Clinical trial results:
A 52-week Randomized, Double-blind, Double-dummy, Active and Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin compared to Glimepiride or Placebo Added to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycemic Control with Metformin Monotherapy

Summary

EudraCT number	2016-001801-17
Trial protocol	SK BG HU
Global end of trial date	06 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	EFC14838

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03332771
WHO universal trial number (UTN)	U1111-1190-7596

Notes:

Sponsors

Sponsor organisation name	Lexicon Pharmaceuticals, Inc.
Sponsor organisation address	8800 Technology Forest Place, The Woodlands, TX, United States, United States, 77381
Public contact	Medical Affairs, Lexicon Pharmaceuticals, Inc., 510 338-6064, medical-information@lexpharma.com
Scientific contact	Medical Affairs, Lexicon Pharmaceuticals, Inc., 510 338-6064, 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	06 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of Sotagliflozin 400 milligrams (mg) compared to glimepiride on HbA1c (glycosylated A1c) reduction at Week 52 in subjects with Type 2 Diabetes (T2D) who have inadequate glycemic control with metformin.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 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: 80
Country: Number of subjects enrolled	Bulgaria: 45
Country: Number of subjects enrolled	Hungary: 136
Country: Number of subjects enrolled	United States: 693
Worldwide total number of subjects	954
EEA total number of subjects	261

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)	635
From 65 to 84 years	315

85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 138 investigative sites in United States, Bulgaria, Hungary, and Slovakia from 01 December 2017 to 06 September 2019.

Pre-assignment

Screening details:

Subjects with a diagnosis of T2D Mellitus were enrolled in 1 of 4 treatment groups: Placebo or Sotagliflozin 200 mg or Sotagliflozin 400 mg or Glimepiride. Subjects were randomly assigned in the ratio of 1:1:2:2 to these reporting groups. Total of 954 subjects were enrolled in the study, from which 952 were randomised and treated.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Following a 2-week run-in period, two Sotagliflozin-matching placebo tablets and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.

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

Dosage and administration details:

Placebo administered as 2 tablets, orally once daily before the first meal of the day.

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

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

Dosage and administration details:

Glimepiride was administered as 2 capsules, once daily before the first meal of the day.

Arm title	Sotagliflozin 400 mg

Arm description:

Following a 2-week run-in period, two Sotagliflozin 200 mg, tablets, and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment

period up to 52 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 was administered as 2 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:

Glimepiride-matching placebo administered as 2 capsules, orally once daily before the first meal of the day.

Arm title	Sotagliflozin 200 mg

Arm description:

Following a 2-week run-in period, one Sotagliflozin 200 mg, tablet and one Sotagliflozin-matching placebo tablet, and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 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 administered as 2 tablets, orally 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 administered as 2 tablets, orally once daily before the first meal of the day.

Arm title	Glimepiride

Arm description:

Following a 2-week run-in period, two Sotagliflozin-matching placebo tablets, and combination of two Glimepiride capsules with adequate dose strengths per dose titration (titrated up to 6mg), taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.

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

Dosage and administration details:

Placebo administered as 2 tablets, orally once daily before the first meal of the day

Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Glimepiride was administered as 2 capsules, once daily before the first meal of the day.

Number of subjects in period 1	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg
Started	159	317	160
Completed	125	266	128
Not completed	34	51	32
Adverse Event	6	4	1
Lost to Follow-up	2	2	1
Poor compliance to protocol	-	1	-
Reason not specified	6	18	16
At the Subject’s Own Request	20	26	14

Number of subjects in period 1	Glimepiride
Started	318
Completed	270
Not completed	48
Adverse Event	3
Lost to Follow-up	2
Poor compliance to protocol	1
Reason not specified	19
At the Subject’s Own Request	23

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Following a 2-week run-in period, two Sotagliflozin-matching placebo tablets and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Following a 2-week run-in period, two Sotagliflozin 200 mg, tablets, and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.	
Reporting group title	Sotagliflozin 200 mg
Reporting group description:	
Following a 2-week run-in period, one Sotagliflozin 200 mg, tablet and one Sotagliflozin-matching placebo tablet, and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.	
Reporting group title	Glimepiride
Reporting group description:	
Following a 2-week run-in period, two Sotagliflozin-matching placebo tablets, and combination of two Glimepiride capsules with adequate dose strengths per dose titration (titrated up to 6mg), taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.	

Reporting group values	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg
Number of subjects	159	317	160
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.8	59.7	58.6
standard deviation	± 11.2	± 10.4	± 9.9
Gender categorical Units: Subjects			
Female	77	157	75
Male	82	160	85
Ethnicity Units: Subjects			
Hispanic or Latino	48	85	53
Not Hispanic or Latino	110	230	106
Unknown or Not Reported	1	2	1
Race Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	3	5	3
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	13	34	19
White	141	269	136
More than one race	1	3	0

Unknown or Not Reported	0	4	0

Hemoglobin A1c (HbA1c)			
Units: percentage of HbA1c			
arithmetic mean	8.12	8.09	8.11
standard deviation	± 0.73	± 0.78	± 0.86
Systolic Blood Pressure (SBP)			
Units: millimetre of mercury (mmHg)			
arithmetic mean	133.23	133.17	132.78
standard deviation	± 14.90	± 14.37	± 13.29

Reporting group values	Glimepiride	Total	
Number of subjects	318	954	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	59.8		
standard deviation	± 9.6	-	
Gender categorical			
Units: Subjects			
Female	143	452	
Male	175	502	
Ethnicity			
Units: Subjects			
Hispanic or Latino	111	297	
Not Hispanic or Latino	207	653	
Unknown or Not Reported	0	4	
Race			
Units: Subjects			
American Indian or Alaska Native	1	2	
Asian	4	15	
Native Hawaiian or Other Pacific Islander	0	4	
Black or African American	36	102	
White	277	823	
More than one race	0	4	
Unknown or Not Reported	0	4	
Hemoglobin A1c (HbA1c)			
Units: percentage of HbA1c			
arithmetic mean	8.07		
standard deviation	± 0.79	-	
Systolic Blood Pressure (SBP)			
Units: millimetre of mercury (mmHg)			
arithmetic mean	134.66		
standard deviation	± 14.43	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Following a 2-week run-in period, two Sotagliflozin-matching placebo tablets and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Following a 2-week run-in period, two Sotagliflozin 200 mg, tablets, and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.	
Reporting group title	Sotagliflozin 200 mg
Reporting group description:	
Following a 2-week run-in period, one Sotagliflozin 200 mg, tablet and one Sotagliflozin-matching placebo tablet, and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.	
Reporting group title	Glimepiride
Reporting group description:	
Following a 2-week run-in period, two Sotagliflozin-matching placebo tablets, and combination of two Glimepiride capsules with adequate dose strengths per dose titration (titrated up to 6mg), taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.	

Primary: Change From Baseline in Hemoglobin A1c % at Week 52

End point title	Change From Baseline in Hemoglobin A1c % at Week 52
End point description:	
Missing data are imputed using the retrieved dropouts imputation method. An analysis of covariance (ANCOVA) model was used for the analysis. Intend to treat (ITT) population included all randomised subjects.	
End point type	Primary
End point timeframe:	
Baseline, Week 52	

End point values	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Glimepiride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	159	317	160	318
Units: percentage of HbA1c				
least squares mean (standard error)	-0.40 (± 0.187)	-0.65 (± 0.101)	-0.49 (± 0.114)	-0.61 (± 0.093)

Statistical analyses

Statistical analysis title	Sotagliflozin 400 mg, Glimepiride
Statistical analysis description:	
The change from baseline to Week 52 is analysed using ANCOVA model with treatment groups,	

randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline HbA1c as a covariate.

Comparison groups	Sotagliflozin 400 mg v Glimepiride
Number of subjects included in analysis	635
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3306
Method	ANCOVA
Parameter estimate	Difference in Least Squares (LS) Mean
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.357
Variability estimate	Standard error of the mean
Dispersion value	0.122

Statistical analysis title	Sotagliflozin 200 mg, Glimepiride

Statistical analysis description:

The change from baseline to Week 52 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline HbA1c as a covariate.

Comparison groups	Sotagliflozin 200 mg v Glimepiride
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7112
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.265
upper limit	0.181
Variability estimate	Standard error of the mean
Dispersion value	0.114

Secondary: Change From Baseline in Hemoglobin A1c % at Week 26

End point title	Change From Baseline in Hemoglobin A1c % at Week 26

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Glimepiride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	159	317	160	318
Units: percentage of HbA1c				
least squares mean (standard error)	-0.41 (± 0.097)	-0.77 (± 0.076)	-0.61 (± 0.098)	-1.02 (± 0.075)

Statistical analyses

Statistical analysis title	Sotagliflozin 400 mg, Glimepiride

Statistical analysis description:

The change from baseline to Week 26 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline HbA1c as a covariate.

Comparison groups	Sotagliflozin 400 mg v Glimepiride
Number of subjects included in analysis	635
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0827
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	0.027
Variability estimate	Standard error of the mean
Dispersion value	0.119

Statistical analysis title	Sotagliflozin 200 mg, Glimepiride

Statistical analysis description:

The change from baseline to Week 26 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline HbA1c as a covariate.

Comparison groups	Glimepiride v Sotagliflozin 200 mg
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-0.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.571
upper limit	-0.167
Variability estimate	Standard error of the mean
Dispersion value	0.103

Secondary: Change From Baseline in Body Weight at Week 26 and 52

End point title	Change From Baseline in Body Weight at Week 26 and 52

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Week 26 and 52

End point values	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Glimepiride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	159	317	160	318
Units: kilogram (kg)				
least squares mean (standard error)				
Week 26	-1.26 (± 0.329)	-2.75 (± 0.257)	-2.24 (± 0.336)	0.70 (± 0.256)
Week 52	-0.47 (± 1.406)	-2.64 (± 0.503)	-1.74 (± 0.707)	0.94 (± 0.452)

Statistical analyses

Statistical analysis title	Placebo, Sotagliflozin 400 mg (Week 26)

Statistical analysis description:

The change from baseline to Week 26 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5, >8.5%) at screening, randomisation strata of SBP (<130,≥ 130 mmHg) at screening, 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	476
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-1.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.173
upper limit	-0.803
Variability estimate	Standard error of the mean
Dispersion value	0.349

Statistical analysis title	Sotagliflozin 400 mg, Glimepiride (Week 52)

Statistical analysis description:

The change from baseline to Week 52 is analysed using analysis of ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, randomisation strata of SBP (<130, ≥130 mmHg) at screening, and country as fixed effects and baseline body weight as a covariate.

Comparison groups	Sotagliflozin 400 mg v Glimepiride
Number of subjects included in analysis	635
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-3.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.651
upper limit	-2.517
Variability estimate	Standard error of the mean
Dispersion value	0.544

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

End point title	Change From Baseline in Systolic Blood Pressure (SBP) for Subjects With SBP ≥130 mmHg at Week 12

End point description:

Missing data are imputed using washout imputation method. An ANCOVA model was used for the analysis. Analysis was performed on ITT population in subjects with baseline SBP ≥130 mmHg.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Glimepiride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	161	81	175
Units: mmHg				
least squares mean (standard error)	-5.34 (± 1.451)	-8.03 (± 1.064)	-9.12 (± 1.466)	-3.86 (± 1.081)

Statistical analyses

Statistical analysis title	Sotagliflozin 400 mg, Glimepiride
Statistical analysis description:	
The change from baseline to Week 12 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, and country as fixed effects, and baseline SBP as a covariate.	
Comparison groups	Sotagliflozin 400 mg v Glimepiride
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-4.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.701
upper limit	-1.65
Variability estimate	Standard error of the mean
Dispersion value	1.288

Statistical analysis title	Placebo, Sotagliflozin 400 mg
Statistical analysis description:	
The change from baseline to Week 12 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.5, >8.5%) at screening, and country as fixed effects, and baseline SBP as a covariate.	
Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0973
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.89
upper limit	0.491

Variability estimate	Standard error of the mean
Dispersion value	0.0973

Secondary: Change From Baseline in Systolic Blood Pressure (SBP) for All Subjects at Week 12

End point title	Change From Baseline in Systolic Blood Pressure (SBP) for All Subjects at Week 12

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Glimepiride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	159	317	160	318
Units: mmHg				
least squares mean (standard error)	-2.64 (± 1.013)	-4.70 (± 0.791)	-4.77 (± 1.033)	-0.68 (± 0.795)

Statistical analyses

Statistical analysis title	Sotagliflozin 400 mg, Glimepiride

Statistical analysis description:

The change from baseline to Week 12 is analysed using ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5, >8.5%) at screening, and country as fixed effects, and baseline SBP as a covariate.

Comparison groups	Sotagliflozin 400 mg v Glimepiride
Number of subjects included in analysis	635
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-4.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.73
upper limit	-2.319
Variability estimate	Standard error of the mean
Dispersion value	0.87

Secondary: Percentage of Subjects With At Least One Documented Symptomatic Hypoglycemic Event (≤70 milligrams per decilitre [mg/dL])

End point title	Percentage of Subjects With At Least One Documented Symptomatic Hypoglycemic Event (≤70 milligrams per decilitre [mg/dL])

End point description:

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Glimepiride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	159	317	160	318
Units: percentage of subjects				
number (not applicable)	0.63	1.26	3.75	16.67

Statistical analyses

Statistical analysis title	Sotagliflozin 400 mg, Glimepiride

Statistical analysis description:

Weighted average of percentage difference between treatment groups from each stratum [randomization strata of HbA1c [≤8.5%, >8.5%] at screening, randomisation strata of mean SBP [<130, ≥130 mmHg] at screening using Cochran-Mantel-Haenszel weights.

Comparison groups	Glimepiride v Sotagliflozin 400 mg
Number of subjects included in analysis	635
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	-15.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.67
upper limit	-11.12

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 subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. Safety population defined as all randomised subjects who had received at least 1 dose of double-blind investigational medicinal product (IMP).

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Glimepiride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	159	317	159	317
Units: percentage of subjects				
number (not applicable)	57.2	59.9	56.6	49.2

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 ≤ 70 mg/dL (3.9 mmol/L)]; Severe [an event requiring assistance of another person to actively administer carbohydrate, glucagon, intravenous glucose or other resuscitative actions] or documented symptomatic hypoglycemia [typical symptoms of hypoglycemia and plasma glucose ≤ 70 mg/dL]. Safety population included all randomised subjects who received at least 1 dose of double-blind investigational medicinal product (IMP).

End point type	Other pre-specified

End point timeframe:

Up to Week 52

End point values	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Glimepiride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	159	317	159	317
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	2.5	4.1	6.3	25.9
Documented symptomatic hypoglycemia	0.6	1.3	3.8	16.7
Severe or documented symptomatic hypoglycemia	0.6	1.3	3.8	16.7

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug to the last dose of study drug (up to 52 weeks) + 2 weeks

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Following a 2-week run-in period, two Sotagliflozin-matching placebo tablets and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.

Reporting group title	Sotagliflozin 400 mg

Reporting group description:

Following a 2-week run-in period, two Sotagliflozin 200 mg, tablets, and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.

Reporting group title	Sotagliflozin 200 mg

Reporting group description:

Following a 2-week run-in period, one Sotagliflozin 200 mg, tablet and one Sotagliflozin-matching placebo tablet, and two Glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.

Reporting group title	Glimepiride

Reporting group description:

Following a 2-week run-in period, two Sotagliflozin-matching placebo tablets, and combination of two Glimepiride capsules with adequate dose strengths per dose titration (titrated up to 6mg), taken orally once daily before the first meal of the day in the double-blind treatment period up to 52 weeks.

Serious adverse events	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 159 (6.92%)	17 / 317 (5.36%)	11 / 159 (6.92%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Breast cancer			
subjects affected / exposed	1 / 159 (0.63%)	1 / 317 (0.32%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma			
subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Prostate cancer			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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			
Hypertension			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Vasculitis			

subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Incarcerated hernia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Influenza like illness			
subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Non-cardiac chest pain			
subjects affected / exposed	2 / 159 (1.26%)	1 / 317 (0.32%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Metrorrhagia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Depression			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
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			
Ankle fracture			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Concussion			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Fall			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Road traffic accident			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft stenosis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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 disorders			
Acute left ventricular failure			

subjects affected / exposed	1 / 159 (0.63%)	1 / 317 (0.32%)	0 / 159 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Angina pectoris			
subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Angina unstable			
subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Atrial fibrillation			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
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 failure			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Coronary artery disease			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Nervous system disorders			
Cerebellar stroke			

subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Hemiparesis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 159 (0.63%)	0 / 317 (0.00%)	0 / 159 (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
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Gastrointestinal disorders			
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Gastrointestinal inflammation			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Small intestinal obstruction			

subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Umbilical hernia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Cholelithiasis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
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			
Cervical spinal stenosis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Musculoskeletal chest pain			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vertebral osteophyte			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cholecystitis infective			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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
Epididymitis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 159 (0.00%)	1 / 317 (0.32%)	0 / 159 (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			
Dehydration			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 159 (0.00%)	0 / 317 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Glimepiride		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 317 (4.42%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			

subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vasculitis			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Death			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Incarcerated hernia			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden cardiac death			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metrorrhagia			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Fibula fracture				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intentional overdose				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 317 (0.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Tibia fracture				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular graft stenosis				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute left ventricular failure				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				

subjects affected / exposed	1 / 317 (0.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	1 / 317 (0.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebellar stroke				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				

subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Retinal haemorrhage				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diverticulum intestinal haemorrhagic				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal inflammation				
subjects affected / exposed	1 / 317 (0.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 317 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				

subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertebral osteophyte			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Cholecystitis infective			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epididymitis			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 317 (0.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia legionella			
subjects affected / exposed	0 / 317 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis chronic			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gout			
subjects affected / exposed	1 / 317 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Sotagliflozin 400 mg	Sotagliflozin 200 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 159 (18.87%)	49 / 317 (15.46%)	21 / 159 (13.21%)
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 159 (6.92%)	14 / 317 (4.42%)	7 / 159 (4.40%)
occurrences (all)	11	15	7
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 159 (6.92%)	14 / 317 (4.42%)	8 / 159 (5.03%)
occurrences (all)	13	17	8
Infections and infestations			
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 159 (1.26%)	19 / 317 (5.99%)	6 / 159 (3.77%)
occurrences (all)	2	26	9
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	8 / 159 (5.03%)	5 / 317 (1.58%)	2 / 159 (1.26%)
occurrences (all)	9	5	2

Non-serious adverse events	Glimepiride		
Total subjects affected by non-serious			

adverse events subjects affected / exposed	22 / 317 (6.94%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	12 / 317 (3.79%) 19		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	7 / 317 (2.21%) 7		
Infections and infestations Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	2 / 317 (0.63%) 2		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 317 (0.63%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2017	The overall reason for this amendment was to update •Changed the EudraCT number •Replaced another objective "Change in SBP for patients with baseline SBP <130 mmHg" with "Changed in SBP for all patients, the subset with baseline SBP <130 mmHg, and the subset with baseline SBP ≥130 mmHg" •Removed requirements for hepatitis serology tests at screening and the related exclusion criterion •Changes in exclusion assessment •Change to the exclusion criteria and guidance on contraceptive methods. Removed urgent coronary revascularizations from the events subject to the Clinical Endpoint Committees (CECs) review
09 April 2018	The overall reason for this amendment was to •Change to exclusion criterion E18 regarding the use of a selective sodium-glucose transporters (SGLT2) inhibitor •Change to guidance on contraceptive methods •Addition of a new section to describe the independent safety assessments for drug-induced liver injuries (DILI) and amputation •Change to a urine laboratory test.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported