Clinical trial results:
A 24-Week, Multicentre, Randomised, Double-blind, Parallel Group, Placebo-controlled Study to Investigate the Effects of Saxagliptin and Sitagliptin in Patients with Type 2 Diabetes Mellitus and Heart Failure

Summary

EudraCT number	2015-004825-14
Trial protocol	ES HU BG
Global end of trial date	23 August 2019

Results information

Result version number	v1 (current)
This version publication date	19 August 2021
First version publication date	19 August 2021

Trial information

Trial identification

Sponsor protocol code	D1680C00016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02917031
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Södertälje, Södertälje, Sweden, 151 85
Public contact	AstraZeneca AB, AstraZeneca AB, +46 766 346712, clinicaltrialtransparency@astrazeneca.com
Scientific contact	AstraZeneca R&D, AstraZeneca R&D, +46 766 346712, clinicaltrialtransparency@astrazeneca.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	24 October 2020

Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2019
Global end of trial reached?	Yes
Global end of trial date	23 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To exclude an increase in left ventricular end diastolic volume (LVEDV) index of greater than 10% of the overall baseline value (non-inferiority margin) in patients with Type 2 Diabetes Mellitus (T2DM) and heart failure (HF) treated with saxagliptin for 24 weeks, compared to placebo

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 2017
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	Bulgaria: 33
Country: Number of subjects enrolled	Chile: 33
Country: Number of subjects enrolled	Hungary: 54
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Russian Federation: 138
Country: Number of subjects enrolled	Thailand: 23
Country: Number of subjects enrolled	Ukraine: 29
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	347
EEA total number of subjects	89

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)	154
From 65 to 84 years	191
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients who met all the inclusion and exclusion criteria were enrolled in 9 countries.

Pre-assignment

Screening details:

Patients with documented Left Ventricular Ejection Fraction (LVEF) ≤ 45% and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) > 300 pg/mL attended a Screening Visit within 28 days before receiving their first dose with saxagliptin, sitagliptin, or placebo.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Saxagliptin

Arm description:

Participants with an eGFR ≥50 mL/min/1.73m^2 received one saxagliptin 5 mg tablet and one sitaglipitin placebo capsule administered orally once daily for a 24-week treatment period. Participants with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of saxagliptin was adjusted to one 2.5 mg tablet.

Arm type	Active comparator
Investigational medicinal product name	Saxagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received one saxagliptin 5 mg tablet administered orally once daily for a 24-week treatment period. Patients with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of saxagliptin was adjusted to one 2.5 mg tablet.

Arm title	Sitagliptin

Arm description:

Patients with an eGFR ≥50 mL/min/1.73m^2 received one sitagliptin 100 mg capsule and one saxagliptin placebo tablet administered orally once daily for a 24-week treatment period. Patients with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of sitagliptin was adjusted to one 50 mg capsule.

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

Dosage and administration details:

Patients received one sitagliptin 100 mg capsule administered orally once daily for a 24-week treatment period. Patients with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of sitagliptin was adjusted to one 50 mg capsule.

Arm title	Placebo

Arm description:

Patients recieved one saxagliptin placebo tablet and one sitagliptin placebo capsule administered orally

once daily for a 24-week treatment period as a control.

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

Dosage and administration details:

Patients received sitagliptin placebo capsule orally once daily for a 24-week treatment period as a control.

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

Dosage and administration details:

Patients received saxagliptin placebo tablet orally once daily for a 24-week treatment period as a control.

Number of subjects in period 1	Saxagliptin	Sitagliptin	Placebo
Started	112	115	120
Completed	94	102	105
Not completed	18	13	15
Physician decision	1	-	-
Adverse event, serious fatal	2	3	4
Reason not specifie	7	5	6
Adverse event, non-fatal	4	1	5
Consent withdrawn by subject	3	3	-
Development of study-specific withdrawal criteria	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Saxagliptin
Reporting group description:	
Participants with an eGFR ≥50 mL/min/1.73m^2 received one saxagliptin 5 mg tablet and one sitaglipitin placebo capsule administered orally once daily for a 24-week treatment period. Participants with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of saxagliptin was adjusted to one 2.5 mg tablet.	
Reporting group title	Sitagliptin
Reporting group description:	
Patients with an eGFR ≥50 mL/min/1.73m^2 received one sitagliptin 100 mg capsule and one saxagliptin placebo tablet administered orally once daily for a 24-week treatment period. Patients with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of sitagliptin was adjusted to one 50 mg capsule.	
Reporting group title	Placebo
Reporting group description:	
Patients recieved one saxagliptin placebo tablet and one sitagliptin placebo capsule administered orally once daily for a 24-week treatment period as a control.	

Reporting group values	Saxagliptin	Sitagliptin	Placebo
Number of subjects	112	115	120
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	54	47	53
From 65-84 years	58	68	67
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	64.6	64.9	66.5
standard deviation	± 7.96	± 9.85	± 7.84
Sex: Female, Male Units: Participants			
Female	35	36	37
Male	77	79	83
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	17	17	15
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	3
White	94	98	102
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	10	16	17
Not Hispanic or Latino	102	99	103
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	347		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	154		
From 65-84 years	193		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	108		
Male	239		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	49		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	4		
White	294		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	43		
Not Hispanic or Latino	304		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Saxagliptin
Reporting group description:	
Participants with an eGFR ≥50 mL/min/1.73m^2 received one saxagliptin 5 mg tablet and one sitaglipitin placebo capsule administered orally once daily for a 24-week treatment period. Participants with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of saxagliptin was adjusted to one 2.5 mg tablet.	
Reporting group title	Sitagliptin
Reporting group description:	
Patients with an eGFR ≥50 mL/min/1.73m^2 received one sitagliptin 100 mg capsule and one saxagliptin placebo tablet administered orally once daily for a 24-week treatment period. Patients with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of sitagliptin was adjusted to one 50 mg capsule.	
Reporting group title	Placebo
Reporting group description:	
Patients recieved one saxagliptin placebo tablet and one sitagliptin placebo capsule administered orally once daily for a 24-week treatment period as a control.	

Primary: Change from baseline in Left Ventricular End Diastolic Volume (LVEDV) index measured by Magnetic Resonance Imaging (MRI) at 24 weeks

End point title	Change from baseline in Left Ventricular End Diastolic Volume (LVEDV) index measured by Magnetic Resonance Imaging (MRI) at 24 weeks[1]
End point description:	
MRI was performed to evaluate LVEDV at baseline and Visit 10 (Week 24). Evaluated to exclude an increase in left ventricular end diastolic volume (LVEDV) index of greater than 10% of the overall baseline value (noninferiority margin) in patients with T2DM and HF treated with saxagliptin for 24 weeks, compared to placebo. Baseline is last assessment on or before the date of first dose.	
End point type	Primary
End point timeframe:	
Baseline to 24 weeks	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was done for Saxagliptin and Placebo as per objective.

End point values	Saxagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	106		
Units: mL/m^2				
arithmetic mean (standard deviation)	-3.395 (± 15.3412)	-0.716 (± 18.1178)		

Statistical analyses

Statistical analysis title	saxagliptin versus placebo.
Statistical analysis description:	
Change from baseline, saxagliptin versus placebo	
Comparison groups	Saxagliptin v Placebo

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.252
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.595
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.04
upper limit	1.85

Secondary: Change from baseline in left ventricular end systolic volume (LVESV) index measured by MRI at 24 weeks.

End point title	Change from baseline in left ventricular end systolic volume (LVESV) index measured by MRI at 24 weeks.[2]

End point description:

Evaluation of the effects of saxagliptin compared to placebo on left ventricular end systolic volume (LVESV) index, after 24 weeks in patients with T2DM and HF.

End point type	Secondary

End point timeframe:

Baseline to week 24

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was done for Saxagliptin and Placebo as per objective.

End point values	Saxagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	106		
Units: mL/m^2				
arithmetic mean (standard deviation)	-2.555 (± 12.4136)	-0.839 (± 17.2458)		

Statistical analyses

Statistical analysis title	Saxagliptin versus Placebo

Statistical analysis description:

Change from baseline, saxagliptin versus placebo

Comparison groups	Saxagliptin v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.425
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.631

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.635
upper limit	2.373

Secondary: Change from baseline in left ventricular ejection fraction (LVEF) measured by MRI at 24 weeks.

End point title	Change from baseline in left ventricular ejection fraction (LVEF) measured by MRI at 24 weeks.[3]

End point description:

Evaluation of the effects of saxagliptin compared to placebo on left ventricular ejection fraction (LVEF) after 24 weeks in patients with T2DM and HF.

End point type	Secondary

End point timeframe:

Baseline to week 24

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was done for Saxagliptin and Placebo as per objective.

End point values	Saxagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	106		
Units: Percentage				
arithmetic mean (standard deviation)	0.533 (± 7.1971)	0.298 (± 7.2843)		

Statistical analyses

Statistical analysis title	Saxagliptin versus Placebo

Statistical analysis description:

Change from baseline, saxagliptin versus placebo

Comparison groups	Saxagliptin v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.925
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.996
upper limit	2.197

Secondary: Change from baseline in left ventricular mass (LVM) measured by MRI at 24 weeks.

End point title	Change from baseline in left ventricular mass (LVM) measured by MRI at 24 weeks.[4]

End point description:

Evaluation of the effects of saxagliptin compared to placebo on left ventricular mass (LVM) after 24 weeks in patients with T2DM and HF.

End point type	Secondary

End point timeframe:

Baseline to week 24

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was done for Saxagliptin and Placebo as per objective.

End point values	Saxagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	106		
Units: Gram				
arithmetic mean (standard deviation)	-4.211 (± 16.6003)	-0.758 (± 16.1763)		

Statistical analyses

Statistical analysis title	Saxagliptin versus placebo

Statistical analysis description:

Change from baseline, saxagliptin versus placebo

Comparison groups	Saxagliptin v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.105
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.605
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.97
upper limit	0.76

Secondary: Change from baseline in NT-proBNP after 24 weeks of treatment

End point title	Change from baseline in NT-proBNP after 24 weeks of treatment[5]

End point description:

Evaluation of the effects of saxagliptin compared to placebo on N-terminal prohormone of brain natriuretic peptide (NT-proBNP) after 24 weeks of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was done for Saxagliptin and Placebo as per objective.

End point values	Saxagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	104		
Units: pg/mL				
arithmetic mean (standard deviation)	-277.525 (± 1324.7471)	-61.895 (± 3415.9525)		

Statistical analyses

Statistical analysis title	Saxagliptin versus placebo

Statistical analysis description:

Change from baseline, saxagliptin versus placebo

Comparison groups	Saxagliptin v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.796
Method	ANCOVA
Parameter estimate	Ratio for relative change
Point estimate	0.971
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.777
upper limit	1.214

Secondary: Number of participants with adverse events

End point title	Number of participants with adverse events

End point description:

Assessment of safety and tolerability of saxagliptin and sitagliptin treatment in patients with T2DM and HF

End point type	Secondary

End point timeframe:

From screening (Days -28 to -1) until Week 28 (follow-up visit)

End point values	Saxagliptin	Sitagliptin	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	115	120	
Units: Participants				
Any AE	53	51	58	
Any severe AE	9	13	14	
Any treatment related AE	3	4	0	
Any AE with outcome Death	2	3	4	
Any SAE	17	19	29	
Any treatment related SAE	0	0	0	
Any SAE leading to discontinuation	1	0	4	
Any AE leading to discontinuation	5	3	7	
Any Adverse event of special interest	12	15	16	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening (Days -28 to -1) until Week 28 (follow-up visit)

Adverse event reporting additional description:

An AEs is the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Saxagliptin

Reporting group description:

Participants with an eGFR ≥50 mL/min/1.73m^2 received one saxagliptin 5 mg tablet and one sitaglipitin placebo capsule administered orally once daily for a 24-week treatment period. Participants with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of saxagliptin was adjusted to one 2.5 mg tablet.

Reporting group title	Placebo

Reporting group description:

Participants recieved one saxagliptin placebo tablet and one sitagliptin placebo capsule administered orally once daily for a 24-week treatment period as a control.

Reporting group title	Sitagliptin

Reporting group description:

Participants with an eGFR ≥50 mL/min/1.73m^2 received one sitagliptin 100 mg capsule and one saxagliptin placebo tablet administered orally once daily for a 24-week treatment period. Participants with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of sitagliptin was adjusted to one 50 mg capsule.

Serious adverse events	Saxagliptin	Placebo	Sitagliptin
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 112 (15.18%)	29 / 120 (24.17%)	19 / 115 (16.52%)
number of deaths (all causes)	2	4	3
number of deaths resulting from adverse events	2	4	3
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Sudden cardiac death			
subjects affected / exposed	0 / 112 (0.00%)	2 / 120 (1.67%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	2 / 2	1 / 1
Cardiac death			
subjects affected / exposed	1 / 112 (0.89%)	0 / 120 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 112 (0.89%)	0 / 120 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Craniocerebral injury			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Femur fracture			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Humerus fracture			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Lower limb fracture			
subjects affected / exposed	1 / 112 (0.89%)	0 / 120 (0.00%)	0 / 115 (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
Pelvic fracture			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 112 (0.89%)	0 / 120 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	7 / 112 (6.25%)	6 / 120 (5.00%)	5 / 115 (4.35%)
occurrences causally related to treatment / all	0 / 9	0 / 7	0 / 5
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 112 (0.89%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 112 (0.00%)	2 / 120 (1.67%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Bradycardia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Coronary artery disease			
subjects affected / exposed	1 / 112 (0.89%)	0 / 120 (0.00%)	0 / 115 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 120 (0.00%)	0 / 115 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea paroxysmal nocturnal			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 120 (0.00%)	0 / 115 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	2 / 115 (1.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral arteriosclerosis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 120 (0.00%)	0 / 115 (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
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Ischaemic stroke			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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			
Enterocolitis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Cystitis haemorrhagic			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 112 (0.89%)	1 / 120 (0.83%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	1 / 112 (0.89%)	0 / 120 (0.00%)	0 / 115 (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
Musculoskeletal and connective tissue disorders			
Back disorder			
subjects affected / exposed	0 / 112 (0.00%)	0 / 120 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Lactic acidosis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 112 (2.68%)	1 / 120 (0.83%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatitis B			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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	1 / 112 (0.89%)	0 / 120 (0.00%)	0 / 115 (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
Laryngitis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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
Sepsis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 120 (0.83%)	0 / 115 (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

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Saxagliptin	Placebo	Sitagliptin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 112 (7.14%)	8 / 120 (6.67%)	9 / 115 (7.83%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 112 (0.89%)	4 / 120 (3.33%)	2 / 115 (1.74%)
occurrences (all)	1	4	2
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 112 (1.79%)	4 / 120 (3.33%)	5 / 115 (4.35%)
occurrences (all)	2	4	5
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	5 / 112 (4.46%)	1 / 120 (0.83%)	3 / 115 (2.61%)
occurrences (all)	5	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2016	Study Objectives and Methods of assigning treatment groups section was updated, SGLT2 stratification factor was added to reflect removal of saxagliptin/dapagliflozin treatment arm and all elements related to dapagliflozin component. PK sampling will no longer be performed for the full study cohort but in a subset of approximately 150 patients.
12 April 2017	Study design and relevant sections in eligibility criteria were updated to lower the NT-proBNP inclusion level lowered to > 400 pg/mL, expansion of HbA1c range to ≥6.5% and ≤10.5%, extension of pre-screening/screening period to 21 days, to allow re-pre-screening/re-screening, remove requirement of enrolment to screening not later than 7 days after pre-screening, and introduction of mandatory cMRI scan quality approval at baseline (before first dose of study medication) and before the visit at week 24.
13 June 2018	Inclusion criteria revised for definition of documented, controlled T2DM (criteria were added in Appendix C), updated for HF medications requirements; removal of normal sinus rhythm requirement on the qualifying ECG. Definitions of analysis sets, variables and statistical methods were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Last subject last visit for this study was on 23Aug2019. After the LSLV, protocol was amended on 14Feb2020. The last amendment did not introduce any changes in how study visits or assessments are done, only statistical analysis were updated.

Notes: