Clinical trial results:
A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3b Trial with a Blinded 104-week Long-term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin in Combination with Metformin Compared to Glimepiride in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone

Summary

EudraCT number	2014-003721-18
Trial protocol	CZ DE HU SE PL RO
Global end of trial date	18 September 2019

Results information

Result version number	v1 (current)
This version publication date	24 June 2020
First version publication date	24 June 2020

Trial information

Trial identification

Sponsor protocol code	CV181-365

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02419612
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, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@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	18 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 August 2017
Global end of trial reached?	Yes
Global end of trial date	18 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the mean change from baseline in haemoglobin A1c (HbA1c) achieved with saxagliptin in co-administration with dapagliflozin added to current background therapy with metformin, compared with glimepiride added to current background therapy with metformin at Week 52.

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 on Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics. Subjects could discontinue the investigational product and assessments at any time at the discretion of the investigator(s). Subjects were also free to withdraw from the study at any time, without prejudice to further treatment.

Background therapy:

Subjects should have been taking the same daily dose of metformin ≥1500 milligrams (mg) for at least 8 weeks prior to the enrollment visit and must not have taken any other antihyperglycemic therapy for more than 14 days (consecutive or not) during 12 weeks prior to screening.

Evidence for comparator:

The active comparator was glimepiride plus background therapy with metformin. Glimepiride, a sulfonylurea (SU), is a widely used antidiabetic treatment. Glimepiride was prescribed according to its approved label. Data from clinical studies indicate that the overall incidence of AEs associated with glimepiride was generally lower compared with other SUs, including a lower risk of hypoglycaemia and weight gain. Key limitations of SU therapies, such as glimepiride, include weight gain and increased risk of hypoglycaemia. Saxagliptin and dapagliflozin have demonstrated a low propensity for hypoglycaemia and either demonstrated weight neutrality (saxagliptin) or moderate weight reduction (dapagliflozin).

Actual start date of recruitment	14 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 112
Country: Number of subjects enrolled	Mexico: 76
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Poland: 73
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 2

Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	Hungary: 71
Country: Number of subjects enrolled	Romania: 51
Worldwide total number of subjects	444
EEA total number of subjects	227

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)	354
From 65 to 84 years	90
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 444 subjects were randomized in this international, multi-center study which was conducted at 88 centers in 10 countries between 14 Aug 2015 and 18 September 2019.

Pre-assignment

Screening details:

The study duration was up to 160 weeks, consisting of a 2-week screening period, 2-week lead-in period, 52-week short-term treatment period, and 104-week long-term treatment period (156 week treatment period). One subject did not start the short-term treatment period and so only 443 subjects received treatment.

Period 1

Period 1 title	Short-Term Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 10mg and Saxagliptin 5mg

Arm description:

Subjects received dapagliflozin 10 mg, saxagliptin 5 mg plus placebo for glimepiride, each administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 10 mg, 1 tablet given orally once daily.

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:

Saxagliptin 5 mg, 1 tablet given orally once daily.

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

Dosage and administration details:

Placebo for glimepiride 1, 2, or 4 mg capsules, given orally once daily.

Arm title	Titrated Glimepiride

Arm description:

Subjects received titrated glimepiride 1, 2, 3, 4, or 6 mg plus placebo for saxagliptin and placebo for dapagliflozin, administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.

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

Dosage and administration details:

Glimepiride 1, 2, or 4 mg capsules, given orally once daily.

Investigational medicinal product name	Placebo for dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for dapagliflozin 10 mg, 1 tablet given orally once daily.

Investigational medicinal product name	Placebo for saxagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for saxagliptin 5 mg, 1 tablet given orally once daily.

Number of subjects in period 1[1]	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride
Started	227	216
Completed	210	194
Not completed	17	22
Adverse event, serious fatal	-	2
Adverse event, non-fatal	1	1
Unspecified	1	4
Consent withdrawn by subject	9	9
Lost to follow-up	6	6

Notes:

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

Justification: One subject that was randomized did not receive treatment and was not included in the baseline population.

Period 2

Period 2 title	Long-Term Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes

Arm title	Dapagliflozin 10mg and Saxagliptin 5mg

Arm description:

Subjects received dapagliflozin 10 mg, saxagliptin 5 mg plus placebo for glimepiride, each administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 10 mg, 1 tablet given orally once daily.

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

Dosage and administration details:

Placebo for glimepiride 1, 2, or 4 mg capsules, given orally once daily.

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:

Saxagliptin 5 mg, 1 tablet given orally once daily.

Arm title	Titrated Glimepiride

Arm description:

Subjects received titrated glimepiride 1, 2, 3, 4, or 6 mg plus placebo for saxagliptin and placebo for dapagliflozin, administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.

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

Dosage and administration details:

Glimepiride 1, 2, or 4 mg capsules, given orally once daily.

Investigational medicinal product name	Placebo for dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for dapagliflozin 10 mg, 1 tablet given orally once daily.

Investigational medicinal product name	Placebo for saxagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for saxagliptin 5 mg, 1 tablet given orally once daily.

Number of subjects in period 2[2]	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride
Started	196	186
Recevied Treatment	196	183
Completed	174	164
Not completed	22	22
Subject Decision	2	4
Non-compliance with Study Drug	1	1
Lack of efficacy	1	1
Adverse event, serious fatal	-	1
Adverse event, non-fatal	-	5
Consent withdrawn by subject	8	2
Unspecified	4	4
Lost to follow-up	6	4

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not all subjects that completed the previous short-term treatment period were eligible to enter the long-term treatment period. Subjects are included in the treatment group to which they were randomized at the start of the short-term double-blind treatment period.

Baseline characteristics

Reporting groups	
Reporting group title	Dapagliflozin 10mg and Saxagliptin 5mg
Reporting group description:	
Subjects received dapagliflozin 10 mg, saxagliptin 5 mg plus placebo for glimepiride, each administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.	
Reporting group title	Titrated Glimepiride
Reporting group description:	
Subjects received titrated glimepiride 1, 2, 3, 4, or 6 mg plus placebo for saxagliptin and placebo for dapagliflozin, administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.	

Reporting group values	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride	Total
Number of subjects	227	216	443
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)	182	171	353
From 65-84 years	45	45	90
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	56.1	56.1	
standard deviation	± 10.11	± 9.23	-
Gender, Male/Female Units:			
Female	110	115	225
Male	117	101	218
Race/Ethnicity, Customized Units: Subjects			
American Indian Or Alaska Native	11	10	21
Black Or African American	4	5	9
Native Hawaiian Or Other Pacific Islander	0	1	1
Other	6	4	10
White	206	196	402

End points

End points reporting groups

Reporting group title	Dapagliflozin 10mg and Saxagliptin 5mg
Reporting group description:	
Subjects received dapagliflozin 10 mg, saxagliptin 5 mg plus placebo for glimepiride, each administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.	
Reporting group title	Titrated Glimepiride
Reporting group description:	
Subjects received titrated glimepiride 1, 2, 3, 4, or 6 mg plus placebo for saxagliptin and placebo for dapagliflozin, administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.	
Reporting group title	Dapagliflozin 10mg and Saxagliptin 5mg
Reporting group description:	
Subjects received dapagliflozin 10 mg, saxagliptin 5 mg plus placebo for glimepiride, each administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.	
Reporting group title	Titrated Glimepiride
Reporting group description:	
Subjects received titrated glimepiride 1, 2, 3, 4, or 6 mg plus placebo for saxagliptin and placebo for dapagliflozin, administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.	
Subject analysis set title	Dapagliflozin 10mg and Saxagliptin 5mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects received dapagliflozin 10 mg, saxagliptin 5 mg plus placebo for glimepiride, each administered orally once daily over the 156-week treatment period. Subjects also continued to receive their metformin dose of at least 1500 mg per day.	
Subject analysis set title	Titrated Glimepiride
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects received titrated glimepiride 1, 2, 3, 4, or 6 mg plus placebo for saxagliptin and placebo for dapagliflozin, administered orally once daily over the 156-week treatment period. Subjects also continued to receive their metformin dose of at least 1500 mg per day.	

Primary: Change from Baseline in HbA1c at Week 52

End point title	Change from Baseline in HbA1c at Week 52
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 is superior to titrated glimepiride plus metformin after 52 weeks of double-blind treatment.	
End point type	Primary
End point timeframe:	
Baseline and Week 52	

End point values	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	212		
Units: % HbA1c				
least squares mean (confidence interval	-1.35 (-1.49 to	-0.98 (-1.12 to		

95%)	-1.22)	-0.84)

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Dapagliflozin 10mg and Saxagliptin 5mg v Titrated Glimepiride
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	-0.18
Variability estimate	Standard error of the mean
Dispersion value	0.099

Secondary: Change from Baseline in Total Body Weight at Week 52

End point title	Change from Baseline in Total Body Weight at Week 52
End point description:	
To examine whether the mean change from baseline in total body weight with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin is superior to titrated glimepiride plus metformin after 52 weeks of double-blind treatment.	
End point type	Secondary
End point timeframe:	
Baseline and Week 52	

End point values	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	214		
Units: kg				
least squares mean (confidence interval 95%)	-3.11 (-3.65 to -2.57)	0.95 (0.38 to 1.51)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Dapagliflozin 10mg and Saxagliptin 5mg v Titrated Glimepiride
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-4.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.84
upper limit	-3.28
Variability estimate	Standard error of the mean
Dispersion value	0.397

Secondary: Percentage of Subjects Achieving a Therapeutic Glycemic Response, Defined as HbA1c < 7.0%, at Week 52

End point title	Percentage of Subjects Achieving a Therapeutic Glycemic Response, Defined as HbA1c < 7.0%, at Week 52

End point description:

Therapeutic glycemic response was defined as HbA1c <7.0%. Subjects rescued or discontinued prior to, and subjects with missing measurement at Week 52 were treated as non-responders. The percentage of subjects with a therapeutic glycemic response is based on the logistic regression method with adjustment for baseline HbA1c.

End point type	Secondary

End point timeframe:

At Week 52

End point values	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	216		
Units: Percentage of Subjects				
number (confidence interval 95%)	44.3 (37.45 to 51.32)	34.3 (27.87 to 41.33)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Dapagliflozin 10mg and Saxagliptin 5mg v Titrated Glimepiride
Number of subjects included in analysis	443

Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.29

Secondary: Change from Baseline in Systolic Blood Pressure (SBP) at Week 52

End point title	Change from Baseline in Systolic Blood Pressure (SBP) at Week 52

End point description:

To examine whether the change from baseline in SBP with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin is superior to titrated glimepiride plus metformin after 52 weeks of double-blind treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	214		
Units: mmHg				
least squares mean (confidence interval 95%)	-2.6 (-4.4 to -0.8)	1.0 (-0.9 to 2.9)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Dapagliflozin 10mg and Saxagliptin 5mg v Titrated Glimepiride
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-3.6
Confidence interval	
level	95 %

sides	2-sided
lower limit	-6.3
upper limit	-1
Variability estimate	Standard error of the mean
Dispersion value	1.35

Secondary: Percentage of Subjects with Treatment Intensification During the 52 Week Short-term Treatment Period

End point title	Percentage of Subjects with Treatment Intensification During the 52 Week Short-term Treatment Period

End point description:

Treatment intensification was defined as the addition of insulin or other glucose-lowering agent for rescue therapy or discontinuation for lack of glycemic control. Time to treatment intensification was censored at end of the 52-week treatment period if treatment intensification had not occurred by then. Subjects rescued at Week 52 were counted as having an event for the analysis. The values presented are the percentage of subjects requiring the addition of insulin or other glucose lowering agent for rescue therapy or discontinuation for lack of glycemic control during the 52-week short-term treatment period.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	216		
Units: Percentage of Subjects				
number (not applicable)	1.3	8.8		

Statistical analyses

Statistical analysis title	Treatment Comparison

Statistical analysis description:

Time to treatment intensification was analyzed using a Cox proportional hazards model.

Comparison groups	Dapagliflozin 10mg and Saxagliptin 5mg v Titrated Glimepiride
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [1]
Method	Regression, Cox Proportional Hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided

lower limit	0.04
upper limit	0.5

Notes:

[1] - This endpoint did not meet the required number of events (n=10) in each treatment arm, hence was excluded from sequential testing.

Secondary: Percentage of Subjects with Treatment Intensification During the 156-Week Short-term plus Long-Term Treatment Period.

End point title	Percentage of Subjects with Treatment Intensification During the 156-Week Short-term plus Long-Term Treatment Period.

End point description:

Treatment intensification was defined as the addition of insulin or other glucose-lowering agent for rescue therapy or discontinuation for lack of glycemic control. Time to treatment intensification was censored at end of 156-week treatment period if treatment intensification had not occurred by then. Subjects rescued at Week 156 were counted as having an event for the analysis. The values presented are the percentage of subjects requiring the addition of insulin or other glucose lowering agent for rescue therapy or discontinuation for lack of glycemic control during the 156-week short-term plus long-term treatment period.

End point type	Secondary

End point timeframe:

Up to Week 156

End point values	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	216		
Units: Percentage of Subjects				
number (not applicable)	37.0	55.6		

Statistical analyses

Statistical analysis title	Treatment Comparison

Statistical analysis description:

Time to treatment intensification was analyzed using a Cox proportional hazards model.

Comparison groups	Dapagliflozin 10mg and Saxagliptin 5mg v Titrated Glimepiride
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox Proportional Hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.68

Secondary: Percentage of Subjects Achieving a Therapeutic Glycemic Response, Defined as HbA1c < 7.0%, at Week 156

End point title	Percentage of Subjects Achieving a Therapeutic Glycemic Response, Defined as HbA1c < 7.0%, at Week 156

End point description:

Therapeutic glycemic response was defined as HbA1c <7.0%. Subjects rescued or discontinued prior to, and subjects with missing measurement at Week 156 were treated as non-responders. The percentage of subjects with a therapeutic glycemic response is based on the logistic regression method with adjustment for baseline HbA1c.

End point type	Secondary

End point timeframe:

At Week 156

End point values	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	216		
Units: Percentage of Subjects				
number (confidence interval 95%)	21.4 (16.30 to 27.64)	11.7 (8.03 to 16.82)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Dapagliflozin 10mg and Saxagliptin 5mg v Titrated Glimepiride
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	3.42
Variability estimate	Standard error of the mean
Dispersion value	0.54

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs), including serious adverse events (SAEs), were collected on or after the date of first dose of short-term study medication and up to and including 4 days (other AEs) or 30 days (SAEs) after last dose. Up to a total of 160 weeks.

Adverse event reporting additional description:

The treated subjects data set for the short-tem plus long-term treatment period consisted of all subjects who received at least 1 dose of double-blind study medication during the short-term double-blind treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Dapagliflozin 10mg and Saxagliptin 5mg

Reporting group description:

Subjects received dapagliflozin 10 mg, saxagliptin 5 mg plus placebo for glimepiride, each administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.

Reporting group title	Titrated Glimepiride

Reporting group description:

Subjects received titrated glimepiride 1, 2, 3, 4, or 6 mg plus placebo for saxagliptin and placebo for dapagliflozin, administered orally once daily. Subjects also continued to receive their metformin dose of at least 1500 mg per day.

Serious adverse events	Dapagliflozin 10mg and Saxagliptin 5mg	Titrated Glimepiride	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 227 (12.78%)	24 / 216 (11.11%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	1	3	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 227 (0.44%)	1 / 216 (0.46%)	
occurrences causally related to	0 / 1	0 / 1	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal cancer			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 227 (0.44%)	2 / 216 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

subjects affected / exposed	2 / 227 (0.88%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
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			
Uterine haemorrhage			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 227 (0.44%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Limb traumatic amputation			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hormone level abnormal			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
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	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 227 (0.00%)	2 / 216 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vertebrobasilar insufficiency			
subjects affected / exposed	2 / 227 (0.88%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Obstructive pancreatitis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 227 (0.88%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 227 (0.88%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Hypoglycaemia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 227 (0.44%)	2 / 216 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 227 (0.44%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall infection			

subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 227 (0.00%)	1 / 216 (0.46%)	
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 10mg and Saxagliptin 5mg	Titrated Glimepiride	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 227 (43.61%)	106 / 216 (49.07%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 227 (3.08%)	18 / 216 (8.33%)	
occurrences (all)	7	18	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 227 (7.93%)	16 / 216 (7.41%)	
occurrences (all)	21	20	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 227 (4.41%)	12 / 216 (5.56%)	
occurrences (all)	11	13	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 227 (5.29%)	7 / 216 (3.24%)	
occurrences (all)	16	8	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	2 / 227 (0.88%)	13 / 216 (6.02%)	
occurrences (all)	2	14	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	23 / 227 (10.13%)	21 / 216 (9.72%)	

occurrences (all)	29	27	
Bronchitis			
subjects affected / exposed	11 / 227 (4.85%)	17 / 216 (7.87%)	
occurrences (all)	15	21	
Influenza			
subjects affected / exposed	9 / 227 (3.96%)	12 / 216 (5.56%)	
occurrences (all)	10	16	
Nasopharyngitis			
subjects affected / exposed	14 / 227 (6.17%)	19 / 216 (8.80%)	
occurrences (all)	20	25	
Pharyngitis			
subjects affected / exposed	6 / 227 (2.64%)	12 / 216 (5.56%)	
occurrences (all)	9	13	
Urinary tract infection			
subjects affected / exposed	31 / 227 (13.66%)	21 / 216 (9.72%)	
occurrences (all)	41	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2015	This amendment added a pharmacogenetics substudy, and amended exploratory pharmacogenetics objectives, informed consent, sample collection, and inclusion and exclusion criteria.
11 March 2015	This amendment clarified the use of glimepiride as the active comparator and that subjects with contraindications to glimepiride should be excluded. It also clarified that subjects could re-enroll in the study if they were a pretreatment failure and that a subject may not have taken any other investigational agent within 30 days prior to study entry. It also clarified that other glucose lowering agents should be considered for rescue therapy.
12 August 2015	This amendment changed discontinuation criterion for creatinine clearance to <60 mL/min and added language for confirmation test.
27 May 2016	This amendment added discontinuation guidelines for ketoacidosis. It also clarified length of time to use contraception, clarified hormonal and nonhormonal forms of contraception, and clarified requirements for vasectomy as a form of contraception. It also defined that subjects with unevaluable data would be removed from the substudies but retained in the base study.
08 February 2018	This amendment added details regarding the Diabetic Ketoacidosis Adjudication Committee and clarification around liver function test abnormalities, adverse events including those leading to lower limb amputation and those with potential risk factor for amputations, confirmed hypoglycemia, magnetic resonance imaging, pregnancy, blinding, investigational medicinal products, efficacy analyses, rescue therapies, and prohibited treatments. It also clarified the definition of the end of the study and incorporated administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported