Clinical trial results:
A 24-week International, Multicenter, Randomized, Open-Label, Active-Controlled, Parallel Group, Phase 3b Trial with a 28-week Extension to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin Compared to Insulin Glargine in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin with or without Sulfonylurea Therapy

Summary

EudraCT number	2015-001702-33
Trial protocol	HU CZ ES SE DK DE
Global end of trial date	10 November 2017

Results information

Result version number	v1 (current)
This version publication date	07 November 2018
First version publication date	07 November 2018

Trial information

Trial identification

Sponsor protocol code	CV181-369

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02551874
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, SE-431 83
Public contact	Global Clinical Lead, AstraZeneca, +46 031 7761000, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +46 031 7761000, 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	10 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2017
Global end of trial reached?	Yes
Global end of trial date	10 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to examine whether the mean change from baseline in hemoglobin A1c (HbA1c) with co-administered saxagliptin 5 milligrams (mg) once daily (QD) and dapagliflozin 10 mg QD plus metformin with or without sulfonylurea (SU) is noninferior to titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 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	United States: 336
Country: Number of subjects enrolled	Mexico: 79
Country: Number of subjects enrolled	South Africa: 43
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Poland: 53
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Hungary: 53
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Romania: 27
Worldwide total number of subjects	643
EEA total number of subjects	185

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)	525
From 65 to 84 years	118
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 112 centers in 11 countries from 20 Oct 2015 to 10 Nov 2017. There were 2 data cut-offs for this study: 8 May 2017 for analyses of the short-term study period (after 24 weeks of open-label treatment) and 10 Nov 2017 for analyses of the short-term plus long-term study period (after 52 weeks of open-label treatment).

Pre-assignment

Screening details:

The study duration was up to 56 weeks, consisting of a 2-week screening period, 2-week lead-in period, 24-week short-term treatment period, and 28-week long-term treatment period.

Pre-assignment period milestones

Number of subjects started	650[1]
Number of subjects completed	643

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not receive randomised treatment: 7

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 650 subjects were randomized overall, and number Started for Pre-assignment period reflects this value. A total of 7 of the 650 randomized subjects did not receive treatment. The randomized subject data set consisted of all randomized subjects who received at least 1 dose of study medication and therefore number in this subject population was 643. Demographic characteristics, including subject enrollment per country, was summarized for the randomized subject data set (ie, 643).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin + Saxagliptin + Metformin

Arm description:

Subjects received dapagliflozin 10 mg and saxagliptin 5 mg, administered orally QD in the morning for the 52-week treatment period (24-week short-term period and 28-week long term period).
Subjects continued to receive their stable dose of metformin with or without SU throughout the study.

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Farxiga, BMS-512148
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 10 mg tablets were administered orally QD in the morning for the 52-week treatment period.

Investigational medicinal product name	Saxagliptin
Investigational medicinal product code	
Other name	Onglyza
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Saxagliptin 5 mg tablets were administered orally QD in the morning for the 52-week treatment period.

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	Glucophage XR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin 500 mg tablets were administered orally per investigator discretion at a dose of no less than 1500 mg per day and not to exceed 2500 mg per day (or maximum locally approved dose) based on the subject's qualifying dose at
screening.

Arm title	Titrated Insulin + Metformin

Arm description:

Subjects were to administer insulin glargine subcutaneously QD at the same time every day for the 52-week treatment period (24-week short-term period and 28-week long term period), following investigator instructions and training. All subjects started with an initial dose of 0.2 units/kg body weight or at least 10 units of insulin per day. Subjects self-titrated the dose of insulin glargine over the first 8 weeks of the study based on daily glucose monitoring. The investigator had the discretion to modify insulin dose based on his/her assessment between Week 8 and Week 12 with the goal to reach an acceptable and stable insulin dose by Week 12.
Subjects continued to receive their stable dose of metformin with or without SU throughout the study.

Arm type	Active comparator
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

All subjects started with an initial dose of 0.2 units/kilogram (kg) body weight or at least 10 units of insulin per day. Subjects self-titrated the dose of insulin glargine over the first 8 weeks of the study based on daily glucose monitoring. Insulin was administered as 100 units/millilitre solution for injection.

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	Glucophage XR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin 500 mg tablets were administered orally per investigator discretion at a dose of no less than 1500 mg per day and not to exceed 2500 mg per day (or maximum locally approved dose) based on the subject's qualifying dose at
screening.

Number of subjects in period 1	Dapagliflozin + Saxagliptin + Metformin	Titrated Insulin + Metformin
Started	324	319
Entered long-term study	306	294
Received treatment in long-term study	295 [2]	284 [3]
Completed	296	287
Not completed	28	32

Reason not reported	10	4
Pregnancy	-	1
Did not enter long-term study	18	25
Lost to follow-up	-	2

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Started = subjects randomized to Dapagliflozin + Saxagliptin + Metformin arm who received treatment in short-term study (324). Intermediate milestones: subjects entering long-term study (306) and subjects receiving treatment in long-term study (295). Completed = subjects completing long-term study (296). Since Started - Completed = Not Completed and Subject Disposition is presented for the overall study, those subjects not entering the long-term study (18) are indicated as non-completers.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Started = subjects randomized to Dapagliflozin + Saxagliptin + Metformin arm who received treatment in short-term study (319). Intermediate milestones: subjects entering long-term study (294) and subjects receiving treatment in long-term study (284). Completed = subjects completing long-term study (287). Since Started - Completed = Not Completed and Subject Disposition is presented for the overall study, those subjects not entering the long-term study (25) are indicated as non-completers.

Baseline characteristics

Reporting groups

Reporting group title	Dapagliflozin + Saxagliptin + Metformin

Reporting group description:

Subjects received dapagliflozin 10 mg and saxagliptin 5 mg, administered orally QD in the morning for the 52-week treatment period (24-week short-term period and 28-week long term period).
Subjects continued to receive their stable dose of metformin with or without SU throughout the study.

Reporting group title	Titrated Insulin + Metformin

Reporting group description:

Subjects were to administer insulin glargine subcutaneously QD at the same time every day for the 52-week treatment period (24-week short-term period and 28-week long term period), following investigator instructions and training. All subjects started with an initial dose of 0.2 units/kg body weight or at least 10 units of insulin per day. Subjects self-titrated the dose of insulin glargine over the first 8 weeks of the study based on daily glucose monitoring. The investigator had the discretion to modify insulin dose based on his/her assessment between Week 8 and Week 12 with the goal to reach an acceptable and stable insulin dose by Week 12.
Subjects continued to receive their stable dose of metformin with or without SU throughout the study.

Reporting group values	Dapagliflozin + Saxagliptin + Metformin	Titrated Insulin + Metformin	Total
Number of subjects	324	319	643
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)	265	260	525
From 65-84 years	59	59	118
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	55.7	55.3	
standard deviation	± 9.52	± 9.63	-
Sex: Female, Male Units: Subjects			
Female	148	148	296
Male	176	171	347
Race, Customized Units: Subjects			
American Indian Or Alaska Native|	12	6	18
Asian|	12	12	24
Black Or African American|	28	35	63
Native Hawaiian Or Other Pacific Islander|	0	1	1
Other|	9	11	20
White|	263	254	517

End points

End points reporting groups

Reporting group title	Dapagliflozin + Saxagliptin + Metformin

Reporting group description:

Subjects received dapagliflozin 10 mg and saxagliptin 5 mg, administered orally QD in the morning for the 52-week treatment period (24-week short-term period and 28-week long term period).
Subjects continued to receive their stable dose of metformin with or without SU throughout the study.

Reporting group title	Titrated Insulin + Metformin

Reporting group description:

Subjects were to administer insulin glargine subcutaneously QD at the same time every day for the 52-week treatment period (24-week short-term period and 28-week long term period), following investigator instructions and training. All subjects started with an initial dose of 0.2 units/kg body weight or at least 10 units of insulin per day. Subjects self-titrated the dose of insulin glargine over the first 8 weeks of the study based on daily glucose monitoring. The investigator had the discretion to modify insulin dose based on his/her assessment between Week 8 and Week 12 with the goal to reach an acceptable and stable insulin dose by Week 12.
Subjects continued to receive their stable dose of metformin with or without SU throughout the study.

Primary: Mean change from baseline in HbA1c at Week 24

End point title	Mean change from baseline in HbA1c at Week 24

End point description:

To examine whether the mean change from baseline in HbA1c with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU is noninferior (noninferiority margin of 0.3%) to titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.
Analysis performed on the randomized subjects data set, consisting of all randomized subjects who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Baseline and Week 24

End point values	Dapagliflozin + Saxagliptin + Metformin	Titrated Insulin + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	319	312		
Units: % HbA1c				
least squares mean (confidence interval 95%)	-1.67 (-1.79 to -1.55)	-1.54 (-1.66 to -1.42)		

Statistical analyses

Statistical analysis title	Change in HbA1c
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Titrated Insulin + Metformin

Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.118 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.085

Notes:

[1] - Non-inferiority was defined by upper bound of 95% CI <0.3%

[2] - Superiority

Secondary: Mean change from baseline in total body weight at Week 24

End point title	Mean change from baseline in total body weight at Week 24

End point description:

To compare the mean change from baseline in total body weight with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment. Analysis performed on subjects in the randomized subject data set with non-missing baseline assessments and at least one post-baseline assessment.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Dapagliflozin + Saxagliptin + Metformin	Titrated Insulin + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	319	313		
Units: kg				
least squares mean (confidence interval 95%)	-1.50 (-1.89 to -1.11)	2.14 (1.75 to 2.54)		

Statistical analyses

Statistical analysis title	Change in total body weight
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Titrated Insulin + Metformin

Number of subjects included in analysis	632
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	-3.09
Variability estimate	Standard error of the mean
Dispersion value	0.282

Secondary: Percentage of subjects with confirmed hypoglycemia at Week 24

End point title	Percentage of subjects with confirmed hypoglycemia at Week 24

End point description:

Hypoglycemia defined as plasma glucose ≤70 mg/dL (3.9 mmol/L). Analysis performed on the randomized subjects data set, consisting of all randomized subjects who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Dapagliflozin + Saxagliptin + Metformin	Titrated Insulin + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	319		
Units: Adjusted % Participants				
number (confidence interval 95%)	21.3 (17.03 to 26.22)	38.4 (32.94 to 44.07)		

Statistical analyses

Statistical analysis title	Confirmed hypoglycemia
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Titrated Insulin + Metformin

Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.62

Secondary: Percentage of subjects achieving a therapeutic glycemic response, without hypoglycaemia, at Week 24

End point title	Percentage of subjects achieving a therapeutic glycemic response, without hypoglycaemia, at Week 24

End point description:

To compare the percentage of subjects achieving a therapeutic glycemic response, defined as HbA1c <7.0%, without any reported hypoglycemia, with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment. Analysis performed on the randomized subjects data set, consisting of all randomized subjects who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Dapagliflozin + Saxagliptin + Metformin	Titrated Insulin + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	319		
Units: Adjusted % Participants				
number (confidence interval 95%)	20.9 (16.69 to 25.83)	13.1 (9.72 to 17.33)		

Statistical analyses

Statistical analysis title	Glycemic response/no hypoglycemia
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Titrated Insulin + Metformin

Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	2.67

Secondary: Percentage of subjects achieving a therapeutic glycemic response at Week 24

End point title	Percentage of subjects achieving a therapeutic glycemic response at Week 24

End point description:

To examine whether the percentage of subjects achieving a therapeutic glycemic response, defined as HbA1c <7.0%, with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU is noninferior (noninferiority margin of 10%) to titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment. Analysis performed on the randomized subjects data set, consisting of all randomized subjects who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Dapagliflozin + Saxagliptin + Metformin	Titrated Insulin + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	319		
Units: Adjusted % Participants				
number (confidence interval 95%)	33.2 (28.00 to 38.79)	33.5 (28.28 to 39.26)		

Statistical analyses

Statistical analysis title	Therapeutic glycemic response
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Titrated Insulin + Metformin

Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Adjusted Percent Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.42
upper limit	6.54

Notes:

[3] - Non-inferiority was defined by lower bound of 95% CI >-10%.

Secondary: Change from baseline in the mean value of 24-hour glucose at Week 2

End point title	Change from baseline in the mean value of 24-hour glucose at Week 2

End point description:

Change from baseline in the mean value of 24-hour glucose readings measured by Continuous Glucose Monitoring with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU is noninferior to titrated insulin glargine plus metformin with or without SU after 2 weeks of open-label treatment. Analysis performed on the randomized subjects data set, consisting of all randomized subjects who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Baseline and Week 2

End point values	Dapagliflozin + Saxagliptin + Metformin	Titrated Insulin + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	133		
Units: mg/deciliter (dL)				
least squares mean (confidence interval 95%)	-48.53 (-53.47 to -43.59)	-28.54 (-33.47 to -23.61)		

Statistical analyses

Statistical analysis title	Change in 24-h glucose
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Titrated Insulin + Metformin
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-19.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.98
upper limit	-13
Variability estimate	Standard error of the mean
Dispersion value	3.55

Notes:

[4] - Non-inferiority was defined by upper bound of 95% CI <12 mg/dL.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline (Day 1) up to Week 52 (24-week short-term treatment period + 28-week long-term treatment period).

Adverse event reporting additional description:

Adverse event (AE) data is reported for the treated subject data set, and included AEs with an onset date on or after the date of first dose of short-term study treatment and up to and including 30 days following the date of last dose of short-term + long-term study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Dapagliflozin + Saxagliptin + Metformin

Reporting group description:

Subjects received dapagliflozin 10 mg and saxagliptin 5 mg, administered orally QD in the morning for the 52-week treatment period (24-week short-term period and 28-week long term period).
Subjects continued to receive their stable dose of metformin with or without sulfonylurea throughout the study.

Reporting group title	Titrated Insulin + Metformin

Reporting group description:

Subjects were to administer insulin glargine subcutaneously QD at the same time every day for the 52-week treatment period (24-week short-term period and 28-week long term period), following investigator instructions and training. All subjects started with an initial dose of 0.2 units/kilogram (kg) body weight or at least 10 units of insulin per day. Subjects self-titrated the dose of insulin glargine over the first 8 weeks of the study based on daily glucose monitoring. The investigator had the discretion to modify insulin dose based on his/her assessment between Week 8 and Week 12 with the goal to reach an acceptable and stable insulin dose by Week 12.
Subjects continued to receive their stable dose of metformin with or without SU throughout the study.

Serious adverse events	Dapagliflozin + Saxagliptin + Metformin	Titrated Insulin + Metformin	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 324 (6.17%)	13 / 319 (4.08%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroadenoma of breast			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer female			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic stress disorder			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			

subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 324 (0.31%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative hernia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lisfranc fracture			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 324 (0.31%)	2 / 319 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 324 (0.62%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	3 / 324 (0.93%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Femoral hernia incarcerated			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders			
Hidradenitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary bladder polyp			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 324 (0.31%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gangrene			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dapagliflozin + Saxagliptin + Metformin	Titrated Insulin + Metformin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 324 (16.98%)	73 / 319 (22.88%)	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 324 (3.70%)	22 / 319 (6.90%)	
occurrences (all)	15	24	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	17 / 324 (5.25%)	23 / 319 (7.21%)	
occurrences (all)	24	26	
Viral upper respiratory tract infection			
subjects affected / exposed	25 / 324 (7.72%)	19 / 319 (5.96%)	
occurrences (all)	28	24	
Influenza			
subjects affected / exposed	8 / 324 (2.47%)	16 / 319 (5.02%)	
occurrences (all)	8	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2016	Addition of discontinuation guidelines due to ketoacidosis, clarification of starting insulin dose to 0.2 units/kg body weight or at least 10 units of insulin per day and addition of language describing investigator modification of insulin-dose titration, and removal of details about discontinuation due to hypoglycemia during the lead-in period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported