Clinical trial results:
A 52-Week, Multi-Centre, Randomised, Parallel-Group, Double-Blind, Active-Controlled, Phase IV Study to Evaluate the Safety and Efficacy of Dapagliflozin or Dapagliflozin plus Saxagliptin compared with Sulphonylurea all given as Add-on Therapy to Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycaemic Control on Metformin Monotherapy

Summary

EudraCT number	2015-002376-24
Trial protocol	DE HU CZ SK PL
Global end of trial date	24 March 2017

Results information

Result version number	v1 (current)
This version publication date	29 March 2018
First version publication date	29 March 2018

Trial information

Trial identification

Sponsor protocol code	D1689C00014

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Cambridge Science Park, Cambridge, United Kingdom, CB4 0FZ
Public contact	Eva Johnsson, MD, PhD, AstraZeneca, +46 031776 24 84, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Eva Johnsson, MD, PhD, AstraZeneca, +46 031776 24 84, 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 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to compare the absolute change from baseline in HbA1c at Week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin.

Protection of trial subjects:

All subjects were monitored throughout the study to ensure adequate glycaemic control.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 September 2015
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: 470
Country: Number of subjects enrolled	Hungary: 167
Country: Number of subjects enrolled	Slovakia: 144
Country: Number of subjects enrolled	Poland: 87
Country: Number of subjects enrolled	Czech Republic: 71
Worldwide total number of subjects	939
EEA total number of subjects	939

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)	684
From 65 to 84 years	255

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Sites were allowed to perform a pre-study screening assessment prior to enrolment Visit to screen for HbA1c criteria. All potentially eligible subjects underwent screening and submitted laboratory samples at Enrolment (Visit 1, 2 weeks prior to randomisation).

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, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 10mg

Arm description:

Dapagliflozin 10mg + Metformin

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

Dosage and administration details:

10 mg, orally, green, plain, diamond-shaped, film-coated tablet

Arm title	Saxagliptin 5mg and Dapagliflozin 10mg

Arm description:

Saxagliptin 5mg and Dapagliflozin 10mg + Metformin

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

Dosage and administration details:

5 mg, orally, plain, yellow, biconvex, round, film-coated tablet

Arm title	Glimepiride 1mg/2mg/4mg

Arm description:

Glimepiride 1mg/2mg/4mg + Metformin

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

Dosage and administration details:

1, 2, or 4 mg, orally, opaque gray capsule

Number of subjects in period 1	Dapagliflozin 10mg	Saxagliptin 5mg and Dapagliflozin 10mg	Glimepiride 1mg/2mg/4mg
Started	314	312	313
Completed	281	298	288
Not completed	33	14	25
Consent withdrawn by subject	8	4	5
Adverse event, non-fatal	7	1	2
Failure to Meet Randomization Criteria	2	-	1
Developed Study Withdrawal Criteria	4	1	2
Lost to follow-up	1	1	3
Other reasons not specified	10	7	12
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Dapagliflozin 10mg
Reporting group description: Dapagliflozin 10mg + Metformin	
Reporting group title	Saxagliptin 5mg and Dapagliflozin 10mg
Reporting group description: Saxagliptin 5mg and Dapagliflozin 10mg + Metformin	
Reporting group title	Glimepiride 1mg/2mg/4mg
Reporting group description: Glimepiride 1mg/2mg/4mg + Metformin	

Reporting group values	Dapagliflozin 10mg	Saxagliptin 5mg and Dapagliflozin 10mg	Glimepiride 1mg/2mg/4mg
Number of subjects	314	312	313
Age, Customized Units: Subjects			
<65|	232	226	226
>=65-<75|	81	86	85
>=75|	1	0	2
Age Continuous Units: Years			
arithmetic mean	57.4	59.2	58.6
standard deviation	± 9.36	± 7.87	± 8.38
Gender, Male/Female Units: Subjects			
Female	112	122	105
Male	202	190	208
Race/Ethnicity, Customized Units: Subjects			
Asian|	1	3	0
Black Or African American|	2	2	2
White|	311	307	311

Reporting group values	Total		
Number of subjects	939		
Age, Customized Units: Subjects			
<65|	684		
>=65-<75|	252		
>=75|	3		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	339		

Male	600		

Race/Ethnicity, Customized Units: Subjects			
Asian|	4		
Black Or African American|	6		
White|	929		

End points

End points reporting groups

Reporting group title	Dapagliflozin 10mg
Reporting group description: Dapagliflozin 10mg + Metformin	
Reporting group title	Saxagliptin 5mg and Dapagliflozin 10mg
Reporting group description: Saxagliptin 5mg and Dapagliflozin 10mg + Metformin	
Reporting group title	Glimepiride 1mg/2mg/4mg
Reporting group description: Glimepiride 1mg/2mg/4mg + Metformin	
Subject analysis set title	Dapaglifozin 10mg
Subject analysis set type	Full analysis
Subject analysis set description: Dapaglifozin 10mg + Metformin	
Subject analysis set title	Saxagliptin 5mg and Dapagliflozin 10mg
Subject analysis set type	Full analysis
Subject analysis set description: Saxagliptin 5mg and Dapagliflozin 10mg + Metformin	
Subject analysis set title	Glimepiride 1mg/2mg/4mg
Subject analysis set type	Full analysis
Subject analysis set description: Glimepiride 1mg/2mg/4mg + Metformin	

Primary: Change in Haemoglobin A1c (HbA1c) from baseline to week 52

End point title	Change in Haemoglobin A1c (HbA1c) from baseline to week 52
End point description: Change in HbA1c from baseline (week 0) to week 52	
End point type	Primary
End point timeframe: Up to Week 52. Values recorded after rescue treatment or collected more than 8 days after the last dose date were excluded from the analysis	

End point values	Dapaglifozin 10mg	Saxagliptin 5mg and Dapagliflozin 10mg	Glimepiride 1mg/2mg/4mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	309	311	305	
Units: HbA1c %				
least squares mean (standard error)	-0.82 (± 0.049)	-1.2 (± 0.046)	-0.99 (± 0.048)	

Statistical analyses

Statistical analysis title	Dapaglifozin vs Glimepiride
Statistical analysis description:	
Non-Inferiority	
Comparison groups	Dapaglifozin 10mg v Glimepiride 1mg/2mg/4mg
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0294
upper limit	0.2986

Notes:

[1] - The non-inferiority (NI) margin was determined to be 0.30% (in absolute terms). A difference of ≤0.30%, in HbA1c change from b/l to wk 52 between the treatment groups was considered clinically equivalent. NI was assessed using the 2-sided 95% CI of adjusted mean difference between dapagliflozin or dapagliflozin plus saxagliptin and glimepiride.

Statistical analysis title	Saxagliptin and Dapagliflozin vs Glimepiride
Statistical analysis description:	
Non-Inferiority	
Comparison groups	Saxagliptin 5mg and Dapagliflozin 10mg v Glimepiride 1mg/2mg/4mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.001 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3443
upper limit	-0.0825

Notes:

[2] - The non-inferiority (NI) margin was determined to be 0.30% (in absolute terms). A difference of ≤0.30%, in HbA1c change from b/l to wk 52 between the treatment groups was considered clinically equivalent. NI was assessed using the 2-sided 95% CI of adjusted mean difference between dapagliflozin or dapagliflozin plus saxagliptin and glimepiride.

[3] - For Superiority

Secondary: Patients with at least one episode of confirmed hypoglycaemia

End point title	Patients with at least one episode of confirmed hypoglycaemia

End point description:

Proportion of patients reporting at least 1 episode of hypoglycaemia (symptomatic + blood glucose <=50 mg/dL) during the double-blind treatment period

End point type	Secondary

End point timeframe:

Up to Week 52. Values recorded after rescue treatment or collected more than 8 days after the last dose date were excluded from the analysis

End point values	Dapaglifozin 10mg	Saxagliptin 5mg and Dapagliflozin 10mg	Glimepiride 1mg/2mg/4mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	311	312	309	
Units: Patients	0	1	13	

Statistical analyses

Statistical analysis title	Dapaglifozin vs Glimepiride
Comparison groups	Dapaglifozin 10mg v Glimepiride 1mg/2mg/4mg
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-4.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.45
upper limit	-1.97
Variability estimate	Standard error of the mean
Dispersion value	1.14

Statistical analysis title	Saxagliptin and Dapagliflozin vs Glimepiride
Comparison groups	Saxagliptin 5mg and Dapagliflozin 10mg v Glimepiride 1mg/2mg/4mg
Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-3.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.21
upper limit	-1.56
Variability estimate	Standard error of the mean
Dispersion value	1.19

Secondary: Change in total body weight from baseline at week 52	
End point title	Change in total body weight from baseline at week 52
End point description: Change in body weight from baseline (week 0) to week 52	
End point type	Secondary
End point timeframe: Over the 52 week treatment period	

End point values	Dapaglifozin 10mg	Saxagliptin 5mg and Dapagliflozin 10mg	Glimepiride 1mg/2mg/4mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	311	312	308	
Units: Weight (kg)				
least squares mean (standard error)	-3.54 (± 0.231)	-3.15 (± 0.219)	1.76 (± 0.224)	

Statistical analyses

Statistical analysis title	Dapaglifozin vs Glimepiride
Comparison groups	Dapaglifozin 10mg v Glimepiride 1mg/2mg/4mg
Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.93
upper limit	-4.67

Statistical analysis title	Saxagliptin and Dapagliflozin vs Glimepiride
Comparison groups	Saxagliptin 5mg and Dapagliflozin 10mg v Glimepiride 1mg/2mg/4mg

Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.52
upper limit	-4.29

Secondary: Change in Fasting Plasma Glucose (FPG) from baseline to week 52

End point title	Change in Fasting Plasma Glucose (FPG) from baseline to week 52

End point description:

Change in FPG from baseline (week 0) to week 52

End point type	Secondary

End point timeframe:

Up to Week 52. Values recorded after rescue treatment or collected more than 8 days after the last dose date were excluded from the analysis

End point values	Dapaglifozin 10mg	Saxagliptin 5mg and Dapagliflozin 10mg	Glimepiride 1mg/2mg/4mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	309	311	308	
Units: FPG (mmol/L)				
least squares mean (standard error)	-1.62 (± 0.106)	-2.08 (± 0.100)	-1.49 (± 0.105)	

Statistical analyses

Statistical analysis title	Dapaglifozin vs Glimepiride
Comparison groups	Dapaglifozin 10mg v Glimepiride 1mg/2mg/4mg
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.374
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.16

Statistical analysis title	Saxagliptin and Dapagliflozin vs Glimepiride
Comparison groups	Saxagliptin 5mg and Dapagliflozin 10mg v Glimepiride 1mg/2mg/4mg
Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.31

Secondary: Time to rescue

End point title	Time to rescue
End point description:	
Time to rescue during the 52 week double blind treatment period	
End point type	Secondary
End point timeframe:	
Over the 52 week treatment period	

End point values	Dapaglifozin 10mg	Saxagliptin 5mg and Dapagliflozin 10mg	Glimepiride 1mg/2mg/4mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	311[4]	312[5]	309[6]	
Units: Number	311	312	309	

Notes:

[4] - Percentage rescued = 18.6

[5] - Percentage rescued = 8.3

[6] - Percentage rescued = 21.4

Statistical analyses

Statistical analysis title	Dapaglifozin vs Glimepiride
Comparison groups	Dapaglifozin 10mg v Glimepiride 1mg/2mg/4mg
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.777
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.35

Statistical analysis title	Saxagliptin and Dapagliflozin vs Glimepiride
Comparison groups	Saxagliptin 5mg and Dapagliflozin 10mg v Glimepiride 1mg/2mg/4mg
Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.57

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Includes adverse events with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of study medication. Includes all data regardless of use of rescue treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Dapagliflozin 10mg
Reporting group description:	
Dapagliflozin 10mg + Metformin	
Reporting group title	Glimepiride 1mg/2mg/4mg
Reporting group description:	
Glimepiride 1mg/2mg/4mg + Metformin	
Reporting group title	Saxagliptin 5mg and Dapagliflozin 10mg
Reporting group description:	
Saxagliptin 5mg and Dapagliflozin 10mg + Metformin	

Serious adverse events	Dapagliflozin 10mg	Glimepiride 1mg/2mg/4mg	Saxagliptin 5mg and Dapagliflozin 10mg
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 313 (12.46%)	35 / 312 (11.22%)	22 / 312 (7.05%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic neuroma			
subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			

subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 313 (0.32%)	1 / 312 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Melanoma recurrent			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Renal neoplasm			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Thyroid cancer			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Acquired phimosis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 313 (0.00%)	2 / 312 (0.64%)	0 / 312 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somatic symptom disorder			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Epicondylitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Femoral neck fracture			

subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
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 fume inhalation disorder			
subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Tendon rupture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
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 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 313 (0.00%)	2 / 312 (0.64%)	0 / 312 (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
Bradyarrhythmia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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 failure congestive			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Coronary artery disease			
subjects affected / exposed	1 / 313 (0.32%)	2 / 312 (0.64%)	3 / 312 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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			
Brain stem infarction			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			

subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 313 (0.64%)	0 / 312 (0.00%)	0 / 312 (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
Essential tremor			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Headache			
subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restless legs syndrome			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Seizure			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Syncope			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Vertebrobasilar insufficiency			

subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Eye disorders			
Vitritis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Gastritis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Pancreatitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Vomiting			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 313 (0.00%)	2 / 312 (0.64%)	0 / 312 (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

Cholelithiasis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 312 (0.32%)	1 / 312 (0.32%)
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 and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Renal and urinary disorders			
Bladder prolapse			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Nephrolithiasis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 312 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Ureterolithiasis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Urethral stenosis			
subjects affected / exposed	2 / 313 (0.64%)	0 / 312 (0.00%)	0 / 312 (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
Urinary incontinence			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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

Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Goitre			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Back pain			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Dupuytren's contracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Fibromyalgia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Intervertebral disc protrusion			
subjects affected / exposed	2 / 313 (0.64%)	2 / 312 (0.64%)	2 / 312 (0.64%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Muscle rigidity			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Osteoarthritis			
subjects affected / exposed	1 / 313 (0.32%)	2 / 312 (0.64%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plantar fasciitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Appendicitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Erysipelas			
subjects affected / exposed	0 / 313 (0.00%)	0 / 312 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 313 (0.00%)	1 / 312 (0.32%)	0 / 312 (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
Micrococcus infection			

subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Pneumonia			
subjects affected / exposed	1 / 313 (0.32%)	1 / 312 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reiter's syndrome			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Scrotal abscess			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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
Urinary tract infection			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 313 (0.32%)	0 / 312 (0.00%)	0 / 312 (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	Dapagliflozin 10mg	Glimepiride 1mg/2mg/4mg	Saxagliptin 5mg and Dapagliflozin 10mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 313 (9.27%)	37 / 312 (11.86%)	31 / 312 (9.94%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	29 / 313 (9.27%)	37 / 312 (11.86%)	31 / 312 (9.94%)
occurrences (all)	40	49	39

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2016	Number of study sites and number of subjects planned, other secondary objectives updated
01 November 2016	To update the HbA1c range and further clarification of hypoglycaemia
12 January 2017	Clarification of analysis set definition and adding superiority test to analyses

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.

None

Notes: