



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Basal Insulin Alone or in Addition to Oral Antidiabetes Drugs (OADs)

Summary

EudraCT number	2016-001804-43
Trial protocol	GB HU CZ SK BG
Global end of trial date	27 September 2019

Results information

Result version number	v1 (current)
This version publication date	20 September 2020
First version publication date	20 September 2020

Trial information

Trial identification

Sponsor protocol code	EFC14868
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03285594
WHO universal trial number (UTN)	U1111-1190-7567

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	27 September 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of sotagliflozin 400 milligram (mg) versus placebo with respect to hemoglobin A1C (HbA1c) reduction at week 18 in subjects with type 2 diabetes mellitus (T2D) who had inadequate glycemic control on basal insulin alone or with oral antidiabetes drugs (OADs).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

Subjects were taking up to any 2 OADs which may include metformin at a stable dosage ≥ 1500 milligrams per day (mg/day) or the maximum tolerated dose (documented).

Evidence for comparator: -

Actual start date of recruitment	15 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	United States: 279
Country: Number of subjects enrolled	Slovakia: 77
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Bulgaria: 57
Country: Number of subjects enrolled	Czech Republic: 49
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Hungary: 46
Worldwide total number of subjects	571
EEA total number of subjects	263

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)	312
From 65 to 84 years	257
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 101 investigative sites in the United States, Bulgaria, Canada, Czech Republic, France, Hungary, Slovakia, the United Kingdom from 15 September 2017 to 27 September 2019.

Pre-assignment

Screening details:

Subjects with a diagnosis of Type 2 Diabetes Mellitus were enrolled in 1 of 3 treatment groups, placebo, sotagliflozin 200 mg and sotagliflozin 400 mg. Subjects were randomised at a ratio of 1:1:2 respectively to 1 of 3 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	Investigator, Monitor, Data analyst, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Following a 4-week run-in period, subjects were randomised to receive matching placebo to sotagliflozin 200 mg administered as 2 tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 55.7 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.

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

Dosage and administration details:

Placebo was administered as 2 tablets (identical to the sotagliflozin 200 mg tablet in appearance), once daily, before the first meal of the day.

Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	HOE901
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine was administered either in the morning or evening, following the Investigator's advice.

Arm title	Sotagliflozin 200 mg
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Arm description:

Following a 4-week run-in period, subjects were randomised to sotagliflozin 200 mg administered as 1 tablet and matching placebo as 1 tablet, once daily, before the first meal of the day in the double-blind treatment period for up to 54.7 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.

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

Dosage and administration details:

Sotagliflozin 200 mg administered as 1 tablet, once daily, before the first meal of the day.

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 1 tablet (identical to the sotagliflozin 200 mg tablet in appearance), once daily, before the first meal of the day.

Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	HOE901
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine was administered either in the morning or evening, following the Investigator's advice.

Arm title	Sotagliflozin 400 mg
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Arm description:

Following a 4-week run-in period, subjects were randomised to sotagliflozin 400 mg administered as 2 tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 54.6 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.

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

Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	HOE901
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine was administered either in the morning or evening, following the Investigator's advice.

Number of subjects in period 1	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Started	144	141	286
Treated	144	141	285
Completed	129	130	249
Not completed	15	11	37
At the subject's own request	10	5	21
Adverse event	2	2	6
Poor compliance to protocol	-	-	1
Reason not specified	3	4	8
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Following a 4-week run-in period, subjects were randomised to receive matching placebo to sotagliflozin 200 mg administered as 2 tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 55.7 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.	
Reporting group title	Sotagliflozin 200 mg
Reporting group description:	
Following a 4-week run-in period, subjects were randomised to sotagliflozin 200 mg administered as 1 tablet and matching placebo as 1 tablet, once daily, before the first meal of the day in the double-blind treatment period for up to 54.7 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Following a 4-week run-in period, subjects were randomised to sotagliflozin 400 mg administered as 2 tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 54.6 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.	

Reporting group values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Number of subjects	144	141	286
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	62.2	62.1	62.7
standard deviation	± 8.9	± 10.2	± 9.1
Gender categorical			
Units: Subjects			
Female	58	65	132
Male	86	76	154
Race			
Units: Subjects			
White	117	124	234
Black or African American	10	10	27
Asian	9	1	6
American Indian or Alaska Native	2	1	2
Native Hawaiian or Other Pacific Islander	0	0	3
Multiple	1	0	1
Not reported	5	4	12
Unknown	0	1	1
Ethnicity			
Units: Subjects			
Hispanic or Latino	12	25	42
Not Hispanic or Latino	129	113	239
Not reported	2	2	4
Unknown	1	1	1

Hemoglobin A1c (HbA1c) Units: percentage of HbA1c arithmetic mean standard deviation	8.76 ± 0.79	8.76 ± 0.83	8.69 ± 0.80
Systolic Blood Pressure (SBP) Units: millimetre of Mercury (mmHg) arithmetic mean standard deviation	137.59 ± 14.12	136.40 ± 15.54	135.84 ± 14.95

Reporting group values	Total		
Number of subjects	571		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	255		
Male	316		
Race Units: Subjects			
White	475		
Black or African American	47		
Asian	16		
American Indian or Alaska Native	5		
Native Hawaiian or Other Pacific Islander	3		
Multiple	2		
Not reported	21		
Unknown	2		
Ethnicity Units: Subjects			
Hispanic or Latino	79		
Not Hispanic or Latino	481		
Not reported	8		
Unknown	3		
Hemoglobin A1c (HbA1c) Units: percentage of HbA1c arithmetic mean standard deviation	-		
Systolic Blood Pressure (SBP) Units: millimetre of Mercury (mmHg) arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Following a 4-week run-in period, subjects were randomised to receive matching placebo to sotagliflozin 200 mg administered as 2 tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 55.7 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.	
Reporting group title	Sotagliflozin 200 mg
Reporting group description: Following a 4-week run-in period, subjects were randomised to sotagliflozin 200 mg administered as 1 tablet and matching placebo as 1 tablet, once daily, before the first meal of the day in the double-blind treatment period for up to 54.7 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description: Following a 4-week run-in period, subjects were randomised to sotagliflozin 400 mg administered as 2 tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 54.6 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.	

Primary: Change from Baseline in Hemoglobin A1c (HbA1c) at Week 18

End point title	Change from Baseline in Hemoglobin A1c (HbA1c) at Week 18
End point description: Intent-to-treat (ITT) population included all randomised subjects irrespective of compliance with the study protocol and procedures. Missing data was imputed using washout multiple imputation under the missing not at random framework. An analysis of covariance (ANCOVA) model was used for the analysis.	
End point type	Primary
End point timeframe: Baseline and Week 18	

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	141	286	
Units: percentage of HbA1c				
least squares mean (standard error)	-0.27 (± 0.073)	-0.72 (± 0.073)	-0.81 (± 0.056)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description: The change from baseline to Week 18 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at Week -1, randomisation strata of mean SBP (<130, ≥130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline HbA1c as a covariate.	

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in Least Square (LS) Means
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.638
upper limit	-0.271
Variability estimate	Standard error of the mean
Dispersion value	0.094

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 18 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at Week -1, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline HbA1c as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.706
upper limit	-0.387
Variability estimate	Standard error of the mean
Dispersion value	0.081

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) at Week 18

End point title	Change from Baseline in Fasting Plasma Glucose (FPG) at Week 18
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End point description:

FPG was performed in fasting state, that is, without any food intake (except for water) for at least 8 hours. ITT population included all randomised subjects irrespective of compliance with the study protocol and procedures. Missing data was imputed using washout multiple imputation method under the missing not at random framework. An ANCOVA model was used for the analysis.

End point type	Secondary
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End point timeframe:
Baseline and Week 18

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	141	286	
Units: milligram per decilitre (mg/dL)				
least squares mean (standard error)	12.882 (\pm 3.6045)	-2.975 (\pm 3.6083)	-8.949 (\pm 2.7550)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description: The change from baseline to Week 18 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at Week -1, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline FPG as a covariate.	
Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-15.858
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.8845
upper limit	-6.8309
Variability estimate	Standard error of the mean
Dispersion value	4.6056

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
Statistical analysis description: The change from baseline to Week 18 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at Week -1, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline FPG as a covariate.	
Comparison groups	Placebo v Sotagliflozin 400 mg

Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-21.832
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.7725
upper limit	-13.8911
Variability estimate	Standard error of the mean
Dispersion value	4.0514

Secondary: Change from Baseline in Body Weight at Week 18

End point title	Change from Baseline in Body Weight at Week 18
End point description:	
ITT population included all randomised subjects irrespective of compliance with the study protocol and procedures. Missing data was imputed using washout multiple imputation under the missing not at random framework. An ANCOVA model was used for the analysis.	
End point type	Secondary
End point timeframe:	
Baseline and Week 18	

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	141	286	
Units: kilogram (kg)				
least squares mean (standard error)	0.36 (± 0.249)	-0.73 (± 0.250)	-1.37 (± 0.190)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description:	
The change from baseline to Week 18 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at Week -1, randomisation strata of mean SBP (<130, ≥130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline body weight as a covariate.	
Comparison groups	Sotagliflozin 200 mg v Placebo

Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.716
upper limit	-0.462
Variability estimate	Standard error of the mean
Dispersion value	0.32

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 18 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at Week -1, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline body weight as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.274
upper limit	-1.183
Variability estimate	Standard error of the mean
Dispersion value	0.278

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

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

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

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	92	171	
Units: mmHg				
least squares mean (standard error)	-4.67 (± 1.470)	-8.58 (± 1.447)	-8.50 (± 1.103)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description:	
The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline SBP as a covariate.	
Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-3.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.642
upper limit	-0.178
Variability estimate	Standard error of the mean
Dispersion value	1.904

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
Statistical analysis description:	
The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline SBP as a covariate.	
Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0239
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-3.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.161
upper limit	-0.507
Variability estimate	Standard error of the mean
Dispersion value	1.697

Secondary: Change from Baseline in SBP at Week 12 for All Subjects

End point title	Change from Baseline in SBP at Week 12 for All Subjects
End point description:	
ITT population included all randomised subjects irrespective of compliance with the study protocol and procedures. Missing data was imputed using washout multiple imputation under the missing not at random framework. An ANCOVA model was used for the analysis.	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	141	286	
Units: mmHg				
least squares mean (standard error)	-0.21 (± 1.120)	-5.15 (± 1.117)	-4.10 (± 0.867)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description:	
The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at Week -1, randomisation strata of mean SBP (<130, ≥130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline SBP as a covariate.	
Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in LS Means
Point estimate	-4.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.73
upper limit	-2.142

Variability estimate	Standard error of the mean
Dispersion value	1.425

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at Week -1, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-3.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.333
upper limit	-1.448
Variability estimate	Standard error of the mean
Dispersion value	1.246

Secondary: Change from Baseline in HbA1c at Week 52

End point title	Change from Baseline in HbA1c at Week 52
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End point description:

ITT population included all randomised subjects irrespective of compliance with the study protocol and procedures. Missing data was imputed using washout multiple imputation under the missing not at random framework. An ANCOVA model was used for the analysis.

End point type	Secondary
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End point timeframe:

Baseline and Week 52

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	141	286	
Units: percentage of HbA1c				
least squares mean (standard error)	0.00 (\pm 0.279)	-0.52 (\pm 0.152)	-0.57 (\pm 0.114)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
Statistical analysis description:	
The change from baseline to Week 52 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at Week -1, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline HbA1c as a covariate.	
Comparison groups	Sotagliflozin 200 mg v Placebo
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1265
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.185
upper limit	0.147
Variability estimate	Standard error of the mean
Dispersion value	0.34

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
Statistical analysis description:	
The change from baseline to Week 52 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at Week -1, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline HbA1c as a covariate.	
Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.074
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.199
upper limit	0.055
Variability estimate	Standard error of the mean
Dispersion value	0.32

Secondary: Change from Baseline in Body Weight at Week 52

End point title	Change from Baseline in Body Weight at Week 52
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End point description:

ITT population included all randomised subjects irrespective of compliance with the study protocol and procedures. Missing data was imputed using washout multiple imputation under the missing not at random framework. An ANCOVA model was used for the analysis.

End point type	Secondary
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End point timeframe:

Baseline and Week 52

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	141	286	
Units: kg				
least squares mean (standard error)	-0.18 (± 0.579)	-1.19 (± 0.620)	-0.83 (± 0.374)	

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 52 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at Week -1, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline body weight as a covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2466
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.707
upper limit	0.696
Variability estimate	Standard error of the mean
Dispersion value	0.868

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo
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Statistical analysis description:

The change from baseline to Week 52 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at Week -1, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at Week -1, randomisation strata of sulfonylureas use (yes, no) at Week -1, and country as fixed effects, and baseline body weight as a covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
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Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.332
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.969
upper limit	0.665
Variability estimate	Standard error of the mean
Dispersion value	0.672

Secondary: Percentage of Subjects with Adverse Events (AEs)

End point title	Percentage of Subjects with Adverse Events (AEs)
End point description:	An AE is any untoward medical occurrence in a subjects or clinical investigation subjects administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Safety population included all randomised subjects who received at least 1 dose of double-blind investigational medicinal product (IMP) (regardless of the amount of treatment administered).
End point type	Secondary
End point timeframe:	First dose of study drug to last dose of study drug (up to 55.7 weeks) + 2 weeks

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	141	285	
Units: percentage of subjects				
number (not applicable)	64.6	54.6	59.3	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects with Hypoglycemic Events

End point title	Percentage of Subjects with Hypoglycemic Events
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 \leq 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 \leq 70 mg/dL]. Safety population included all randomised subjects who received at least 1 dose of double-blind investigational medicinal product (IMP) (regardless of the amount of treatment administered).

End point type	Other pre-specified
End point timeframe:	
Up to 55.7 weeks	

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	141	285	
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	62.5	56	62.8	
Documented symptomatic hypoglycemia	44.4	41.8	46	
Severe or documented symptomatic hypoglycemia	44.4	41.8	46	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Deaths: Up to approximately 60 weeks; Adverse Events: First dose of study drug to last dose of study drug (up to 55.7 weeks) + 2 weeks

Adverse event reporting additional description:

Safety population included all randomised subjects who had received at least 1 dose of double-blind investigational medicinal product (regardless of the amount of treatment administered). Hypoglycemia was captured and handled separately from other adverse events and is reported in the endpoint section.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Following a 4-week run-in period, subjects were randomised to receive matching placebo to sotagliflozin 200 mg administered as 2 tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 55.7 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.

Reporting group title	Sotagliflozin 200 mg
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Reporting group description:

Following a 4-week run-in period, subjects were randomised to sotagliflozin 200 mg administered as 1 tablet and matching placebo as 1 tablet, once daily, before the first meal of the day in the double-blind treatment period for up to 54.7 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.

Reporting group title	Sotagliflozin 400 mg
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Reporting group description:

Following a 4-week run-in period, subjects were randomised to sotagliflozin 400 mg administered as 2 tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 54.6 weeks. Background therapy with insulin glargine (with or without OADs) continued throughout the study.

Serious adverse events	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 144 (11.11%)	19 / 141 (13.48%)	28 / 285 (9.82%)
number of deaths (all causes)	2	1	6
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
B-cell lymphoma			

subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (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
Basal cell carcinoma			
subjects affected / exposed	1 / 144 (0.69%)	1 / 141 (0.71%)	0 / 285 (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
Bladder cancer			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to bone			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Prostate cancer			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Aortic stenosis			

subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			

subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
Sleep apnoea syndrome			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
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			
Jaw fracture			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative thrombosis			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
Subdural haematoma			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (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

Tendon injury			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 144 (1.39%)	0 / 141 (0.00%)	2 / 285 (0.70%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 144 (0.69%)	1 / 141 (0.71%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 144 (2.08%)	0 / 141 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Coronary artery disease			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	2 / 285 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
Left ventricular failure			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial ischaemia			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (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
Reperfusion arrhythmia			

subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (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
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
Syncope			
subjects affected / exposed	1 / 144 (0.69%)	1 / 141 (0.71%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal artery thrombosis			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy proliferative			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
Pancreatitis chronic			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
Enlarged uvula			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (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
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal haematoma			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
Urethral stenosis			

subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
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			
Back pain			
subjects affected / exposed	0 / 144 (0.00%)	2 / 141 (1.42%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (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
Bursitis			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
Infected bite			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteomyelitis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (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
Pyelonephritis chronic			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal abscess			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
Scrotal abscess			
subjects affected / exposed	1 / 144 (0.69%)	0 / 141 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (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
Diabetic ketoacidosis			

subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 144 (0.00%)	0 / 141 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 144 (0.00%)	1 / 141 (0.71%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 144 (20.83%)	18 / 141 (12.77%)	45 / 285 (15.79%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 144 (4.86%)	9 / 141 (6.38%)	14 / 285 (4.91%)
occurrences (all)	9	9	15
Upper respiratory tract infection			
subjects affected / exposed	8 / 144 (5.56%)	1 / 141 (0.71%)	14 / 285 (4.91%)
occurrences (all)	10	1	17
Urinary tract infection			

subjects affected / exposed occurrences (all)	8 / 144 (5.56%) 11	6 / 141 (4.26%) 6	11 / 285 (3.86%) 16
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all)	9 / 144 (6.25%) 9	4 / 141 (2.84%) 4	10 / 285 (3.51%) 10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2017	Amendment 2: 1. Change to the exclusion criteria and guidance on contraceptive methods. 2. Change to the exclusion criteria and temporary IMP discontinuation. 3. Change to exclusion assessment. 4. Change to the general guidelines for reporting of adverse events. 5. Change to the events for Clinical Endpoint Committee (CEC) adjudication. 6. Changes to the observation period for safety endpoints. 7. Change to hepatitis serology test at screening and related exclusion. 8. Change to code breaking related to pharmacokinetic (PK) laboratory. 9. Change to the definition of one events of special interest (EOSI) "volume depletion". 10. Change to definition of baseline. 11. Change to instruction for blood pressure measurement. 12. Change to other study objectives and other endpoints. 13. Change to urine laboratory test. 14. Other minor changes for corrections of inconsistency or administration clarification.
06 March 2018	Amendment 3: 1. New secondary objectives are added to evaluate the long-term efficacy of sotagliflozin based on HbA1c reduction over 52 weeks of treatment. 2. Corresponding to the additional secondary objectives, new secondary endpoints are added to assess these objectives. 3. Addition of a new section to describe the independent safety assessments for drug-induced liver injuries (DILI) and amputation. 4. Change to the description of the continuous glucose monitoring (CGM) sub-study. 5. Change to exclusion criterion E15. 6. Change to the non-investigational medicinal product (NIMP) Lantus dosing regimen. 7. 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