Clinical trial results:
A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of LX4211 as Adjunct Therapy in Adult Patients with Type 1 Diabetes Mellitus Who Have Inadequate Glycemic Control with Insulin Therapy

Summary

EudraCT number	2014-005153-39
Trial protocol	SK AT ES LT DE GB HU BE SE NL PL BG RO IT
Global end of trial date	23 June 2017

Results information

Result version number	v1 (current)
This version publication date	09 July 2018
First version publication date	09 July 2018

Trial information

Trial identification

Sponsor protocol code	LX4211.1-310-T1DM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02421510
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lexicon Pharmaceuticals, Inc.
Sponsor organisation address	8800 Technology Forest Place, The Woodlands, TX, 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	23 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate superiority of either LX4211 400 mg or 200 mg versus placebo on glycosylated hemoglobin A1C (A1C) reduction at Week 24 when used as an adjunct therapy in adult subjects with type 1 diabetes mellitus (T1D) who have inadequate glycemic control with insulin therapy.

Protection of trial subjects:

All subjects were required to sign an informed consent.

Background therapy:

Insulin via pump or multiple daily injections.

Evidence for comparator: -

Actual start date of recruitment	25 May 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	Israel: 49
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 156
Country: Number of subjects enrolled	Romania: 71
Country: Number of subjects enrolled	Slovakia: 35
Country: Number of subjects enrolled	Spain: 105
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 36
Country: Number of subjects enrolled	Austria: 25
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Bulgaria: 45
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 79
Country: Number of subjects enrolled	Hungary: 69
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Lithuania: 25
Worldwide total number of subjects	782
EEA total number of subjects	726

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)	749
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 96 investigative sites throughout 16 European countries and 1 non-European country from 21 May 2015 to 23 June 2017.

Pre-assignment

Screening details:

995 subjects were screened and 800 subjects entered in a single blind 6-week placebo run-in period. 782 subjects with a diagnosis of Type 1 diabetes mellitus were randomized equally in 1 of 3 treatment groups: sotagliflozin 400 milligrams (mg), sotagliflozin 200 mg or 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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Two placebo-matching sotagliflozin tablets, once daily, orally, before the first meal of the day for 24 weeks followed by a 28-week extension period.

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

Dosage and administration details:

Placebo-matching sotagliflozin (two tablets), once daily, while fasting (before the first meal of the day).

Arm title	Sotagliflozin 200 mg

Arm description:

Sotagliflozin 200 mg (one 200 mg tablet and one placebo tablet), once daily, orally, before the first meal of the day for 24 weeks followed by a 28-week extension period.

Arm type	Active comparator
Investigational medicinal product name	Sotagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

sotagliflozin 200 mg (one 200 mg tablet and one placebo tablet) daily, while fasting (before the first meal of the day).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matching sotagliflozin (one tablet), once daily with sotagliflozin 200 mg , while fasting (before the first meal of the day).

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 followed by a 28-week extension period.

Arm type	Active comparator
Investigational medicinal product name	Sotagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg (two 200 mg tablets), once daily, while fasting (before the first meal of the day).

Number of subjects in period 1	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Started	258	261	263
Completed the 24 Week Treatment Period	236	239	240
Completed	225	226	227
Not completed	33	35	36
Physician decision	1	1	3
Death	1	-	-
Pregnancy	1	1	-
Adverse event	9	10	18
Noncompliance with study drug	1	-	-
Lost to follow-up	1	1	-
Other - unspecified	4	2	3
Withdrawal by subject	14	18	12
Protocol deviation	1	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Two placebo-matching sotagliflozin tablets, once daily, orally, before the first meal of the day for 24 weeks followed by a 28-week extension period.	
Reporting group title	Sotagliflozin 200 mg
Reporting group description:	
Sotagliflozin 200 mg (one 200 mg tablet and one placebo tablet), once daily, orally, before the first meal of the day for 24 weeks followed by a 28-week extension period.	
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 followed by a 28-week extension period.	

Reporting group values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Number of subjects	258	261	263
Age categorical			
Units: Subjects			
Adults (18-64 years)	244	252	253
From 65-84 years	14	9	10
Age continuous			
Units: years			
arithmetic mean	39.7	42.3	41.7
standard deviation	± 13.42	± 13.59	± 13.23
Gender categorical			
Units: Subjects			
Female	124	122	130
Male	134	139	133
Insulin Delivery Method			
Units: Subjects			
Continuous Subcutaneous Insulin Infusion (CSII)	66	68	67
Multiple Daily Injections (MDI)	192	193	196
Hemoglobin A1C			
Units: Subjects			
≤8.5%	200	203	204
>8.5%	58	58	59
Hemoglobin A1C Value at Actual Week -2 Value			
Some sites entered the wrong Week -2 A1C stratum for some subjects at randomization. This value is based on the stratum subjects should have been categorized based on their actual Week -2 A1C value.			
Units: Subjects			
≤8.5%	202	205	208
>8.5%	56	56	55
Body Weight			
Units: kilograms (kg)			
arithmetic mean	81.08	81.93	81.97
standard deviation	± 16.857	± 17.386	± 17.963
Duration of Diabetes			

Units: years			
arithmetic mean	18.1	18.2	18.9
standard deviation	± 10.72	± 10.82	± 11.18
Daily Total Insulin Dose			
Units: International units per kilogram (IU/kg)			
arithmetic mean	0.75	0.73	0.74
standard deviation	± 0.295	± 0.277	± 0.267

Reporting group values	Total		
Number of subjects	782		
Age categorical			
Units: Subjects			
Adults (18-64 years)	749		
From 65-84 years	33		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	376		
Male	406		
Insulin Delivery Method			
Units: Subjects			
Continuous Subcutaneous Insulin Infusion (CSII)	201		
Multiple Daily Injections (MDI)	581		
Hemoglobin A1C			
Units: Subjects			
≤8.5%	607		
>8.5%	175		
Hemoglobin A1C Value at Actual Week -2 Value			
Some sites entered the wrong Week -2 A1C stratum for some subjects at randomization. This value is based on the stratum subjects should have been categorized based on their actual Week -2 A1C value.			
Units: Subjects			
≤8.5%	615		
>8.5%	167		
Body Weight			
Units: kilograms (kg)			
arithmetic mean			
standard deviation	-		
Duration of Diabetes			
Units: years			
arithmetic mean			
standard deviation	-		
Daily Total Insulin Dose			
Units: International units per kilogram (IU/kg)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Two placebo-matching sotagliflozin tablets, once daily, orally, before the first meal of the day for 24 weeks followed by a 28-week extension period.	
Reporting group title	Sotagliflozin 200 mg
Reporting group description:	
Sotagliflozin 200 mg (one 200 mg tablet and one placebo tablet), once daily, orally, before the first meal of the day for 24 weeks followed by a 28-week extension period.	
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 followed by a 28-week extension period.	

Primary: Change from Baseline in A1C at Week 24

End point title	Change from Baseline in A1C at Week 24
End point description:	
Baseline value was defined as the last value collected prior to the first dose of double-blind study medication. Least square (LS) means were obtained from a mixed-effects model for repeated measures (MMRM) that included fixed, categorical effects of treatment, randomization strata of insulin delivery method (MDI, CSII), randomization strata of Week -2 A1C (≤8.5%, >8.5%), time (study week), a treatment-by-time interaction, and Baseline A1C-by-time interaction as a covariate. A negative change from Baseline (a lower A1C value at Week 24) indicates an improvement. Analyses included subjects from the modified intent to treat (mITT) population, all randomly assigned subjects who had taken at least 1 dose of study drug, analyzed according to their randomized treatment.	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	239	239	241	
Units: percentage of A1C				
least squares mean (standard error)	-0.02 (± 0.044)	-0.39 (± 0.044)	-0.37 (± 0.043)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), 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 200 mg

Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.058

Notes:

[1] - Sotagliflozin 200 mg versus Placebo.

[2] - Threshold for significance ≤0.05

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

LS means and p-values were obtained from Mixed effect Model Repeat Measurement (MMRM) model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), 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	480
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	-0.24

Notes:

[3] - Sotagliflozin 400 mg versus Placebo.

[4] - Threshold for significance ≤0.05

Secondary: Percentage of Subjects with A1C <7.0% at Week 24 and No Episode of Severe Hypoglycemia, and No Episode of Diabetic Ketoacidosis (DKA) from Randomization to Week 24

End point title	Percentage of Subjects with A1C <7.0% at Week 24 and No Episode of Severe Hypoglycemia, and No Episode of Diabetic Ketoacidosis (DKA) from Randomization to Week 24

End point description:

The composite endpoint included fasting blood samples for the assessment of Hemoglobin A1C to determine the subjects with a value <7.0% and a central blinded adjudication process to determine whether subjects experienced either DKA or Severe Hypoglycemia. Only positively adjudicated severe hypoglycemia and diabetic ketoacidosis were included in the analysis. Analyses included subjects from the mITT population.

End point type	Secondary

End point timeframe:
Randomization to Week 24

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	258	261	263	
Units: percentage of subjects				
number (not applicable)	15.1	31.4	32.3	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

P-values were obtained from a CMH test stratified by the different levels of the randomization stratification factors of insulin delivery method (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%). The 95% CL were calculated using asymptotic Wald method. Only positively adjudicated severe hypoglycemia and diabetic ketoacidosis were included in the analysis.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.17
upper limit	23.43

Notes:

[5] - Sotagliflozin 200 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[6] - Threshold for significance ≤0.05

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

P-values were obtained from a CMH test stratified by the different levels of the randomization stratification factors of insulin delivery method (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%). The 95% CL were calculated using asymptotic Wald method.

Comparison groups	Sotagliflozin 400 mg v Placebo

Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.06
upper limit	24.35

Notes:

[7] - Sotagliflozin 400 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.

[8] - Threshold for significance ≤0.05

Secondary: Change from Baseline in Body Weight at Week 24

End point title	Change from Baseline in Body Weight at Week 24

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 subjects 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 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	240	240	241	
Units: kg				
least squares mean (standard error)	0.11 (± 0.201)	-1.88 (± 0.200)	-2.47 (± 0.199)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), time (study week), and a treatment-by-time interaction as fixed categorical effects.

Comparison groups	Placebo v Sotagliflozin 200 mg

Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001 [10]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-1.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.53
upper limit	-1.44
Variability estimate	Standard error of the mean
Dispersion value	0.276

Notes:

[9] - Sotagliflozin 200 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[10] - Threshold for significance ≤0.05

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), time (study week), and a treatment-by-time interaction as fixed categorical effects.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.001 [12]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-2.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.12
upper limit	-2.04
Variability estimate	Standard error of the mean
Dispersion value	0.276

Notes:

[11] - Sotagliflozin 400 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[12] - Threshold for significance ≤0.05

Secondary: Change from Baseline in Mean Daily Bolus Insulin Dose at Week 24

End point title	Change from Baseline in Mean Daily Bolus Insulin Dose at Week 24

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 change from Baseline indicated a reduction in the amount of

bolus insulin used and a positive change from Baseline indicated an increase in the amount of bolus insulin used between Baseline and Week 24. Analyses included subjects from the mITT population.

End point type	Secondary
End point timeframe:	
Baseline to Week 24	

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	238	237	239	
Units: IU/day				
least squares mean (standard error)	-1.19 (± 0.635)	-4.38 (± 0.636)	-4.78 (± 0.634)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), time (study week), and 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 200 mg
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.001 [14]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.86
upper limit	-1.53
Variability estimate	Standard error of the mean
Dispersion value	0.847

Notes:

[13] - Sotagliflozin 200 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[14] - Threshold for significance ≤0.05

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), time (study week), and 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	477
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.001 [16]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-3.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.25
upper limit	-1.93
Variability estimate	Standard error of the mean
Dispersion value	0.845

Notes:

[15] - Sotagliflozin 400 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[16] - Threshold for significance ≤0.05

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) at Week 24

End point title	Change from Baseline in Fasting Plasma Glucose (FPG) at Week 24

End point description:

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 change from Baseline indicates a lower glucose at Week 24 compared to Baseline and a positive change from Baseline indicates an increase in glucose at Week 24 compared to Baseline. Analyses included subjects 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 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	239	237	239	
Units: milligram per deciliter (mg/dL)				
least squares mean (standard error)	8.8 (± 3.95)	-12.8 (± 3.97)	-16.9 (± 3.96)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), time (study week), and a treatment-by-time interaction as fixed categorical effects, and Baseline Fasting Plasma Glucose-by-time interaction as a

covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.001 [18]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-21.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.2
upper limit	-11
Variability estimate	Standard error of the mean
Dispersion value	5.38

Notes:

[17] - Sotagliflozin 200 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[18] - Threshold for significance ≤0.05

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), time (study week), and a treatment-by-time interaction as fixed categorical effects, and Baseline Fasting Plasma Glucose-by-time interaction as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.001 [20]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-25.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.2
upper limit	-15.1
Variability estimate	Standard error of the mean
Dispersion value	5.37

Notes:

[19] - Sotagliflozin 400 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[20] - Threshold for significance ≤0.05

Secondary: Change from Baseline in Diabetes Treatment Satisfaction Questionnaire (DTSQ) Score at Week 24

End point title	Change from Baseline in Diabetes Treatment Satisfaction Questionnaire (DTSQ) Score at Week 24

End point description:

The DTSQ instrument contains 8 items assessing overall treatment satisfaction, treatment convenience and flexibility, satisfaction with understanding of diabetes, willingness to continue present treatment and to recommend it to others, and frequency of unacceptably high and unacceptably low blood glucose levels. 6 items (excluding perceived hyperglycemia and hypoglycemia items) were scored using a 7-point scale where 0=very dissatisfied to 6= very satisfied for a total possible score of 0 to 36, where higher scores indicate higher satisfaction. 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 positive change from Baseline indicates improvement. Analyses included subjects from the mITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	228	229	240	
Units: score on a scale				
least squares mean (standard error)	-0.1 (± 0.28)	1.9 (± 0.28)	1.6 (± 0.28)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), time (study week), and a treatment-by-time interaction as fixed categorical effects, and Baseline DTSQs Total score-by-time interaction as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.001 [22]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	0.37

Notes:

[21] - Sotagliflozin 200 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.

[22] - Threshold for significance ≤0.05

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), time (study week), and a treatment-by-time interaction as fixed categorical effects, and Baseline DTSQs Total score-by-time interaction as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.001 [24]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[23] - Sotagliflozin 400 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[24] - Threshold for significance ≤0.05

Secondary: Change from Baseline in 2-Item Diabetes Distress Screen 2 (DDS2) Score at Week 24

End point title	Change from Baseline in 2-Item Diabetes Distress Screen 2 (DDS2) Score at Week 24

End point description:

DDS2 is a 2-item diabetes distress screening instrument where subjects rated the degree to which the following items caused distress: (1) feeling overwhelmed by the demands of living with diabetes, and (2) feeling that I am often failing with my diabetes regimen using a 6-point scale: where 1=no distress to 5=severe distress for a total possible score of 2 to 10. LS means were obtained from MMRM model including all available post Baseline values. A negative change from Baseline indicates improvement Analyses included subjects from the mITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232	232	243	
Units: score on a scale				
least squares mean (standard error)	0.0 (± 0.12)	-0.3 (± 0.12)	-0.4 (± 0.11)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), time (study week), and a treatment-by-time interaction as fixed categorical effects, and Baseline DDS2 Total score-by-time interaction as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.025 [26]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.15

Notes:

[25] - Sotagliflozin 200 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[26] - Threshold for significance ≤0.05

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

LS means and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%), time (study week), and a treatment-by-time interaction as fixed categorical effects, and Baseline DDS2 Total score-by-time interaction as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.003 [28]
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.15

Notes:

[27] - Sotagliflozin 400 mg versus Placebo. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[28] - Threshold for significance ≤0.05

Secondary: Percent Change from Baseline in Body Weight at Week 24

End point title	Percent Change from Baseline in Body Weight at Week 24

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 percent change from Baseline indicates a loss in body weight from Baseline to Week 24. Analyses included subjects 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 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	240	240	241	
Units: percent change in body weight				
least squares mean (standard error)	0.10 (± 0.245)	-2.38 (± 0.245)	-2.99 (± 0.244)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose and up to 30 days after the last dose of double-blind study treatment. Some AEs may have been attributed to the long-term effects of study drug; included even if the onset was >30 days after the last dose of study drug (up to 393 days).

Adverse event reporting additional description:

Safety Population consisted of all randomly assigned subjects treated with at least 1 dose of study drug, analyzed according to their actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Two placebo-matching sotagliflozin tablets, once daily, orally, before the first meal of the day for 24 weeks followed by a 28-week extension period.

Reporting group title	Sotagliflozin 200 mg

Reporting group description:

Sotagliflozin 200 mg (one 200 mg tablet and one placebo tablet), once daily, orally, before the first meal of the day for 24 weeks followed by a 28-week extension period.

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 followed by a 28-week extension period.

Serious adverse events	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 258 (6.59%)	26 / 261 (9.96%)	21 / 263 (7.98%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 258 (0.39%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer metastatic			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			

subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive breast carcinoma			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			

subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hypoglycaemic unconsciousness			
subjects affected / exposed	3 / 258 (1.16%)	2 / 261 (0.77%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	2 / 3	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic seizure			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			

subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular headache			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 258 (0.39%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angle closure glaucoma			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedematous pancreatitis			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prepyloric stenosis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goiter			

subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 258 (0.00%)	2 / 261 (0.77%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 258 (0.39%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ecthyma			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis viral			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyoderma			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus infection			
subjects affected / exposed	0 / 258 (0.00%)	1 / 261 (0.38%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 258 (0.00%)	7 / 261 (2.68%)	12 / 263 (4.56%)
occurrences causally related to treatment / all	0 / 0	5 / 7	8 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 258 (0.00%)	2 / 261 (0.77%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 258 (0.39%)	0 / 261 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketosis			
subjects affected / exposed	0 / 258 (0.00%)	0 / 261 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 258 (17.83%)	52 / 261 (19.92%)	64 / 263 (24.33%)
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 258 (3.88%)	12 / 261 (4.60%)	20 / 263 (7.60%)
occurrences (all)	13	18	29
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	40 / 258 (15.50%)	44 / 261 (16.86%)	49 / 263 (18.63%)
occurrences (all)	58	60	70

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2015	Amendment 1: -Continuous glucose monitoring (CGM) measure deleted for Week 51 and Week 52 in main study periods; -Unscheduled visits added for subject follow-up as needed; -Investigators were not responsible for supplying insulin/analogs; subjects were to continue to use their own background insulin regimen; -Glycemic goals revised per 2015 American Diabetes Association (ADA) standards for medical care; -Investigator was expected to evaluate PPG after first dose of study drug and continue reduction in insulin-to-carbohydrate (I/C) ratio; -Deleted fasting status requirement to allow subjects to treat or avoid hypoglycemic episodes and collect laboratory samples in a nonfasting status; -Contraindications added for CGM device; -Prohibited medications added for CGM substudy; -New text for DKA recognition and management; -Insulin titration to start at Week -5.
15 May 2015	Amendment 2: -Frequency of bolus removed as efficacy endpoint; -Additional text to clarify vitamin D supplementation in study subjects; -Added text to clarify childbearing potential and acceptable methods of contraception.
19 October 2015	Amendment 3: -Number of sites increased to 110 to meet enrollment targets; -Clarification and flexibility added for target number of subjects in each substudy; -Inclusion of beta-hydroxybutyrate (BHB) meter distribution to all participating subjects; -Insulin adjustment clarified for subjects undergoing Mixed Meal on Day 1; -Phosphorus:creatinine ratio (PCR) added for subjects in the dual-energy X-ray absorptiometry (DEXA) substudy; -Included all events of metabolic acidosis for adjudication per FDA recommendation; -Added precautions to minimize risk of DKA in case of planned procedures/surgeries; -Addition of option for pooling data for substudies between 309 and 310; -Removed efficacy analysis of storage samples; -Data from completed digoxin drug-drug interaction study added; -Added ±5 minute time window in collection of 2-hour postprandial glucose (PPG).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported