)	22	41	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	55 / 703 (7.82%)	41 / 699 (5.87%)	
occurrences (all)	62	46	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2015	Amendment 1: -Instruction that patients taking concomitant digoxin (or other P-gp substrates) should be evaluated for dose adjustments as necessary (based on data from LX4211.1- 114-NRM) -Inclusion of Beta-Hydroxybutyrate (BHB) meter to be distributed to patients -Text clarification for temporary study drug interruption in case of AEs -Inclusion of all cases of metabolic acidosis as events of special interest (EOSI) (as per FDA recommendation)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported