Clinical trial results:
An Exploratory, Randomized, Double-blind, Placebo-controlled, Parallel Arm Trial of the Safety and Pharmacodynamic Activity of Sotagliflozin in Hemodynamically Stable Patients with Worsening Heart Failure

Summary

EudraCT number	2017-002774-39
Trial protocol	NL IT
Global end of trial date	17 August 2019

Results information

Result version number	v1 (current)
This version publication date	04 October 2020
First version publication date	04 October 2020

Trial information

Trial identification

Sponsor protocol code	PDY15079

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03292653
WHO universal trial number (UTN)	U1111-1190-7962

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	17 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is the assessment of safety and tolerability of Sotagliflozin, added to the standard of care treatment, in hemodynamically stable subjects hospitalized for worsening of heart failure, compared to placebo.

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	04 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	United States: 29
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Netherlands: 2
Worldwide total number of subjects	32
EEA total number of subjects	2

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)	20
From 65 to 84 years	11

85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 6 investigative sites in the United States, Canada, and the Netherlands from 04 December 2017 to 17 August 2019.

Pre-assignment

Screening details:

Subjects with a diagnosis of Congestive Heart Failure (CHF), were enrolled in 1 of 3 treatment groups, Placebo, Sotagliflozin 200 milligrams (mg) and Sotagliflozin 400 mg.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects were randomised to matching placebo to Sotagliflozin administered as two tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.

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

Dosage and administration details:

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

Arm title	Sotagliflozin 200 mg

Arm description:

Subjects were randomised to one Sotagliflozin 200 mg tablet administered and one matching placebo tablet, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.

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 was administered as one tablet (identical to the Sotagliflozin 200 mg tablet in appearance), orally once daily.

Investigational medicinal product name	Sotagliflozin 200 mg
Investigational medicinal product code	
Other name	SAR439954
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sotagliflozin 200 mg was administered as one tablet, orally once daily.

Arm title	Sotagliflozin 400 mg

Arm description:

Subjects were randomised to Sotagliflozin 400 mg administered as two tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.

Arm type	Experimental
Investigational medicinal product name	Sotagliflozin 400 mg
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 Sotagliflozin 200 mg tablets, orally once daily.

Number of subjects in period 1[1]	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Started	10	10	11
Completed	10	10	10
Not completed	0	0	1
Adverse event	-	-	1

Notes:

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

Justification: Number of subjects reported in the baseline period is for treated population. The number of subjects in the worldwide is for randomised population.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects were randomised to matching placebo to Sotagliflozin administered as two tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.	
Reporting group title	Sotagliflozin 200 mg
Reporting group description:	
Subjects were randomised to one Sotagliflozin 200 mg tablet administered and one matching placebo tablet, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Subjects were randomised to Sotagliflozin 400 mg administered as two tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.	

Reporting group values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Number of subjects	10	10	11
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60.8	55.1	65.1
standard deviation	± 13.05	± 12.84	± 13.41
Gender categorical Units: Subjects			
Female	3	0	4
Male	7	10	7
Race Units: Subjects			
White	4	5	6
Black or African American	6	5	4
Not Reported	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	10	10	10

Reporting group values	Total		
Number of subjects	31		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	7		
Male	24		
Race Units: Subjects			
White	15		
Black or African American	15		
Not Reported	1		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	30		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects were randomised to matching placebo to Sotagliflozin administered as two tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.	
Reporting group title	Sotagliflozin 200 mg
Reporting group description:	
Subjects were randomised to one Sotagliflozin 200 mg tablet administered and one matching placebo tablet, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Subjects were randomised to Sotagliflozin 400 mg administered as two tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.	

Primary: Percentage of Subjects with Adverse Events (AEs), Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), AEs Leading to Discontinuation From the Investigational Medicinal Product (IMP) and Deaths

End point title	Percentage of Subjects with Adverse Events (AEs), Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), AEs Leading to Discontinuation From the Investigational Medicinal Product (IMP) and Deaths[1]

End point description:

AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. SAEs: an event that results in death; an event that, in the view of the investigator, places the subjects at immediate risk of death (a life-threatening event); an outcome that results in a congenital anomaly/birth defect diagnosed in a child of a subject; an event that requires or prolongs inpatient hospitalization; an event that results in persistent or significant disability/incapacity. AESI: is an adverse event (serious or nonserious) of scientific and medical concern, specific to the IMP or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Safety population included all randomised subjects who had exposure to any amount of IMP.

End point type	Primary

End point timeframe:

Baseline up to Day 14

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was planned to be reported for this endpoint.

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	11	
Units: percentage of subjects				
number (not applicable)				
AEs	40	30	45.5	
SAEs	10	0	0	
AESIs	0	0	0	
AEs Leading to Discontinuation From the IMP	0	0	9.1	
Deaths	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hemoconcentration as Assessed by Changes in Albumin to Day 14

End point title	Change From Baseline in Hemoconcentration as Assessed by Changes in Albumin to Day 14

End point description:

Pharmacodynamic (PD) population included all randomised and treated subjects who had valid values of the main PD parameters at baseline and Day 14 End of Treatment (EOT).

End point type	Primary

End point timeframe:

Baseline to Day 14

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[2]	6[3]	9[4]	
Units: grams per litre (g/L)				
least squares mean (standard error)	1.17 (± 2.71)	2.44 (± 2.40)	0.15 (± 2.14)	

Notes:

[2] - The number of subjects analysed is the number of subjects with available data.

[3] - The number of subjects analysed is the number of subjects with available data.

[4] - The number of subjects analysed is the number of subjects with available data.

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo

Statistical analysis description:

Analysis of Covariance (ANCOVA) model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic,
ejection fraction status (reduced/preserved) with baseline plasma volume as the covariate.

Comparison groups	Sotagliflozin 200 mg v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.736
Method	ANCOVA
Parameter estimate	Difference in Least Square (LS) Means
Point estimate	1.26

Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.4
upper limit	7.93
Variability estimate	Standard error of the mean
Dispersion value	3.64

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline plasma volume as the covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7694
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.22
upper limit	5.18
Variability estimate	Standard error of the mean
Dispersion value	3.38

Primary: Change From Baseline in Hemoconcentration as Assessed by Changes in Hematocrit to Day 14

End point title	Change From Baseline in Hemoconcentration as Assessed by Changes in Hematocrit to Day 14

End point description:

PD population included all randomised and treated subjects who had valid values of the main PD parameters at baseline and Day 14 (EOT).

End point type	Primary

End point timeframe:

Baseline to Day 14

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	9[5]	10[6]	
Units: ratio				
least squares mean (standard error)	0.02 (± 0.02)	-0.02 (± 0.02)	-0.01 (± 0.02)	

Notes:

[5] - The number of subjects analysed is the number of subjects with available data.

[6] - The number of subjects analysed is the number of subjects with available data.

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline plasma volume as the covariate.

Comparison groups	Sotagliflozin 200 mg v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.184
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.09
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline plasma volume as the covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3397
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.07
upper limit	0.02

Variability estimate	Standard error of the mean
Dispersion value	0.03

Primary: Change From Baseline in Hemoconcentration as Assessed by Changes in Hemoglobin to Day 14

End point title	Change From Baseline in Hemoconcentration as Assessed by Changes in Hemoglobin to Day 14

End point description:

PD population included all randomised and treated subjects who had valid values of the main PD parameters at baseline and Day 14 (EOT).

End point type	Primary

End point timeframe:

Baseline to Day 14

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	9[7]	10[8]	
Units: g/L				
least squares mean (standard error)	8.16 (± 6.80)	-8.91 (± 6.02)	-3.94 (± 5.37)	

Notes:

[7] - The number of subjects analysed is the number of subjects with available data.

[8] - The number of subjects analysed is the number of subjects with available data.

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline plasma volume as the covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-17.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	-33.79
upper limit	-0.35
Variability estimate	Standard error of the mean
Dispersion value	9.12

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline plasma volume as the covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1878
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-12.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	-27.65
upper limit	3.46
Variability estimate	Standard error of the mean
Dispersion value	8.49

Primary: Change From Baseline in Hemoconcentration as Assessed by Changes in Total Protein to Day 14

End point title	Change From Baseline in Hemoconcentration as Assessed by Changes in Total Protein to Day 14

End point description:

PD population included all randomised and treated subjects who had valid values of the main PD parameters at baseline and Day 14 (EOT).

End point type	Primary

End point timeframe:

Baseline to Day 14

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[9]	6[10]	9[11]	
Units: g/L				
least squares mean (standard error)	5.31 (± 4.32)	0.49 (± 3.83)	-1.05 (± 3.41)	

Notes:

[9] - The number of subjects analysed is the number of subjects with available data.

[10] - The number of subjects analysed is the number of subjects with available data.

[11] - The number of subjects analysed is the number of subjects with available data.

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline plasma volume as the covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4269
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-4.82
Confidence interval	
level	90 %
sides	2-sided
lower limit	-15.45
upper limit	5.8
Variability estimate	Standard error of the mean
Dispersion value	5.8

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline plasma volume as the covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2684
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-6.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	-16.24
upper limit	3.52
Variability estimate	Standard error of the mean
Dispersion value	5.39

Primary: Changes From Baseline in Plasma Volume to Day 14

End point title	Changes From Baseline in Plasma Volume to Day 14

End point description:

Change in plasma volume in millilitres (ml) was assessed by the indicator dilution method using 131I-labelled human albumin. PD population included all randomised and treated subjects who had valid values of the main PD parameters at baseline and Day 14 (EOT).

End point type	Primary

End point timeframe:

Baseline to 14 Days

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[12]	6[13]	5[14]	
Units: ml				
least squares mean (standard error)	-525.00 (± 433.19)	322.20 (± 359.23)	-35.67 (± 392.43)	

Notes:

[12] - The number of subjects analysed is the number of subjects with available data.

[13] - The number of subjects analysed is the number of subjects with available data.

[14] - The number of subjects analysed is the number of subjects with available data.

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline plasma volume as the covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1761
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	847.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-210.46
upper limit	1904.86
Variability estimate	Standard error of the mean
Dispersion value	576.98

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline plasma volume as the covariate.

Comparison groups	Placebo v Sotagliflozin 400 mg

Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4202
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	489.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	-572.68
upper limit	1551.34
Variability estimate	Standard error of the mean
Dispersion value	579.35

Secondary: Change From Baseline in Erythropoietin to Day 14

End point title	Change From Baseline in Erythropoietin to Day 14

End point description:

Change in erythropoietin international units per litre (IU/L) was measured by chemiluminescent enzyme-labelled immunometric assay. PD population included all randomised and treated subjects who had valid values of the main PD parameters at baseline and Day 14 (EOT).

End point type	Secondary

End point timeframe:

Baseline to Day 14

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[15]	7[16]	10[17]	
Units: international units per litre (IU/L)				
least squares mean (standard error)	0.03 (± 5.92)	13.78 (± 6.26)	-0.07 (± 5.04)	

Notes:

[15] - The number of subjects analysed is the number of subjects with available data.

[16] - The number of subjects analysed is the number of subjects with available data.

[17] - The number of subjects analysed is the number of subjects with available data.

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline erythropoietin as the covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1242
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	13.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.03
upper limit	28.53
Variability estimate	Standard error of the mean
Dispersion value	8.53

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline erythropoietin as the covariate.

Comparison groups	Sotagliflozin 400 mg v Placebo
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9903
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.49
upper limit	13.3
Variability estimate	Standard error of the mean
Dispersion value	7.73

Secondary: Change From Baseline in NT-proBNP to Day 14

End point title	Change From Baseline in NT-proBNP to Day 14

End point description:

Change in NT-proBNP picomoles per litre (pmol/L) was measured by standard electrochemiluminescence immunoassay. PD population included all randomised and treated subjects who had valid values of the main PD parameters at baseline and Day 14 (EOT).

End point type	Secondary

End point timeframe:

Baseline to Day 14

End point values	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[18]	6[19]	9[20]	
Units: picomoles per litre (pmol/L)				
least squares mean (standard error)	91.36 (± 78.04)	-59.53 (± 81.28)	86.10 (± 65.87)	

Notes:

[18] - The number of subjects analysed is the number of subjects with available data.

[19] - The number of subjects analysed is the number of subjects with available data.

[20] - The number of subjects analysed is the number of subjects with available data.

Statistical analyses

Statistical analysis title	Sotagliflozin 200 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline NT-proBNP as the covariate.

Comparison groups	Placebo v Sotagliflozin 200 mg
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2121
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-150.89
Confidence interval	
level	90 %
sides	2-sided
lower limit	-353.57
upper limit	51.78
Variability estimate	Standard error of the mean
Dispersion value	116.09

Statistical analysis title	Sotagliflozin 400 mg Vs Placebo

Statistical analysis description:

ANCOVA model with fixed effects for treatment and stratification factors of baseline subject status (diabetic/non-diabetic), ejection fraction status (reduced/preserved) with baseline NT-proBNP as the covariate.

Comparison groups	Sotagliflozin 400 mg v Placebo

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9574
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-5.26
Confidence interval	
level	90 %
sides	2-sided
lower limit	-174.4
upper limit	163.87
Variability estimate	Standard error of the mean
Dispersion value	96.88

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug to last dose of study drug (up to Day 14) + 2 weeks

Adverse event reporting additional description:

Safety population included all randomised subjects who had exposure to any amount of IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects were randomised to matching placebo to Sotagliflozin administered as two tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.

Reporting group title	Sotagliflozin 200 mg

Reporting group description:

Subjects were randomised to one Sotagliflozin 200 mg tablet administered and one matching placebo tablet, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.

Reporting group title	Sotagliflozin 400 mg

Reporting group description:

Subjects were randomised to Sotagliflozin 400 mg administered as two tablets, once daily, before the first meal of the day in the double-blind treatment period for up to 14 days.

Serious adverse events	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 11 (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

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

Non-serious adverse events	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	3 / 10 (30.00%)	5 / 11 (45.45%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Myocardial infarction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	1 / 11 (9.09%)
occurrences (all)	2	1	1
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Rectal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hypoxia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Stress			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Fluid intake reduced			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 January 2018	Amendment 1: 1. Added EudraCT and World Health Organization (WHO) Universal Trial numbers. 2. Added exclusion of History of Type 1 Diabetes Mellitus. 3. Removed the exclusion of high dose thiazide diuretic. 4. Added exclusion of lower extremity diabetic complications requiring treatment. 5. Screening duration was updated. 6. Guidance for stopping rules were updated. 7. Appendices for sample collection were removed.
14 March 2018	Amendment 2: 1. Added that exploratory analysis may be performed for safety reasons as requested by the Data Monitoring Committee (DMC) or Ethics committee that would not result in changes to the protocol. 2. Clarified procedures for subjects who were not discharged.
01 August 2019	Amendment 3: 1. Removed 200 mg arm from cohort 3 without replacing subjects. 2. Reduce the burden off the subjects-traveling to the site by reducing the visit. 3. Removed pharmacokinetic (PK) assessments from the cohort 3. 4. Clarified that tachycardia >130 at screening is grounds for exclusion. 5. Removed reference to the interim analysis. 6. Removed the requirement to eat 15 minutes after investigational medicinal product (IMP) administration in cohort 3.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported