Clinical trial results:
A 26-week Randomized, Double-blind, Controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin compared to Empagliflozin, and Placebo in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Dipeptidyl Peptidase 4 Inhibitor (DPP4(i)) With or Without Metformin

Summary

EudraCT number	2016-001803-22
Trial protocol	GB CZ ES LV SK BG FR IT
Global end of trial date	16 May 2019

Results information

Result version number	v1 (current)
This version publication date	01 June 2020
First version publication date	01 June 2020

Trial information

Trial identification

Sponsor protocol code	EFC14867

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03351478
WHO universal trial number (UTN)	U1111-1190-7607

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	16 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of sotagliflozin versus placebo on hemoglobin A1c (HbA1c) reduction in subjects with type 2 diabetes (T2D) who have inadequate glycemic control on a Dipeptidyl Peptidase 4 Inhibitor (DPP4(i)) with or without metformin.

Protection of trial subjects:

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

Background therapy:

Subjects were enrolled with a background therapy consisting of their existing dipeptidyl peptidase 4 inhibitor (DPP4[i]) treatment and metformin treatment.

Evidence for comparator: -	
Actual start date of recruitment	27 November 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	Slovakia: 73
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Bulgaria: 59
Country: Number of subjects enrolled	Czech Republic: 126
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Latvia: 42
Country: Number of subjects enrolled	Canada: 59
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Mexico: 87
Country: Number of subjects enrolled	Russian Federation: 104
Country: Number of subjects enrolled	United States: 148
Worldwide total number of subjects	770
EEA total number of subjects	372

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)	539
From 65 to 84 years	230
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 160 investigative sites in Bulgaria, Canada, Czechia, France, Italy, Latvia, Mexico, Russian Federation, Slovakia, Spain, United Kingdom and the United States from 27 November 2017 to 16 May 2019

Pre-assignment

Screening details:

Subjects with a diagnosis of Type 2 Diabetes Mellitus were enrolled in 1 of 3 treatment groups, Sotagliflozin, Empagliflozin, or placebo. Subjects were randomly assigned in the ratio of 2:2:1 to these reporting groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sotagliflozin 400 mg

Arm description:

Following a 2-week run-in period, sotagliflozin 400 mg (milligrams) administered as two 200 mg tablets and one placebo capsule (identical to empagliflozin capsule in appearance), once daily before the first meal of the day for up to 26 weeks.

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

Dosage and administration details:

Sotagliflozin 400 mg was administered as two tablets, once daily before the first meal of the day.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as one capsule (identical to the empagliflozin capsule in appearance), once daily before the first meal of the day.

Arm title	Empagliflozin 25 mg

Arm description:

Following a 2-week run-in period, placebo matching sotagliflozin administered as two tablets (identical to sotagliglozin in appearance) and one capsule of empagliflozin 25 mg, once daily before the first meal of the day for up to 26 weeks.

Arm type	Active comparator

Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin 25 mg capsule was administered, 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 two tablets (identical to sotagliflozin in appearance), once daily before the first meal of the day.

Arm title	Placebo

Arm description:

Following a 2-week run-in period, placebo given as two placebo tablets (identical to sotagliflozin) and one placebo capsule (identical to empagliflozin) once daily before the first meal of the day for up to 26 weeks.

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

Dosage and administration details:

Placebo was administered as one capsule (identical to the empagliflozin capsule in appearance), 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 two tablets (identical to sotagliflozin in appearance), once daily before the first meal of the day.

Number of subjects in period 1	Sotagliflozin 400 mg	Empagliflozin 25 mg	Placebo
Started	307	309	154
Completed	293	292	147
Not completed	14	17	7
At the subject's own request	11	12	5
Adverse event	1	2	1
Poor compliance to protocol	1	-	-
Lost to follow-up	-	-	1
Reason not Specified	1	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Following a 2-week run-in period, sotagliflozin 400 mg (milligrams) administered as two 200 mg tablets and one placebo capsule (identical to empagliflozin capsule in appearance), once daily before the first meal of the day for up to 26 weeks.	
Reporting group title	Empagliflozin 25 mg
Reporting group description:	
Following a 2-week run-in period, placebo matching sotagliflozin administered as two tablets (identical to sotagliglozin in appearance) and one capsule of empagliflozin 25 mg, once daily before the first meal of the day for up to 26 weeks.	
Reporting group title	Placebo
Reporting group description:	
Following a 2-week run-in period, placebo given as two placebo tablets (identical to sotagliflozin) and one placebo capsule (identical to empagliflozin) once daily before the first meal of the day for up to 26 weeks.	

Reporting group values	Sotagliflozin 400 mg	Empagliflozin 25 mg	Placebo
Number of subjects	307	309	154
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.9	59.7	59.8
standard deviation	± 9.7	± 9.6	± 9.6
Gender categorical Units: Subjects			
Female	141	158	75
Male	166	151	79
Race Units: Subjects			
White	256	257	137
Black or African American	13	13	5
Asian	17	11	4
American Indian or Alaska Native	18	21	8
Native Hawaiian or other Pacific Islander	2	0	0
Multiple	0	1	0
Not Reported	1	6	0
Ethnicity Units: Subjects			
Hispanic or Latino	56	66	33
Not Hispanic or Latino	251	243	121
Hemoglobin A1c (HbA1c) Units: percentage of HBA1c			
arithmetic mean	8.23	8.21	8.21
standard deviation	± 0.84	± 0.93	± 0.93
Systolic Blood Pressure (SBP)			

Units: Millimetre of Mercury (mmHg)			
arithmetic mean	134.55	131.64	133.19
standard deviation	± 13.56	± 12.18	± 12.53

Reporting group values	Total		
Number of subjects	770		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	374		
Male	396		
Race			
Units: Subjects			
White	650		
Black or African American	31		
Asian	32		
American Indian or Alaska Native	47		
Native Hawaiian or other Pacific Islander	2		
Multiple	1		
Not Reported	7		
Ethnicity			
Units: Subjects			
Hispanic or Latino	155		
Not Hispanic or Latino	615		
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	Sotagliflozin 400 mg
Reporting group description:	
Following a 2-week run-in period, sotagliflozin 400 mg (milligrams) administered as two 200 mg tablets and one placebo capsule (identical to empagliflozin capsule in appearance), once daily before the first meal of the day for up to 26 weeks.	
Reporting group title	Empagliflozin 25 mg
Reporting group description:	
Following a 2-week run-in period, placebo matching sotagliflozin administered as two tablets (identical to sotagliglozin in appearance) and one capsule of empagliflozin 25 mg, once daily before the first meal of the day for up to 26 weeks.	
Reporting group title	Placebo
Reporting group description:	
Following a 2-week run-in period, placebo given as two placebo tablets (identical to sotagliflozin) and one placebo capsule (identical to empagliflozin) once daily before the first meal of the day for up to 26 weeks.	

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

End point title	Change from Baseline in Hemoglobin A1c (HbA1c) % at Week 26
End point description:	
Intent-to-treat (ITT) population included all randomised subjects. Missing data are imputed using the retrieved dropouts imputation method. An analysis of covariance (ANCOVA) model was used for the analysis.	
End point type	Primary
End point timeframe:	
Baseline, Week 26	

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	309	154	
Units: percentage of HbA1c				
least squares mean (standard error)	-0.7 (± 0.1)	-0.8 (± 0.1)	-0.3 (± 0.1)	

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo
Statistical analysis description:	
The change from baseline to Week 26 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterised with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No), randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline HbA1c as a covariate.	
Comparison groups	Sotagliflozin 400 mg v Placebo

Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in Least Square (LS) Means
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.09

Statistical analysis title	Sotagliflozin vs Empagliflozin

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterised with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No), randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline HbA1c as a covariate.

Comparison groups	Sotagliflozin 400 mg v Empagliflozin 25 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.145
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.28
Variability estimate	Standard error of the mean
Dispersion value	0.08

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

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

End point description:

Subjects from the ITT population, all randomised subjects with data available at the given time point for analysis. Missing data are imputed using washout imputation method. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:
Baseline, Week 12

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	146[1]	151[2]	84[3]	
Units: mmHg				
least squares mean (standard error)	-5.6 (± 1.3)	-6.7 (± 1.3)	-3.5 (± 1.5)	

Notes:

[1] - Number analysed is the number of subjects evaluated for the endpoint.

[2] - Number analysed is the number of subjects evaluated for the endpoint.

[3] - Number analysed is the number of subjects evaluated for the endpoint.

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The change from baseline to Week 12 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterised with treatment groups, randomisation strata of HbA1c (≤ 8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No) and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Sotagliflozin 400 mg v Placebo
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1529
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.87
upper limit	0.76
Variability estimate	Standard error of the mean
Dispersion value	1.43

Statistical analysis title	Sotagliflozin vs Empagliflozin

Statistical analysis description:

The change from baseline to Week 12 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterised with treatment groups, randomisation strata of HbA1c (≤ 8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No) and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Empagliflozin 25 mg v Sotagliflozin 400 mg

Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3377
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	3.55
Variability estimate	Standard error of the mean
Dispersion value	1.21

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

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

End point description:

ITT population included all randomised subjects. Missing data are imputed using washout imputation method under the missing not at random framework. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	309	154	
Units: millimole per litre (mmol/L)				
least squares mean (standard error)	-1.3 (± 0.2)	-1.2 (± 0.9)	-0.4 (± 0.2)	

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterized with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No), randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline 2-hour postprandial glucose as a covariate.

Comparison groups	Sotagliflozin 400 mg v Placebo

Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.21

Statistical analysis title	Sotagliflozin vs Empagliflozin

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterised with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No), randomisation strata of mean SBP (<130, ≥ 130 mmHg) at screening, and country as fixed effects, and baseline 2-hour postprandial glucose as a covariate.

Comparison groups	Empagliflozin 25 mg v Sotagliflozin 400 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8397
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.17

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) at Week 26

End point title	Change from Baseline in Fasting Plasma Glucose (FPG) at Week 26

End point description:

ITT population included all randomised subjects. Missing data are imputed using the retrieved dropouts imputation method. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	309	154	
Units: mmol/L				
least squares mean (standard error)	-1.3 (± 0.2)	-1.6 (± 0.2)	-0.5 (± 0.2)	

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterized with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No), randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline fasting plasma glucose as a covariate.

Comparison groups	Sotagliflozin 400 mg v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	-0.35
Variability estimate	Standard error of the mean
Dispersion value	0.23

Statistical analysis title	Sotagliflozin vs Empagliflozin

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterized with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No), randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline fasting plasma glucose as a covariate.

Comparison groups	Empagliflozin 25 mg v Sotagliflozin 400 mg

Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1339
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.2

Secondary: Change from Baseline in Body Weight at Week 26

End point title	Change from Baseline in Body Weight at Week 26

End point description:

ITT population included all randomised subjects. Missing data are imputed using the retrieved dropouts imputation method. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	309	154	
Units: kilogram (kg)				
least squares mean (standard error)	-2.7 (± 0.3)	-3.2 (± 0.3)	-0.5 (± 0.3)	

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterised with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No), randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline weight as a covariate.

Comparison groups	Sotagliflozin 400 mg v Placebo

Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.95
upper limit	-1.54
Variability estimate	Standard error of the mean
Dispersion value	0.36

Statistical analysis title	Sotagliflozin vs Empagliflozin

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterised with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No), randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline weight as a covariate.

Comparison groups	Sotagliflozin 400 mg v Empagliflozin 25 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1407
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	1.19
Variability estimate	Standard error of the mean
Dispersion value	0.34

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

End point title	Change from Baseline in Sitting SBP at Week 12 for all Subjects

End point description:

ITT population included all randomised subjects. Missing data are imputed using the retrieved dropouts imputation method. An ANCOVA model was used for the analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	309	154	
Units: mmHg				
least squares mean (standard error)	-1.7 (± 0.8)	-2.8 (± 0.8)	0.4 (± 1.0)	

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterised with treatment groups, randomisation strata of HbA1c (≤ 8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No) and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Sotagliflozin 400 mg v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0325
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.89
upper limit	-0.17
Variability estimate	Standard error of the mean
Dispersion value	0.95

Statistical analysis title	Sotagliflozin vs Empagliflozin

Statistical analysis description:

The change from baseline to Week 26 is analysed using an ANCOVA model using multiple imputations to fill in missing data and is parameterised with treatment groups, randomisation strata of HbA1c (≤ 8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No) and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Empagliflozin 25 mg v Sotagliflozin 400 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1565
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	2.63
Variability estimate	Standard error of the mean
Dispersion value	0.78

Secondary: Percentage of Subjects with HbA1c <6.5% at Week 26

End point title	Percentage of Subjects with HbA1c <6.5% at Week 26
End point description:	
ITT population included all randomised subjects.	
End point type	Secondary
End point timeframe:	
Week 26	

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	309	154	
Units: percentage of subjects				
number (not applicable)	12.1	11.7	3.9	

Statistical analyses

Statistical analysis title	Sotagliflozin vs Placebo
Statistical analysis description:	
Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No), and the randomisation strata of mean SBP (<130, ≥130 mmHg) at screening. Missing data at Week 26 were assigned a status of nonresponder in the analysis.	
Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0048
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.36
upper limit	12.89

Secondary: Percentage of Subjects with HbA1c <7.0% at Week 26

End point title	Percentage of Subjects with HbA1c <7.0% at Week 26
End point description:	
ITT population included all randomised subjects.	
End point type	Secondary
End point timeframe:	
Week 26	

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	309	154	
Units: percentage of subjects				
number (not applicable)	32.6	35.6	15.6	

Statistical analyses

Statistical analysis title	Sotagliflozin Vs Placebo
Statistical analysis description:	
Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of metformin use at screening (Yes, No), and the randomisation strata of mean SBP (<130, ≥130 mmHg) at screening. Missing data at Week 26 were assigned a status of nonresponder in the analysis.	
Comparison groups	Sotagliflozin 400 mg v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	16.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.26
upper limit	24.52

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug to last dose of study drug (up to 26 weeks) + 4 weeks (Approximately 30 weeks)

Adverse event reporting additional description:

Safety population included all randomised subjects who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Sotagliflozin

Reporting group description:

Following a 2-week run-in period, sotagliflozin administered as two tablets and one placebo capsule (identical to empagliflozin capsule in appearance), once daily before the first meal of the day for up to 26 weeks.

Reporting group title	Empagliflozin

Reporting group description:

Following a 2-week run-in period, empagliflozin administered as two placebo tablets (identical to sotagliflozin in appearance) and one capsule of empagliflozin, once daily before the first meal of the day for up to 26 weeks.

Reporting group title	Placebo

Reporting group description:

Following a 2-week run-in period, placebo given as two placebo tablets (identical to sotagliflozin) and one placebo capsule (identical to empagliflozin) once daily before the first meal of the day for up to 26 weeks.

Serious adverse events	Sotagliflozin	Empagliflozin	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 307 (3.26%)	13 / 309 (4.21%)	9 / 154 (5.84%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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
Adenocarcinoma of colon			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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

Meningioma			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Laryngeal cancer			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Nasal cavity cancer			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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
Hypertensive crisis			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 154 (0.65%)
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			
Atrial flutter			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Sinus node dysfunction			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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
Right ventricular failure			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial fibrosis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 307 (0.00%)	2 / 309 (0.65%)	0 / 154 (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
Ischaemic stroke			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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
Blood and lymphatic system disorders			

Abdominal lymphadenopathy			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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			
Umbilical hernia			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Diverticulum intestinal			
subjects affected / exposed	0 / 307 (0.00%)	2 / 309 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 154 (0.65%)
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, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 154 (0.65%)
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 embolism			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Pulmonary infarction			

subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Pulmonary mass			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Gallbladder polyp			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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 / 307 (0.33%)	0 / 309 (0.00%)	0 / 154 (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
Diverticulitis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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

Infection			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Pneumonia			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Urosepsis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 154 (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
Vestibular neuronitis			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 154 (0.65%)
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: 2 %

Non-serious adverse events	Sotagliflozin	Empagliflozin	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 307 (18.89%)	68 / 309 (22.01%)	39 / 154 (25.32%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 307 (2.28%)	8 / 309 (2.59%)	6 / 154 (3.90%)
occurrences (all)	9	11	7
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 307 (0.98%)	5 / 309 (1.62%)	6 / 154 (3.90%)
occurrences (all)	3	5	6
Diarrhoea			

subjects affected / exposed	10 / 307 (3.26%)	8 / 309 (2.59%)	5 / 154 (3.25%)
occurrences (all)	10	10	6
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 307 (1.95%)	3 / 309 (0.97%)	4 / 154 (2.60%)
occurrences (all)	6	3	5
Infections and infestations			
Genital infection fungal			
subjects affected / exposed	7 / 307 (2.28%)	5 / 309 (1.62%)	0 / 154 (0.00%)
occurrences (all)	7	6	0
Influenza			
subjects affected / exposed	5 / 307 (1.63%)	9 / 309 (2.91%)	5 / 154 (3.25%)
occurrences (all)	6	9	6
Nasopharyngitis			
subjects affected / exposed	12 / 307 (3.91%)	20 / 309 (6.47%)	5 / 154 (3.25%)
occurrences (all)	12	21	6
Urinary tract infection			
subjects affected / exposed	11 / 307 (3.58%)	8 / 309 (2.59%)	2 / 154 (1.30%)
occurrences (all)	13	9	3
Vulvovaginal mycotic infection			
subjects affected / exposed	5 / 307 (1.63%)	10 / 309 (3.24%)	1 / 154 (0.65%)
occurrences (all)	5	12	1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	6 / 307 (1.95%)	6 / 309 (1.94%)	9 / 154 (5.84%)
occurrences (all)	6	7	11
Any Hypoglycaemia			
subjects affected / exposed	2 / 307 (0.65%)	9 / 309 (2.91%)	7 / 154 (4.55%)
occurrences (all)	6	17	8
Documented Symptomatic Hypoglycaemia			
subjects affected / exposed	1 / 307 (0.33%)	8 / 309 (2.59%)	3 / 154 (1.95%)
occurrences (all)	1	15	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2017	Amendment 1: 1. Change to the Exclusion criteria and temporary investigational medicinal product (IMP) discontinuation. 2. Change to the exclusion criteria and guidance on contraceptive methods. 3. Change to exclusion assessment. 4.Change to the general guidelines for reporting of adverse events. 5. Change to hepatitis serology test at screening and related exclusion. 6. Change to the definition of one event(s) of special interest (EOSI) "volume depletion". 7. Change to urine laboratory test. 8. Change to instruction for blood pressure measurement. 9. Other minor changes for corrections of inconsistency or administration were listed.
11 April 2018	Amendment 2: 1. Addition of a new section to describe the independent safety assessments for drug-induced liver injuries (DILI) and amputation. 2. Change to exclusion criterion E20 regarding the use of a selective sodium-glucose cotransport type 2 (SGLT2) inhibitor. 3. Change to the definition of baseline for estimated glomerular filtration rate (eGFR). 4. Change to the description of the objectives and endpoints for the Ambulatory Blood Pressure Monitoring (ABPM) substudy. 5. Update to the statistical analysis for the primary and secondary study endpoints, compliance analysis, and multiplicity considerations. 6. 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