Clinical trial results:
A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Ertugliflozin (MK-8835/PF-04971729) in Subjects with Type 2 Diabetes Mellitus with Stage 3 Chronic Kidney Disease Who Have Inadequate Glycemic Control on Background Antihyperglycemic Therapy

Summary

EudraCT number	2013-003587-31
Trial protocol	GB HU BG RO
Global end of trial date	28 September 2016

Results information

Result version number	v1 (current)
This version publication date	21 September 2017
First version publication date	21 September 2017

Trial information

Trial identification

Sponsor protocol code	MK-8835-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01986855
WHO universal trial number (UTN)	-
Other trial identifiers	Pfizer Protocol Number: B1521016

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	28 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 September 2016
Global end of trial reached?	Yes
Global end of trial date	28 September 2016
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 ertugliflozin (MK-8835/PF-04971729) in participants with type 2 diabetes mellitus with Stage 3 Chronic Kidney Disease (CKD) who have inadequate glycemic control on background antihyperglycemic therapy. The duration of this trial will be up to 67 weeks. This will consist of a 1-week Screening Period, a 10-week wash-off period from metformin, if needed, and a 2-week placebo run-in period, a 52-week double-blind treatment period, and a 14-day post-treatment follow-up period. The primary objective of this trial is to assess the Hemoglobin A1C (A1C)-lowering efficacy of the addition of ertugliflozin compared to the addition of placebo with an underlying hypothesis that addition of treatment with ertugliflozin provides greater reduction in A1C compared to the addition of placebo; the primary objective will be tested for both 5-mg and 15-mg doses of ertugliflozin.

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.

Participants who meet progressively more stringent glycemic rescue criteria had their antihyperglycemic agent (AHA) regimen adjusted or initiate treatment with a new AHA medication(s), with intensification of the participant's regimen managed as considered appropriate by the investigator. Participants on insulin should maintain a stable dose unless they meet glycemic rescue criteria.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 25
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	Colombia: 14
Country: Number of subjects enrolled	Hungary: 59
Country: Number of subjects enrolled	Israel: 41
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Philippines: 39
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Romania: 45
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	South Africa: 13

Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	United States: 135
Worldwide total number of subjects	468
EEA total number of subjects	158

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)	163
From 65 to 84 years	301
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 13 countries, including 171 trial centers; 1709 participants were screened and 468 were randomized.

Pre-assignment

Screening details:

Eligible participants began a ≥10-week metformin wash-off during which participant's AHAs could be adjusted. All participants entered a 2-week placebo run-in period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ertugliflozin 5 mg

Arm description:

Ertugliflozin, oral, 5-mg tablet once daily for 52 weeks. Participants also received a 10-mg matching placebo tablet once daily for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Ertugliflozin
Investigational medicinal product code	
Other name	MK-8835 PF-04971729
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral, 5-mg tablet once daily for 52 weeks

Arm title	Ertugliflozin 15 mg

Arm description:

Ertugliflozin, oral, 5-mg and 10-mg tablet once daily for 52 weeks

Arm type	Experimental
Investigational medicinal product name	Ertugliflozin
Investigational medicinal product code	
Other name	MK-8835 PF-04971729
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral, 5-mg and a 10-mg tablet once daily for 52 weeks

Arm title	Placebo

Arm description:

Placebo, oral, tablet, 5-mg or 5-mg and 10-mg tablet once daily for 52 weeks

Arm type	Placebo

Investigational medicinal product name	Placebo to Ertugliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral, 5-mg tablet once daily for 52 weeks or a 5-mg and a 10-mg tablet once daily for 52 weeks

Number of subjects in period 1	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
Started	158	156	154
Treated	158	155	154
Completed	145	142	143
Not completed	13	14	11
Consent withdrawn by subject	7	8	5
Screen Failure	-	1	-
Adverse event, non-fatal	1	-	-
Death	3	4	4
Participant Moved	-	-	2
Lost to follow-up	2	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ertugliflozin 5 mg
Reporting group description:	
Ertugliflozin, oral, 5-mg tablet once daily for 52 weeks. Participants also received a 10-mg matching placebo tablet once daily for 52 weeks.	
Reporting group title	Ertugliflozin 15 mg
Reporting group description:	
Ertugliflozin, oral, 5-mg and 10-mg tablet once daily for 52 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo, oral, tablet, 5-mg or 5-mg and 10-mg tablet once daily for 52 weeks	

Reporting group values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
Number of subjects	158	156	154
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)	50	58	55
From 65-84 years	107	96	98
85 years and over	1	2	1
Age Continuous			
Units: Years			
arithmetic mean	66.7	67.5	67.5
standard deviation	± 8.3	± 8.5	± 8.9
Gender, Male/Female			
Units: Subjects			
Female	74	80	82
Male	84	76	72
Estimated glomerular filtration rate (eGFR)			
Stratification Factor: eGFR (mL/min/1.73m^2)			
Units: Subjects			
≥30 to <45	52	53	54
≥45 to <60	106	103	100
Insulin at randomization			
Stratification Factor: Insulin at randomization? (Yes/No)			
Units: Subjects			
(No)	69	68	66
(Yes)	89	88	88

Baseline A1C			
n=154, 151, 152, 457			
Units: Percentage			
arithmetic mean	8.2	8.17	8.08
standard deviation	± 1.02	± 0.87	± 0.89
Baseline Weight			
Units: Kilograms			
arithmetic mean	89.4	85.8	90.4
standard deviation	± 22.5	± 17.4	± 18.9
Baseline Fasting Plasma Glucose (FPG)			
n=157, 155, 154, 466			
Units: mg/dL			
arithmetic mean	160.7	157.5	156.9
standard deviation	± 56.5	± 47.8	± 56.4

Reporting group values	Total		
Number of subjects	468		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	163		
From 65-84 years	301		
85 years and over	4		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	236		
Male	232		
Estimated glomerular filtration rate (eGFR)			
Stratification Factor: eGFR (mL/min/1.73m^2)			
Units: Subjects			
≥30 to <45	159		
≥45 to <60	309		
Insulin at randomization			
Stratification Factor: Insulin at randomization? (Yes/No)			
Units: Subjects			
(No)	203		
(Yes)	265		
Baseline A1C			
n=154, 151, 152, 457			
Units: Percentage			

arithmetic mean standard deviation	- 		
Baseline Weight Units: Kilograms arithmetic mean standard deviation	- 		
Baseline Fasting Plasma Glucose (FPG)			
n=157, 155, 154, 466			
Units: mg/dL arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Ertugliflozin 5 mg
Reporting group description:	
Ertugliflozin, oral, 5-mg tablet once daily for 52 weeks. Participants also received a 10-mg matching placebo tablet once daily for 52 weeks.	
Reporting group title	Ertugliflozin 15 mg
Reporting group description:	
Ertugliflozin, oral, 5-mg and 10-mg tablet once daily for 52 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo, oral, tablet, 5-mg or 5-mg and 10-mg tablet once daily for 52 weeks	

Primary: Change from Baseline in A1C at Week 26 - Excluding Rescue Approach

End point title	Change from Baseline in A1C at Week 26 - Excluding Rescue Approach
End point description:	
A1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). This change from baseline reflects the Week 26 A1C minus the Week 0 A1C. Excluding rescue approach data analysis excluded all data following the initiation of rescue therapy at any time point, in order to avoid the confounding influence of the rescue therapy. The analysis population included all randomized participants who took at least 1 dose of study treatment and had at least 1 assessment at or after baseline for the change from baseline at Week 26 A1C endpoint.	
End point type	Primary
End point timeframe:	
Baseline and Week 26	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	155	154	
Units: Percentage				
least squares mean (confidence interval 95%)	-0.29 (-0.44 to -0.14)	-0.41 (-0.56 to -0.27)	-0.26 (-0.41 to -0.11)	

Statistical analyses

Statistical analysis title	Difference in the least squares means
Comparison groups	Ertugliflozin 5 mg v Placebo

Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.807 [1]
Method	Constrained longitudinal data anal. cLDA
Parameter estimate	Difference in the least squares means
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.18

Notes:

[1] - The cLDA model included fixed effects for treatment, time, eGFR stratum (<45 or ≥45 mL/min/1.73m^2), baseline treatment with insulin stratum (yes/no) and the interaction of time by treatment. Time was treated as a categorical variable.

Statistical analysis title	Difference in the least squares means
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.155 [2]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in the least squares means
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.06

Notes:

[2] - The cLDA model included fixed effects for treatment, time, eGFR stratum (<45 or ≥45 mL/min/1.73m^2), baseline treatment with insulin stratum (yes/no) and the interaction of time by treatment. Time was treated as a categorical variable.

Primary: Percentage of Participants Who Experienced an Adverse Event (AE)

End point title	Percentage of Participants Who Experienced an Adverse Event (AE)

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 received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

Up to 54 weeks

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	155	154	
Units: Percentage of participants				
number (not applicable)	84.8	74.2	81.2	

Statistical analyses

Statistical analysis title	Difference in Percentages vs. Placebo
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentages vs. Placebo
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	12.1

Statistical analysis title	Difference in Percentages vs. Placebo
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentages vs. Placebo
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.3
upper limit	2.3

Primary: Percentage of Participants Who Discontinued Study Treatment due to an AE

End point title	Percentage of Participants Who Discontinued Study Treatment due to an AE

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 received at least 1 dose of study treatment.

End point type	Primary

End point timeframe: Up to 52 weeks

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	155	154	
Units: Percentage of participants				
number (not applicable)	8.2	3.9	5.2	

Statistical analyses

Statistical analysis title	Difference in Percentages vs. Placebo
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentages vs. Placebo
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	9

Statistical analysis title	Difference in Percentages vs. Placebo
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentages vs. Placebo
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	3.7

Secondary: Change from Baseline in A1C at Week 26 - Baseline eGFR ≥45 to <60 mL/min/1.73m^2 Stratum - Excluding Rescue Approach

End point title	Change from Baseline in A1C at Week 26 - Baseline eGFR ≥45 to <60 mL/min/1.73m^2 Stratum - Excluding Rescue Approach

End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). This change from baseline reflects the Week 26 A1C minus the Week 0 A1C. Excluding rescue approach data analysis excluded all data following the initiation of rescue therapy at any time point, in order to avoid the confounding influence of the rescue therapy. The analysis population included all randomized participants with a Baseline eGFR of ≥45 to <60 mL/min/1.73m^2, who took at least 1 dose of study treatment, and had at least 1 assessment at or after baseline for the change from baseline at Week 26 A1C endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	97	99	
Units: Percentage				
least squares mean (confidence interval 95%)	-0.31 (-0.49 to -0.13)	-0.37 (-0.56 to -0.18)	-0.28 (-0.47 to -0.08)	

Statistical analyses

Statistical analysis title	Difference in the least squares means
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.828 [3]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in the least squares means
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.23

Notes:

[3] - The cLDA model included fixed effects for treatment, time, baseline treatment with insulin stratum (yes/no), and the interaction of time by treatment. Time was treated as a categorical variable.

Statistical analysis title	Difference in the least squares means
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.496 [4]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in the least squares means
Point estimate	-0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.17

Notes:

[4] - The cLDA model included fixed effects for treatment, time, baseline treatment with insulin stratum (yes/no), and the interaction of time by treatment. Time was treated as a categorical variable.

Secondary: Change from Baseline in Body Weight at Week 26 - Baseline eGFR ≥45 to <60 mL/min/1.73m^2 Stratum - Excluding Rescue Approach

End point title	Change from Baseline in Body Weight at Week 26 - Baseline eGFR ≥45 to <60 mL/min/1.73m^2 Stratum - Excluding Rescue Approach

End point description:

This change from baseline reflects the Week 26 body weight minus the Week 0 body weight. Excluding rescue approach data analysis excluded all data following the initiation of rescue therapy at any time point, in order to avoid the confounding influence of the rescue therapy. The analysis population included all randomized participants with a Baseline eGFR of ≥45 to <60 mL/min/1.73m^2, who took at least 1 dose of study treatment, and had at least 1 assessment at or after baseline for the change from baseline at Week 26 body weight endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	97	99	
Units: Kilograms				
least squares mean (confidence interval 95%)	-1.31 (-1.86 to -0.76)	-1.39 (-1.97 to -0.81)	0.46 (-0.13 to 1.04)	

Statistical analyses

Statistical analysis title	Difference in the least squares means
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [5]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in the least squares means
Point estimate	-1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.57
upper limit	-0.96

Notes:

[5] - The cLDA model included fixed effects for treatment, time, baseline treatment with insulin stratum (yes/no) and the interaction of time by treatment. Time was treated as a categorical variable. P-value is nominal.

Statistical analysis title	Difference in the least squares means
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [6]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in the least squares means
Point estimate	-1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.66
upper limit	-1.02

Notes:

[6] - The cLDA model included fixed effects for treatment, time, baseline treatment with insulin stratum (yes/no) and the interaction of time by treatment. Time was treated as a categorical variable. P-value is nominal.

Secondary: Change from Baseline in Sitting Systolic Blood Pressure at Week 26 - Baseline eGFR ≥45 to <60 mL/min/1.73m^2 Stratum - Excluding Rescue Approach

End point title	Change from Baseline in Sitting Systolic Blood Pressure at Week 26 - Baseline eGFR ≥45 to <60 mL/min/1.73m^2 Stratum - Excluding Rescue Approach

End point description:

This change from baseline reflects the Week 26 sitting systolic blood pressure minus the Week 0 sitting systolic blood pressure. Excluding rescue approach data analysis excluded all data following the initiation of rescue therapy at any time point, in order to avoid the confounding influence of the rescue therapy. The analysis population included all randomized participants with a Baseline eGFR of ≥45 to <60 mL/min/1.73m^2, who took at least 1 dose of study treatment, and had at least 1 assessment at or after baseline for the change from baseline at Week 26 sitting systolic blood pressure endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	97	99	
Units: mmHg				
least squares mean (confidence interval 95%)	-2.33 (-4.98 to 0.33)	-4.36 (-7.11 to -1.62)	-0.9 (-3.73 to 1.92)	

Statistical analyses

Statistical analysis title	Difference in the least squares means
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.451 [7]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in the least squares means
Point estimate	-1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.13
upper limit	2.29

Notes:

[7] - The cLDA model included fixed effects for treatment, time, baseline treatment with insulin stratum (yes/no) and the interaction of time by treatment. Time was treated as a categorical variable.

Statistical analysis title	Difference in the least squares means
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.072 [8]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in the least squares means
Point estimate	-3.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.24
upper limit	0.31

Notes:

[8] - The cLDA model included fixed effects for treatment, time, baseline treatment with insulin stratum (yes/no) and the interaction of time by treatment. Time was treated as a categorical variable.

Secondary: Change from Baseline in FPG at Week 26 - Baseline eGFR ≥45 to <60 mL/min/1.73m^2 Stratum - Excluding Rescue Approach

End point title	Change from Baseline in FPG at Week 26 - Baseline eGFR ≥45 to <60 mL/min/1.73m^2 Stratum - Excluding Rescue Approach

End point description:

This change from baseline reflects the Week 26 FPG minus the Week 0 FPG. Excluding rescue approach data analysis excluded all data following the initiation of rescue therapy at any time point, in order to avoid the confounding influence of the rescue therapy. The analysis population included all randomized participants with a Baseline eGFR ≥45 to <60 mL/min/1.73m^2, who took at least 1 dose of study treatment, and had at least 1 assessment at or after baseline for the change from baseline at Week 26 FPG endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	97	99	
Units: mg/dL				
least squares mean (confidence interval 95%)	-11.76 (-21.07 to -2.45)	-20.47 (-30.2 to -10.73)	-4.95 (-15.03 to 5.13)	

Statistical analyses

Statistical analysis title	Difference in the least squares means
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.291 [9]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in the least squares means
Point estimate	-6.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.47
upper limit	5.85

Notes:

[9] - The cLDA model included fixed effects for treatment, time, baseline treatment with insulin stratum (yes/no) and the interaction of time by treatment. Time was treated as a categorical variable.

Statistical analysis title	Difference in the least squares means
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.019 [10]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in the least squares means
Point estimate	-15.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.5
upper limit	-2.53

Notes:

[10] - The cLDA model included fixed effects for treatment, time, baseline treatment with insulin stratum (yes/no) and the interaction of time by treatment. Time was treated as a categorical variable. P-value is nominal.

Secondary: Percentage of Participants With A1C <7.0% (<53 mmol/mol) at Week 26 - Baseline eGFR ≥45 to <60 mL/min/1.73m^2 Stratum - Excluding Rescue Approach

End point title	Percentage of Participants With A1C <7.0% (<53 mmol/mol) at Week 26 - Baseline eGFR ≥45 to <60 mL/min/1.73m^2

	Stratum - Excluding Rescue Approach

End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). Excluding rescue approach data analysis excluded all data following the initiation of rescue therapy at any time point, in order to avoid the confounding influence of the rescue therapy. The analysis population included all randomized participants with a Baseline eGFR ≥45 to <60 mL/min/1.73m^2, who took at least 1 dose of study medication, and had at least 1 assessment at Week 26 for the percentage of participants with an A1C <7% at Week 26 endpoint.

End point type	Secondary

End point timeframe:

Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	97	99	
Units: Percentage of participants				
number (not applicable)	16.2	11.3	12.1	

Statistical analyses

Statistical analysis title	Adjusted Odds Ratio relative to Placebo
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.713 [11]
Method	Logistic regression model
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	2.56

Notes:

[11] - Logistic regression model fitted with terms for treatment, baseline A1C and baseline treatment with insulin stratum (yes/no).

Statistical analysis title	Adjusted Odds Ratio relative to Placebo
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.89 [12]
Method	Logistic regression model
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	2.55

Notes:

[12] - Logistic regression model fitted with terms for treatment, baseline A1C and baseline treatment with insulin stratum (yes/no).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 54 weeks

Adverse event reporting additional 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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo, oral, tablet, 5-mg or 5-mg and 10-mg tablet once daily for 52 weeks

Reporting group title	Ertugliflozin 15 mg

Reporting group description:

Ertugliflozin, oral, tablet, 5-mg and 10-mg tablet once daily for 52 weeks

Reporting group title	Ertugliflozin 5 mg

Reporting group description:

Ertugliflozin, oral, 5-mg tablet once daily for 52 weeks. Participants also received a 10-mg matching placebo tablet once daily for 52 weeks.

Serious adverse events	Placebo	Ertugliflozin 15 mg	Ertugliflozin 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 154 (15.58%)	30 / 155 (19.35%)	26 / 158 (16.46%)
number of deaths (all causes)	4	4	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoma in situ of skin			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			

subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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
Prostatic adenoma			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
General disorders and administration site conditions			

Cardiac death			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Sudden death			
subjects affected / exposed	1 / 154 (0.65%)	1 / 155 (0.65%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 154 (0.65%)	1 / 155 (0.65%)	0 / 158 (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
Dyspnoea			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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
Epistaxis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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			
Confusional state			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular pressure increased			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Humerus fracture			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
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 myocardial infarction			
subjects affected / exposed	0 / 154 (0.00%)	3 / 155 (1.94%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 154 (0.00%)	4 / 155 (2.58%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Bundle branch block left			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Cardiogenic shock			

subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Coronary artery disease			
subjects affected / exposed	2 / 154 (1.30%)	1 / 155 (0.65%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 154 (0.00%)	2 / 155 (1.29%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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 arteriosclerosis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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
Haemorrhagic stroke			

subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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
Ischaemic stroke			
subjects affected / exposed	2 / 154 (1.30%)	0 / 155 (0.00%)	0 / 158 (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
Sciatic nerve palsy			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymph node haemorrhage			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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 / 154 (0.00%)	2 / 155 (1.29%)	0 / 158 (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
Cyclic vomiting syndrome			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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
Inguinal hernia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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
Peritoneal haemorrhage			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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			
Diabetic foot			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			

subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Nephrolithiasis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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 retention			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cellulitis			
subjects affected / exposed	0 / 154 (0.00%)	3 / 155 (1.94%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	0 / 158 (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
Diarrhoea infectious			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Escherichia urinary tract infection			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Extradural abscess			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Gastroenteritis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 154 (0.65%)	1 / 155 (0.65%)	2 / 158 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			

subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Pyelonephritis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Sepsis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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	0 / 154 (0.00%)	2 / 155 (1.29%)	0 / 158 (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
Viral infection			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 154 (0.00%)	0 / 155 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Hyperkalaemia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (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
Hypoglycaemia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Ertugliflozin 15 mg	Ertugliflozin 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 154 (44.16%)	62 / 155 (40.00%)	82 / 158 (51.90%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 154 (0.65%)	2 / 155 (1.29%)	9 / 158 (5.70%)
occurrences (all)	1	2	10
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 154 (5.84%)	4 / 155 (2.58%)	10 / 158 (6.33%)
occurrences (all)	9	4	10
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 154 (1.30%)	3 / 155 (1.94%)	9 / 158 (5.70%)
occurrences (all)	2	3	9
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 154 (3.90%)	2 / 155 (1.29%)	8 / 158 (5.06%)
occurrences (all)	7	2	8
Nasopharyngitis			

subjects affected / exposed	7 / 154 (4.55%)	6 / 155 (3.87%)	9 / 158 (5.70%)
occurrences (all)	8	6	10
Upper respiratory tract infection			
subjects affected / exposed	7 / 154 (4.55%)	11 / 155 (7.10%)	9 / 158 (5.70%)
occurrences (all)	8	12	9
Urinary tract infection			
subjects affected / exposed	15 / 154 (9.74%)	12 / 155 (7.74%)	9 / 158 (5.70%)
occurrences (all)	20	13	11
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	45 / 154 (29.22%)	32 / 155 (20.65%)	49 / 158 (31.01%)
occurrences (all)	216	281	423

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

After unblinding, analysis of retained plasma samples revealed unreported metformin use by ~17% of participants. Neither dose nor frequency of the protocol-prohibited metformin use is known. This potentially confounds glycemic analyses.

Notes: