Clinical trial results:
A randomized, double-blind, parallel-group, 2-treatment multiple dose study to assess the intestinal, metabolic and cardiovascular effects of an 8 weeks treatment with sotagliflozin once daily (QD) as compared with empagliflozin QD in type 2 diabetes mellitus (T2DM) subjects with mild to moderate hypertension.

Summary

EudraCT number	2017-002309-36
Trial protocol	DE
Global end of trial date	18 April 2019

Results information

Result version number	v1 (current)
This version publication date	02 May 2020
First version publication date	02 May 2020

Trial information

Trial identification

Sponsor protocol code	PDY15010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03462069
WHO universal trial number (UTN)	U1111-1186-2962

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 Avenue Pierre Brossolette, Chilly Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi-aventis Recherche & Développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi-aventis Recherche & Développement, Contact-US@sanofi.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	05 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the metabolic and gastrointestinal pharmacodynamic (PD) effects of an 8 weeks treatment with 400 milligram (mg) sotagliflozin once daily (QD) to an 8 weeks treatment to empagliflozin QD in mild or moderate hypertensive type 2 diabetes mellitus (T2DM) subjects on a stable treatment regimen with metformin and an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) under standardised diet conditions.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject was participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Stable treatment with metformin and ACE inhibitor or ARB was used as background therapy.

Evidence for comparator: -

Actual start date of recruitment	06 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	24
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at a single center in Germany. A total of 137 subjects were screened between 06-March-2018 and 16 February 2019. Of which, 96 subjects were screen failures due to inclusion/exclusion criteria not met.

Pre-assignment

Screening details:

A total of 41 subjects were randomized and treated in the study.

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	Sotagliflozin 400 mg

Arm description:

Subjects received sotagliflozin 400 mg tablet QD along with a placebo (for empagliflozin) prior to the first meal of the day for 56 days (Days 1 to 56).

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

Dosage and administration details:

Sotagliflozin 2*200 mg tablets were administered orally with 240 millilitre (mL) of water once a day prior to the first meal of the day.

Arm title	Empagliflozin 25 mg

Arm description:

Subjects received one empagliflozin 25 mg capsule along with 2 placebo (for sotagliflozin) prior to the first meal of the day for 56 days (Days 1 to 56).

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

Dosage and administration details:

Empagliflozin 25 mg capsule was administered orally with 240 mL of water once a day prior to the first meal of the day.

Number of subjects in period 1	Sotagliflozin 400 mg	Empagliflozin 25 mg
Started	20	21
Completed	19	20
Not completed	1	1
Other than specified	-	1
Poor compliance to protocol	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Subjects received sotagliflozin 400 mg tablet QD along with a placebo (for empagliflozin) prior to the first meal of the day for 56 days (Days 1 to 56).	
Reporting group title	Empagliflozin 25 mg
Reporting group description:	
Subjects received one empagliflozin 25 mg capsule along with 2 placebo (for sotagliflozin) prior to the first meal of the day for 56 days (Days 1 to 56).	

Reporting group values	Sotagliflozin 400 mg	Empagliflozin 25 mg	Total
Number of subjects	20	21	41
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	61.0	61.3	
standard deviation	± 8.4	± 8.1	-
Gender categorical Units: Subjects			
Female	4	4	8
Male	16	17	33

End points

End points reporting groups

Reporting group title	Sotagliflozin 400 mg
Reporting group description:	
Subjects received sotagliflozin 400 mg tablet QD along with a placebo (for empagliflozin) prior to the first meal of the day for 56 days (Days 1 to 56).	
Reporting group title	Empagliflozin 25 mg
Reporting group description:	
Subjects received one empagliflozin 25 mg capsule along with 2 placebo (for sotagliflozin) prior to the first meal of the day for 56 days (Days 1 to 56).	

Primary: Mean Change From Baseline in 24-Hour Urinary Glucose Excretion (UGE) to Week 8

End point title	Mean Change From Baseline in 24-Hour Urinary Glucose Excretion (UGE) to Week 8
End point description:	
The 24-hour UGE was calculated from the 4-fractioned 24-hour urine collection, separately on Day -1 (Baseline) and on Week 8 (Day 56). Analysis was performed on PD population which included all subjects with no major or critical deviations related to investigational medicinal products (IMP) and/or PD procedures and measurements, for whom the PD data were considered sufficient and interpretable. Here, 'number of subject analysed' = subjects evaluable for this end-point.	
End point type	Primary
End point timeframe:	
Baseline to Week 8	

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: millimoles (mmoL)				
least squares mean (standard error)	130.941 (± 13.587)	158.424 (± 13.196)		

Statistical analyses

Statistical analysis title	Sotagliflozin versus Empagliflozin
Statistical analysis description:	
Analysis was performed using Linear fixed effects model with treatment group (Sotagliflozin 400 mg, Empagliflozin 25 mg) as fixed effects and baseline 24-hour UGE value as covariate.	
Comparison groups	Sotagliflozin 400 mg v Empagliflozin 25 mg

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1604
Method	Linear fixed effects model
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	27.483
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.474
upper limit	66.441
Variability estimate	Standard error of the mean
Dispersion value	19.126

Primary: Mean Change From Baseline in 24-Hour Urine Creatinine to Week 8

End point title	Mean Change From Baseline in 24-Hour Urine Creatinine to Week 8

End point description:

The 24-hour urine creatinine concentration was calculated from the 4-fractioned 24-hour urine collection divided by the total urine volume collected within 24 hours, separately on Day -1 (Baseline) and Week 8 (Day 56). Analysis was performed on PD population. Here, 'number of subject analysed' = subjects evaluable for this end-point.

End point type	Primary

End point timeframe:

Baseline to Week 8

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: gram per millilitre (g/mL)				
least squares mean (standard error)	-0.205 (± 0.052)	-0.358 (± 0.051)		

Statistical analyses

Statistical analysis title	Sotagliflozin versus Empagliflozin

Statistical analysis description:

Analysis was performed using Linear fixed effects model with treatment group (Sotagliflozin 400 mg, Empagliflozin 25 mg) as fixed effects and baseline 24-hour urine creatinine concentration value as covariate.

Comparison groups	Sotagliflozin 400 mg v Empagliflozin 25 mg

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0433
Method	Linear fixed effects model
Parameter estimate	LS Mean Difference
Point estimate	-0.153
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.302
upper limit	-0.005
Variability estimate	Standard error of the mean
Dispersion value	0.073

Primary: Mean Change From Baseline in 48-Hour Fecal Firmicutes/Bacteroidetes Ratio to Week 8

End point title	Mean Change From Baseline in 48-Hour Fecal Firmicutes/Bacteroidetes Ratio to Week 8

End point description:

The 48-hour ratio of the firmicutes over bacteroidetes classes of bacteria was calculated from Firmicutes/bacteroidetes ratios and weight of stool portion measured separately on Day -2 and -1 (Baseline) and on Week 8 (Day 55 and 56). Analysis was performed on PD population. Here, 'number of subject analysed' = subjects evaluable for this end-point.

End point type	Primary

End point timeframe:

Baseline to Week 8

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: ratio				
least squares mean (standard error)	-74.11 (± 36.95)	-60.15 (± 40.51)		

Statistical analyses

Statistical analysis title	Sotagliflozin versus Empagliflozin

Statistical analysis description:

Analysis was performed using Linear fixed effects model with treatment group (Sotagliflozin 400 mg, Empagliflozin 25 mg) as fixed effects and baseline 48-hour Firmicutes/bacteroidetes ratio value as covariate.

Comparison groups	Sotagliflozin 400 mg v Empagliflozin 25 mg

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8017
Method	Linear fixed effects model
Parameter estimate	LS Mean Difference
Point estimate	13.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-98.55
upper limit	126.46
Variability estimate	Standard error of the mean
Dispersion value	55.09

Primary: Mean Change From Baseline in Incremental AUC0:00-14:00 Hour of Plasma Glucose to Week 8

End point title	Mean Change From Baseline in Incremental AUC0:00-14:00 Hour of Plasma Glucose to Week 8

End point description:

The incremental area under the plasma glucose concentration time curve over 14 hours (AUC0-14h) after standardized meals was calculated using the linear trapezoidal rule by correcting the post meal values for the glucose measured pre-meal. Baseline was defined as Day-1 and Week 8 was defined as Day 56. Analysis was performed on PD population. Here, 'number of subject analysed' = subjects evaluable for this end-point.

End point type	Primary

End point timeframe:

Baseline to Week 8

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: hour*milligram per decilitre (hr*mg/dL)				
least squares mean (standard error)	-103.05 (± 38.55)	-73.66 (± 37.46)		

Statistical analyses

Statistical analysis title	Sotagliflozin versus Empagliflozin

Statistical analysis description:

Analysis was performed using Linear fixed effects model with treatment group (Sotagliflozin 400 mg, Empagliflozin 25 mg) as fixed effects and baseline Glucose (plasma) incremental AUC0:00-14:00-hour value as covariate.

Comparison groups	Sotagliflozin 400 mg v Empagliflozin 25 mg

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5889
Method	Linear fixed effects model
Parameter estimate	LS Mean Difference
Point estimate	29.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-80.27
upper limit	139.05
Variability estimate	Standard error of the mean
Dispersion value	53.83

Primary: Mean Change From Baseline in Incremental AUC0:00-14:00 Hour of C-peptide to Week 8

End point title	Mean Change From Baseline in Incremental AUC0:00-14:00 Hour of C-peptide to Week 8

End point description:

The incremental area under the C-peptide concentration time curve over 14 hours (AUC0-14h) after standardized meals was calculated using the linear trapezoidal rule by correcting the post meal values for the C-peptide measured pre-meal. Baseline was defined as Day-1 and Week 8 was defined as Day 56. Analysis was performed on PD population. Here, 'number of subject analysed' = subjects evaluable for this end-point.

End point type	Primary

End point timeframe:

Baseline to Week 8

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: hour*nanomoles per liter (h*nmol/L)				
least squares mean (standard error)	-2.42 (± 0.73)	-1.91 (± 0.73)		

Statistical analyses

Statistical analysis title	Sotagliflozin versus Empagliflozin

Statistical analysis description:

Analysis was performed using Linear fixed effects model with treatment group (Sotagliflozin 400 mg, Empagliflozin 25 mg) as fixed effects and baseline C-peptide (plasma) incremental AUC0:00-14:00 hour value as covariate.

Comparison groups	Sotagliflozin 400 mg v Empagliflozin 25 mg

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6297
Method	Linear fixed effects model
Parameter estimate	LS Mean Difference
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	2.62
Variability estimate	Standard error of the mean
Dispersion value	1.04

Primary: Mean Change From Baseline in Incremental AUC0:00-14:00 Hour of Active GLP-1 to Week 8

End point title	Mean Change From Baseline in Incremental AUC0:00-14:00 Hour of Active GLP-1 to Week 8

End point description:

The incremental area under the Active GLP-1 concentration time curve over 14 hours (AUC0-14h) after standardized meals was calculated using the linear trapezoidal rule by correcting the post meal values for the Active GLP-1 measured pre-meal. Baseline was defined as Day-1 and Week 8 was defined as Day 56. Analysis was performed on PD population. Here, 'number of subject analysed' = subjects evaluable for this end-point.

End point type	Primary

End point timeframe:

Baseline to Week 8

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: hour*nanogram per litre (h*ng/L)				
least squares mean (standard error)	22.51 (± 9.47)	-8.41 (± 9.47)		

Statistical analyses

Statistical analysis title	Sotagliflozin versus Empagliflozin

Statistical analysis description:

Analysis was performed using Linear fixed effects model with treatment group (Sotagliflozin 400 mg, Empagliflozin 25 mg) as fixed effects and baseline Active GLP1 (plasma) incremental AUC0:00-14:00 hour value as covariate.

Comparison groups	Sotagliflozin 400 mg v Empagliflozin 25 mg

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0273
Method	Linear fixed effects model
Parameter estimate	LS Mean Difference
Point estimate	-30.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.16
upper limit	-3.68
Variability estimate	Standard error of the mean
Dispersion value	13.39

Secondary: Mean Change From Baseline in Blood Pressure (Systolic and Diastolic) to Week 8

End point title	Mean Change From Baseline in Blood Pressure (Systolic and Diastolic) to Week 8

End point description:

Average 24-hour mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured as per ambulatory blood pressure monitoring (ABPM) at baseline (from Day -3 to Day 1) and at Week 8 (from Day 54 to Day 57). Analysis was performed on PD population. Here, 'number of subjects analysed' = subjects evaluable for this end-point.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: millimetres of mercury (mmHg)				
least squares mean (standard error)				
SBP	-4.6 (± 1.5)	-7.9 (± 1.4)		
DBP	-2.3 (± 0.9)	-3.7 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Echocardiography: Change From Baseline in Left Ventricular End-Diastolic Diameter (LVEDD) and Left Ventricular Ejection Fraction (LVEF) to Week 8

End point title	Echocardiography: Change From Baseline in Left Ventricular End-Diastolic Diameter (LVEDD) and Left Ventricular Ejection Fraction (LVEF) to Week 8

End point description:

Baseline was defined as Day -3 and Week 8 was defined as Day 54. Analysis was performed on PD population. Here, 'n'=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: unit in categories				
arithmetic mean (standard deviation)				
LVEDD (mm) (n=19,20)	-0.9 (± 2.7)	-0.9 (± 3.7)		
LVEF (percent) (n=18,19)	5.1 (± 7.9)	3.0 (± 10.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Aortic augmentation index at 75 Beats per Minute (bpm) (%) to Week 8

End point title	Change From Baseline in Aortic augmentation index at 75 Beats per Minute (bpm) (%) to Week 8

End point description:

Pulse wave velocity was measured through aortic augmentation index at 75 bpm. Aortic augmentation index is the ratio of the augmentation pressure to the central pulse pressure, expressed as a percentage. Pulse wave velocity was assessed at baseline (Day -2) and Week 8 (Day 55), and device used was Sphygmocor XCEL (or equivalent device). Analysis was performed on PD population.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: percentage				
least squares mean (standard error)	-0.05 (± 2.19)	-1.03 (± 2.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Volume to Week 8

End point title	Change From Baseline in Plasma Volume to Week 8

End point description:

The plasma volume was estimated using the indocyanine-green (ICG) dilution method. Plasma volume was calculated for each subject on Day -3 (Baseline) and on Day 54 (on treatment). Analysis was performed on PD population. Here, 'subjects analysed' = subjects evaluable for this end-point.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	19		
Units: Litre (L)				
least squares mean (standard error)	0.116 (± 0.201)	-0.228 (± 0.185)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous Glucose Monitoring (CGM): Mean Change From Baseline in Average Diurnal Glucose Exposure to Week 8

End point title	Continuous Glucose Monitoring (CGM): Mean Change From Baseline in Average Diurnal Glucose Exposure to Week 8

End point description:

Baseline was defined as Day -4, Day -3 and Day -2 and Week 8 as Day 53, Day 54 and Day 55. Analysis was performed on PD population. Here, 'number of subjects analysed' = subjects evaluable for this end-point.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Sotagliflozin 400 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: milligram per decilitre (mg/dL)				
least squares mean (standard error)	-21.254 (± 4.027)	-28.697 (± 3.780)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from time of first dose of study drug up to end of study (Day 70) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment emergent AEs (TEAEs) that developed/worsened during 'on-treatment period' (from first IMP administration up to 10 days (1 day for hypoglycemia) after the last administration of IMP). Analysis was performed on safety population that included all subjects exposed to IMP (regardless of the amount of treatment administered).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Sotagliflozin 400 mg

Reporting group description:

Subjects received sotagliflozin 400 mg tablet QD along with a placebo (for empagliflozin) prior to the first meal of the day for 56 days (Days 1 to 56).

Reporting group title	Empagliflozin 25 mg

Reporting group description:

Subjects received one empagliflozin 25 mg capsule along with 2 placebo (for sotagliflozin) prior to the first meal of the day for 56 days (Days 1 to 56).

Serious adverse events	Sotagliflozin 400 mg	Empagliflozin 25 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Sotagliflozin 400 mg	Empagliflozin 25 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)	13 / 21 (61.90%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Catheter Site Haematoma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Infusion Site Hypersensitivity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Medical Device Site Haematoma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Erectile Dysfunction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Pruritus Genital			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Investigations			
Urine Viscosity Abnormal			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	3 / 20 (15.00%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
Contusion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Muscle Strain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Extrasystoles			

subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness Postural			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Paraesthesia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Sciatica			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Abdominal Pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Dry Mouth			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Faeces Discoloured			

subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Skin Hypopigmentation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Micturition Urgency			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Polyuria			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Urge Incontinence			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Muscle Spasms			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal Pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Neck Pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Pain In Extremity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Genital Infection Fungal			
subjects affected / exposed	2 / 20 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Nasopharyngitis			
subjects affected / exposed	4 / 20 (20.00%)	2 / 21 (9.52%)	
occurrences (all)	4	2	
Sinusitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Tinea Infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Urinary Tract Infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Hypoglycaemia			

subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 21 (4.76%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2018	The following changes were made: - justified why no formal sample size was performed; clarified the reasons for withdrawal of a subject upon the Principal Investigator's (PI's) decision or at the specific request of the sponsor; modified the age range for inclusion from 18 to 75 years to 18 to 74 years of age; added an additional exclusion criterion to specify known hypersensitivity to sotagliflozin, empagliflozin, or any excipient of these drug products; justified the initiation of empagliflozin dosing at the highest approved dose level of 25 mg QD without prior up-titration from 10 mg QD. Additional references with clinical safety data of this dosing regimen with empagliflozin were added; clarified the safety analyses of hypoglycemic events; modified inclusion criterion to exclude explicitly individuals under institutionalization due to regulatory or juridical order; exclusion criterion was clarified regarding exclusion of subjects depending on study site, the PI, or the Sponsor; specified the 1996 version of the Declaration of Helsinki; enforced the wording for the requirement of signing the Inform Consent Form prior to a subject's participation in the clinical trial.
11 April 2018	The following changes were made:- inclusion criteria for glycosylated hemoglobin A1C (HbA1c) and body weight ranges were modified to better harmonize the study population with the Phase 3 program of sotagliflozin in T2DM subjects. The range of HbA1c was modified to 6.5%-11%. Body weight was modified to at least 50 kg, if male, and at least 40 kg, if female; in the main selection criteria, it was clarified that SBP was to be in the range of 140-179 mm Hg. The DBP range was removed in the main selection criteria; the safety parameter, serum β-hydroxybutyrate, was assessed at screening, Day -5, the first outpatient visit, Day 52, and end-of-study visit. Additionally, this parameter was part of the PD lab on Day -1 and Day 56; the amount of blood sampling was slightly reduced for several parameters; hematology parameters for cardiovascular panel were analyzed from safety hematology tube; amylase and lipase were added to the parameters assessed in laboratory tests (biochemistry).
30 August 2018	The following changes were made:- a drug washout/switch period was added for eligible subjects who were on beta-blockers and/or thiazides to switch to ACE inhibitor or ARB to be able to participate in the study. Also, the upper limit of body mass index was changed from 35 kilogram per meter square (kg/m^2) to 38 kg/m^2; it was clarified that subjects on thiazides had to switch to ACE inhibitors or ARB to be eligible for study participation; it was clarified that, if possible, fecal calprotectin and intestinal alkaline phosphatase and GIP plasma profiles would be investigated; the total study duration with and without the drug washout/switch period was clarified; a new inclusion criterion was added to allow eligible subjects who were on beta-blockers and/or thiazides to participate in the study after switching to ACE inhibitor or ARB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported