Clinical trial results:
A Phase III, Multicenter, Randomized, Double-Blind, Active-Comparator-Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Ertugliflozin (MK-8835/PF-04971729) Compared With the Addition of Glimepiride in Subjects With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin

Summary

EudraCT number	2013-003582-34
Trial protocol	CZ LT HU SK RO
Global end of trial date	18 April 2017

Results information

Result version number	v1 (current)
This version publication date	26 April 2018
First version publication date	26 April 2018

Trial information

Trial identification

Sponsor protocol code	8835-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01999218
WHO universal trial number (UTN)	-
Other trial identifiers	Merck protocol number: MK-8835-002

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the efficacy and safety of the addition of ertugliflozin (MK-8835/PF04971729) compared with the addition of glimepiride in participants with T2DM who have inadequate glycemic control on metformin. The duration of the trial will be up to approximately 122 weeks. This will include a 1-week screening period, an up to 13-week wash-off/titration/dose stabilization period, a 2-week placebo run-in period, a 104-week double-blind, active comparator-controlled treatment period, and a posttreatment telephone contact 14 days after the last dose of study drug. The primary hypothesis of this study is that after 52 weeks, the change from baseline in hemoglobin A1c (A1C) in participants treated with the addition of ertugliflozin 15 mg once daily is non-inferior compared with that in participants treated with the addition of glimepiride.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

The following additional measures defined for this individual study were in place for the protection of trial participants: During Year 1, participants who were on the maximum labeled dose (6 or 8 mg q.d.) or maximum tolerated dose (if lower than maximum dose) of glimepiride/matching placebo for at least two weeks and who met progressively more stringent glycemic rescue criteria received open-label sitagliptin glycemic rescue medication. The dose of sitagliptin was initiated according to the local country label.

Background therapy:

Participants remained on their stable dose of metformin (≥1500 mg/day) while they received blinded investigational product during the double-blind treatment period.

Evidence for comparator: -

Actual start date of recruitment	16 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 59
Country: Number of subjects enrolled	Canada: 101
Country: Number of subjects enrolled	Czech Republic: 76
Country: Number of subjects enrolled	Hungary: 68
Country: Number of subjects enrolled	Korea, Republic of: 82
Country: Number of subjects enrolled	Lithuania: 28
Country: Number of subjects enrolled	Mexico: 74
Country: Number of subjects enrolled	Philippines: 75

Country: Number of subjects enrolled	Poland: 92
Country: Number of subjects enrolled	Romania: 109
Country: Number of subjects enrolled	Russian Federation: 120
Country: Number of subjects enrolled	Slovakia: 84
Country: Number of subjects enrolled	South Africa: 38
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	Ukraine: 20
Country: Number of subjects enrolled	United States: 283
Worldwide total number of subjects	1326
EEA total number of subjects	457

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)	990
From 65 to 84 years	335
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in Argentina, Canada, Czech Republic, Hungary, South Korea, Lithuania, Mexico, Philippines, Poland, Romania, Russia, Slovakia, South Africa, Taiwan, Ukraine, and the United States. Male and female participants with Type 2 diabetes mellitus of at least 18 years of age were screened for enrollment in this trial.

Pre-assignment

Screening details:

A total of 1326 participants were randomized. Ten randomized participants from one trial site were excluded from all final analyses (Week 104 and beyond), and one randomized participant did not receive treatment.

Period 1

Period 1 title	Study Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Ertugliflozin 5 mg

Arm description:

Ertugliflozin 5 mg once daily (QD) from Day 1 to Week 104

Arm type	Experimental
Investigational medicinal product name	Ertugliflozin (MK-8835)
Investigational medicinal product code	
Other name	MK-8835
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ertugliflozin 5 mg once daily (QD) from Day 1 to Week 104

Arm title	Ertugliflozin 15 mg

Arm description:

Ertugliflozin 15 mg QD from Day 1 to Week 104

Arm type	Experimental
Investigational medicinal product name	Ertugliflozin (MK-8835)
Investigational medicinal product code	
Other name	MK-8835
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ertugliflozin 15 mg QD from Day 1 to Week 104

Arm title	Glimepiride

Arm description:

Glimepiride to a maximum of 8 mg QD from Day 1 to Week 104

Arm type	Active comparator

Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Glimepiride to a maximum of 8 mg QD from Day 1 to Week 104

Number of subjects in period 1	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride
Started	448	441	437
Treated	448	440	437
Treated (excluding 1 trial site)	445	435	435
Completed	339	340	327
Not completed	109	101	110
Adverse event, serious fatal	7	1	2
Physician decision	1	4	6
Screen failure	-	1	-
Hyperglycemia	18	17	17
Consent withdrawn by subject	28	29	34
Treated but excluded at 1 trial site	3	5	2
Participant moves	2	5	3
Excluded Medication	1	1	2
Creatinine/eGFR	-	-	1
Study Terminated By Sponsor	7	5	12
Adverse event, non-fatal	9	7	7
Non-Compliance With Study Drug	6	4	1
Lost to follow-up	22	17	18
Lack of efficacy	1	-	1
Protocol deviation	4	5	4

Baseline characteristics

Reporting groups	
Reporting group title	Ertugliflozin 5 mg
Reporting group description:	
Ertugliflozin 5 mg once daily (QD) from Day 1 to Week 104	
Reporting group title	Ertugliflozin 15 mg
Reporting group description:	
Ertugliflozin 15 mg QD from Day 1 to Week 104	
Reporting group title	Glimepiride
Reporting group description:	
Glimepiride to a maximum of 8 mg QD from Day 1 to Week 104	

Reporting group values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride
Number of subjects	448	441	437
Age categorical			
The analysis population included all randomized participants.			
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)	327	329	334
From 65-84 years	120	112	103
85 years and over	1	0	0
Age Continuous			
The analysis population included all randomized participants.			
Units: years			
arithmetic mean	58.8	58.0	57.8
standard deviation	± 9.7	± 9.9	± 9.2
Sex: Female, Male			
The analysis population included all randomized participants.			
Units: Subjects			
Female	221	250	213
Male	227	191	224
Race (NIH/OMB)			
The analysis population included all randomized participants.			
Units: Subjects			
American Indian or Alaska Native	5	3	5
Asian	81	86	73
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	17	19	25
White	332	316	318
More than one race	13	17	16
Unknown or Not Reported	0	0	0

Prior Antihyperglycemic Medication (Monotherapy or Dual Therapy)			
All randomized participants with information on or baseline data of prior antihyperglycemic medication use			
Units: Subjects			
Prior Antihyperglycemic Medication	448	439	437
No Prior Use & Not on Antihyperglycemic Medication	0	1	0
Data not available	0	1	0
Body Weight			
The analysis population included all randomized and treated participants (N=448, 440, 437).			
Units: Kilograms			
arithmetic mean	87.9	85.6	86.8
standard deviation	± 18.9	± 19.1	± 20.7
Hemoglobin A1C			
The analysis population included all randomized participants with a baseline A1C measurement (N=448, 440, 437).			
Units: Percentage			
arithmetic mean	7.81	7.80	7.76
standard deviation	± 0.60	± 0.60	± 0.60
Sitting Systolic Blood Pressure			
The analysis population included all randomized participants with a baseline sitting systolic blood pressure measurement (N=448, 440, 437).			
Units: Millimeters of mercury			
arithmetic mean	130.2	130.8	129.9
standard deviation	± 12.8	± 12.4	± 12.0
Estimated Glomerular Filtration Rate (eGFR)			
The analysis population included all randomized and treated participants (N=448, 440, 437).			
Units: milliliters/minute/1.73 meters^2			
arithmetic mean	88.3	86.7	86.6
standard deviation	± 18.7	± 18.3	± 18.5

Reporting group values	Total		
Number of subjects	1326		
Age categorical			
The analysis population included all randomized participants.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	990		
From 65-84 years	335		
85 years and over	1		
Age Continuous			
The analysis population included all randomized participants.			
Units: years			
arithmetic mean			
standard deviation	-		

Sex: Female, Male			
The analysis population included all randomized participants.			
Units: Subjects			
Female	684		
Male	642		
Race (NIH/OMB)			
The analysis population included all randomized participants.			
Units: Subjects			
American Indian or Alaska Native	13		
Asian	240		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	61		
White	966		
More than one race	46		
Unknown or Not Reported	0		
Prior Antihyperglycemic Medication (Monotherapy or Dual Therapy)			
All randomized participants with information on or baseline data of prior antihyperglycemic medication use			
Units: Subjects			
Prior Antihyperglycemic Medication	1324		
No Prior Use & Not on Antihyperglycemic Medication	1		
Data not available	1		
Body Weight			
The analysis population included all randomized and treated participants (N=448, 440, 437).			
Units: Kilograms			
arithmetic mean			
standard deviation	-		
Hemoglobin A1C			
The analysis population included all randomized participants with a baseline A1C measurement (N=448, 440, 437).			
Units: Percentage			
arithmetic mean			
standard deviation	-		
Sitting Systolic Blood Pressure			
The analysis population included all randomized participants with a baseline sitting systolic blood pressure measurement (N=448, 440, 437).			
Units: Millimeters of mercury			
arithmetic mean			
standard deviation	-		
Estimated Glomerular Filtration Rate (eGFR)			
The analysis population included all randomized and treated participants (N=448, 440, 437).			
Units: milliliters/minute/1.73 meters^2			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Ertugliflozin 5 mg
Reporting group description:	
Ertugliflozin 5 mg once daily (QD) from Day 1 to Week 104	
Reporting group title	Ertugliflozin 15 mg
Reporting group description:	
Ertugliflozin 15 mg QD from Day 1 to Week 104	
Reporting group title	Glimepiride
Reporting group description:	
Glimepiride to a maximum of 8 mg QD from Day 1 to Week 104	

Primary: Change from Baseline in Hemoglobin A1C (A1C) at Week 52: Excluding Rescue Approach

End point title	Change from Baseline in Hemoglobin A1C (A1C) at Week 52: Excluding Rescue Approach
End point description:	
A1C is a blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). A1C represents the percentage of glycated hemoglobin. This change from baseline reflects the Week 52 A1C minus the Week 0 A1C. A negative number indicates a reduction in A1C level. Participants who met glycemic rescue criteria received open-label sitagliptin glycemic rescue medication, and all data following the initiation of rescue therapy were excluded from the analysis. The primary study objective was the MK-8835 15 mg vs. glimepiride comparison; the MK-8835 5mg vs glimerpiride comparison was a secondary study objective. The analysis population included all randomized, treated participants with at least one A1C measurement (baseline or a post-baseline).	
End point type	Primary
End point timeframe:	
Baseline and Week 52	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	448	440	437	
Units: Percent				
least squares mean (confidence interval 95%)	-0.56 (-0.65 to -0.47)	-0.64 (-0.73 to -0.55)	-0.74 (-0.83 to -0.65)	

Statistical analyses

Statistical analysis title	Difference in the Least Squares Means
Statistical analysis description:	
Constrained Longitudinal Data Analysis (cLDA) model with fixed effects for treatment, time, prior antihyperglycemic medication (monotherapy or dual therapy), baseline eGFR (continuous) and the interaction of time by treatment.	
Comparison groups	Ertugliflozin 15 mg v Glimepiride

Number of subjects included in analysis	877
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.22

Notes:

[1] - Non-inferiority is declared if the upper bound of the two-sided 95% confidence interval (CI) for the mean difference is less than 0.3%.

Statistical analysis title	Difference in the Least Squares Means

Statistical analysis description:

Based on cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (monotherapy or dual therapy), baseline eGFR (continuous) and the interaction of time by treatment.

Comparison groups	Ertugliflozin 5 mg v Glimepiride
Number of subjects included in analysis	885
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in the Least Squares means
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.3

Notes:

[2] - Non-inferiority is declared if the upper bound of the two-sided 95% confidence interval (CI) for the mean difference is less than 0.3%.

Primary: Percentage of Participants Experiencing An Adverse Event (AE) Up to Week 106

End point title	Percentage of Participants Experiencing An Adverse Event (AE) Up to Week 106

End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The analysis population included all randomized participants who took at least one dose of trial treatment, 10 randomized participants from one trial site were excluded from these analyzes, and one randomized participant did not receive treatment.

End point type	Primary

End point timeframe:

Up to Week 106

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	445	435	435	
Units: Percentage of Participants				
number (not applicable)	70.1	71.3	69.7	

Statistical analyses

Statistical analysis title	Difference in % vs. Glimepiride
Statistical analysis description: Based on Miettinen & Nurminen method	
Comparison groups	Ertugliflozin 15 mg v Glimepiride
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs. Glimepiride
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	7.7

Statistical analysis title	Difference in % vs. Glimepiride
Statistical analysis description: Based on Miettinen & Nurminen method	
Comparison groups	Ertugliflozin 5 mg v Glimepiride
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs. Glimepiride
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	6.5

Primary: Percentage of Participants Discontinuing Study Treatment Due to an AE Up to Week 104

End point title	Percentage of Participants Discontinuing Study Treatment Due to an AE Up to Week 104

End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding,

symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The analysis population included all randomized participants who took at least one dose of trial treatment, 10 randomized participants from one trial site were excluded from these analyzes, and one randomized participant did not receive treatment.

End point type	Primary

End point timeframe:

Up to Week 104

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	445	435	435	
Units: Percentage of Participants				
number (not applicable)	6.5	8.0	5.1	

Statistical analyses

Statistical analysis title	Difference in % vs. Glimepiride
Statistical analysis description: Based on Miettinen & Nurminen method	
Comparison groups	Ertugliflozin 15 mg v Glimepiride
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs. Glimepiride
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	6.4

Statistical analysis title	Difference in % vs. Glimepiride
Statistical analysis description: Based on Miettinen & Nurminen method	
Comparison groups	Ertugliflozin 5 mg v Glimepiride
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs. Glimepiride
Point estimate	1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	4.7

Secondary: Percentage of Participants with an Adverse Event of Symptomatic Hypoglycemia Up to Week 52: Excluding Rescue Approach

End point title	Percentage of Participants with an Adverse Event of Symptomatic Hypoglycemia Up to Week 52: Excluding Rescue Approach

End point description:

Symptomatic hypoglycemia was an event with clinical symptoms reported by the investigator as hypoglycemia (biochemical documentation not required). Participants who met glycemic rescue criteria received open-label sitagliptin glycemic rescue medication, and all data following the initiation of rescue therapy were excluded from the analysis. The analysis population included all randomized participants who took at least one dose of trial treatment.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	448	440	437	
Units: Percentage of Participants				
number (not applicable)	3.1	5.2	19.2	

Statistical analyses

Statistical analysis title	Difference in % vs. Glimepiride

Statistical analysis description:

Based on Miettinen & Nurminen method

Comparison groups	Ertugliflozin 15 mg v Glimepiride
Number of subjects included in analysis	877
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Based on Miettinen & Nurminen method
Parameter estimate	Difference in % vs. Glimepiride
Point estimate	-14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.4
upper limit	-9.8

Statistical analysis title	Difference in % vs. Glimepiride
Statistical analysis description: Based on Miettinen & Nurminen method	
Comparison groups	Ertugliflozin 5 mg v Glimepiride
Number of subjects included in analysis	885
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Based on Miettinen & Nurminen method
Parameter estimate	Difference in % vs. Glimepiride
Point estimate	-16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.3
upper limit	-12.2

Secondary: Change from Baseline in Body Weight at Week 52 Excluding Rescue Approach

End point title	Change from Baseline in Body Weight at Week 52 Excluding Rescue Approach
End point description: This change from baseline reflects the Week 52 body weight minus the Week 0 body weight. Participants who met glycemic rescue criteria received open-label sitagliptin glycemic rescue medication, and all data following the initiation of rescue therapy were excluded from the analysis. The analysis population included all randomized, treated participants with at least one body weight measurement (baseline or a post-baseline).	
End point type	Secondary
End point timeframe: Baseline and Week 52	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	448	440	437	
Units: Kilograms				
least squares mean (confidence interval 95%)	-2.96 (-3.31 to -2.61)	-3.38 (-3.73 to -3.03)	0.91 (0.56 to 1.25)	

Statistical analyses

Statistical analysis title	Difference in LSM vs. Glimepiride

Statistical analysis description:

Fixed effects for treatment, time, interaction of time by treatment, prior antihyperglycemic medication (monotherapy or dual therapy), and baseline eGFR (continuous).

Comparison groups	Ertugliflozin 15 mg v Glimepiride
Number of subjects included in analysis	877
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Constrained Longitudinal Data analysis
Parameter estimate	Difference in LSM vs. Glimepiride
Point estimate	-4.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.77
upper limit	-3.8

Statistical analysis title	Difference in LSM vs. Glimepiride

Statistical analysis description:

Constrained Longitudinal Data analysis with fixed effects for treatment, time, interaction of time by treatment, prior antihyperglycemic medication (monotherapy or dual therapy), and baseline eGFR (continuous).

Comparison groups	Ertugliflozin 5 mg v Glimepiride
Number of subjects included in analysis	885
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in the LSM vs. Glimepiride
Point estimate	-3.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.36
upper limit	-3.38

Secondary: Change from Baseline in Sitting Systolic Blood Pressure (SBP) at Week 52 Excluding Rescue Approach

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

End point description:

This change from baseline reflects the Week 52 SBP minus the Week 0 SBP. Participants who met glycemic rescue criteria received open-label sitagliptin glycemic rescue medication, and all data following the initiation of rescue therapy were excluded from the analysis. The analysis population included all randomized, treated participants with at least one SBP measurement (baseline or a post-baseline).

End point type	Secondary
End point timeframe:	
Baseline and Week 52	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	448	440	437	
Units: mmHg				
least squares mean (confidence interval 95%)	-2.25 (-3.36 to -1.13)	-3.81 (-4.91 to -2.71)	0.95 (-0.15 to 2.06)	

Statistical analyses

Statistical analysis title	Difference in the LSM vs. Glimepiride
Statistical analysis description:	
Constrained Logitudinal Data Analysis with fixed effects for treatment, time, interaction of time by treatment, prior anthyperglycemic medication (monotherapy or dual therapy), and baseline eGFR (continuous).	
Comparison groups	Ertugliflozin 15 mg v Glimepiride
Number of subjects included in analysis	877
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Constrained Logitudinal Data Analysis
Parameter estimate	Difference in the LSM vs. Glimepiride
Point estimate	-4.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.29
upper limit	-3.25

Statistical analysis title	Difference in the LSM vs. Glimepiride
Statistical analysis description:	
Constrained Logitudinal Data Analysis with fixed effects for treatment, time, interaction of time by treatment, prior anthyperglycemic medication (monotherapy or dual therapy), and baseline eGFR (continuous).	
Comparison groups	Ertugliflozin 5 mg v Glimepiride

Number of subjects included in analysis	885
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Constrained Logitudinal Data Analysis
Parameter estimate	Difference in the LSM vs. Glimepiride
Point estimate	-3.2
Confidence interval	
level	Other: 0 %
sides	2-sided
lower limit	-4.73
upper limit	-1.67

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 106

Adverse event reporting additional description:

The safety analysis population included all randomized participants who took at least one dose of trial treatment, 10 randomized participants from one trial site were excluded from these analyzes, and one randomized participant did not receive treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Ertugliflozin 5 mg

Reporting group description:

Ertugliflozin 5 mg once daily (QD) from Day 1 to Week 104

Reporting group title	Ertugliflozin 15 mg

Reporting group description:

Ertugliflozin 15 mg QD from Day 1 to Week 104

Reporting group title	Glimepiride

Reporting group description:

Glimepiride to a maximum of 8 mg QD from Day 1 to Week 104

Serious adverse events	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 445 (9.21%)	32 / 435 (7.36%)	30 / 435 (6.90%)
number of deaths (all causes)	7	2	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast carcinoma			
subjects affected / exposed	0 / 445 (0.00%)	2 / 435 (0.46%)	0 / 435 (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
Breast ductal carcinoma			

subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Cancer of sigmoid colon (excl rectosigmoid)			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Colon cancer			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Intraductal papilloma of breast			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive breast carcinoma			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Malignant melanoma			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Metatypical basal cell carcinoma			

subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple myeloma			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Ovarian cystadenoma			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Pelvic neoplasm			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Prostate cancer			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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 papillary carcinoma			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubular adenocarcinoma gastric			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Uterine fibroids			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Uterine leiomyoma			

subjects affected / exposed	1 / 445 (0.22%)	1 / 435 (0.23%)	0 / 435 (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
Vascular disorders			
Diabetic peripheral angiopathy			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leg ischaemia			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
General disorders and administration site conditions			
Incarcerated hernia			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Multi-organ failure			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Weakness generalised			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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

Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menometrorrhagia			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adult respiratory distress syndrome			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Asthma aggravated			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choanal polyp			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive airways disease exacerbated			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Chronic obstructive pulmonary disease exacerbation			

subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Obstructive chronic bronchitis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
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 failure			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Vocal cord nodule			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Psychiatric disorders			
Depression aggravated			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Depression worsened			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Recurrent depressive disorder			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerular filtration rate decreased			

subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Face injury			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Knee ligament injury			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee sprain			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Ligament rupture			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Ligament sprain			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar sprain			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Lumbar strain			

subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral (joint) (ligament) sprain			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malleolar fracture			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Neck strain			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pertrochanteric fracture of femur, closed			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Polytraumatism			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Shoulder sprain			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Spinal column injury			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic brain injury			

subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Upper limb fracture			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 445 (0.22%)	1 / 435 (0.23%)	0 / 435 (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
Acute myocardial infarction			
subjects affected / exposed	1 / 445 (0.22%)	1 / 435 (0.23%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Angina pectoris aggravated			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Angina unstable			
subjects affected / exposed	2 / 445 (0.45%)	0 / 435 (0.00%)	2 / 435 (0.46%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation aggravated			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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			
subjects affected / exposed	1 / 445 (0.22%)	1 / 435 (0.23%)	0 / 435 (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
Coronary artery disease			

subjects affected / exposed	2 / 445 (0.45%)	0 / 435 (0.00%)	0 / 435 (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
Myocardial infarction			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Single vessel disease			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Triple vessel disease			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple cerebral infarction			

subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Stroke			
subjects affected / exposed	2 / 445 (0.45%)	0 / 435 (0.00%)	0 / 435 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract aggravated			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chorioretinal folds			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iridocyclitis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratitis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Senile cataract			

subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Anal ulcer			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Gastritis			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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 bleeding			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Umbilical hernia			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Ventral hernia			

subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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 acute			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Cholelithiasis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Chronic calculous cholecystitis			
subjects affected / exposed	0 / 445 (0.00%)	2 / 435 (0.46%)	0 / 435 (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
Jaundice extrahepatic obstructive			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Skin and subcutaneous tissue disorders			
Foot ulcer			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Renal and urinary disorders			
Chronic retention of urine			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Haematuria			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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

Hydronephrosis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Kidney stone			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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 failure acute			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Calcifying tendinitis of shoulder			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Osteoarthritis aggravated			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Pain in thigh			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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

Rotator cuff syndrome			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis NOS			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Vertebral pain			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cervicitis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Diabetic gangrene			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene toe			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Influenza A virus infection			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Klebsiella sepsis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Lobar pneumonia			

subjects affected / exposed	2 / 445 (0.45%)	0 / 435 (0.00%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pelvic inflammatory disease			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Pneumonia			
subjects affected / exposed	1 / 445 (0.22%)	1 / 435 (0.23%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Purulent appendicitis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (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
Recurrent urinary tract infection			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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
Septic shock			
subjects affected / exposed	0 / 445 (0.00%)	1 / 435 (0.23%)	0 / 435 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sigmoid diverticulitis			
subjects affected / exposed	1 / 445 (0.22%)	0 / 435 (0.00%)	0 / 435 (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 / 445 (0.22%)	1 / 435 (0.23%)	0 / 435 (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
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	0 / 445 (0.00%)	0 / 435 (0.00%)	1 / 435 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 445 (24.72%)	104 / 435 (23.91%)	165 / 435 (37.93%)
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 445 (5.62%)	19 / 435 (4.37%)	19 / 435 (4.37%)
occurrences (all)	27	22	20
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 445 (2.92%)	12 / 435 (2.76%)	22 / 435 (5.06%)
occurrences (all)	17	12	24
Infections and infestations			
Common cold			
subjects affected / exposed	21 / 445 (4.72%)	17 / 435 (3.91%)	23 / 435 (5.29%)
occurrences (all)	31	29	31
Upper respiratory tract infection			
subjects affected / exposed	27 / 445 (6.07%)	14 / 435 (3.22%)	18 / 435 (4.14%)
occurrences (all)	39	19	27
Urinary tract infection			
subjects affected / exposed	27 / 445 (6.07%)	28 / 435 (6.44%)	29 / 435 (6.67%)
occurrences (all)	30	33	36
Metabolism and nutrition disorders			
Asymptomatic hypoglycaemia			
subjects affected / exposed	7 / 445 (1.57%)	4 / 435 (0.92%)	27 / 435 (6.21%)
occurrences (all)	11	5	87
Hypoglycaemia			

subjects affected / exposed occurrences (all)	14 / 445 (3.15%) 31	25 / 435 (5.75%) 53	82 / 435 (18.85%) 470

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2015	Amendment 1 - The source for glimepiride/matching placebo changed. The original glimepiride/matching placebo supplies were provided as tablets but were then switched to capsules.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported