Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study With A 78-Week Extension To Evaluate The Efficacy And Safety Of Ertugliflozin In Subjects With Type 2 Diabetes Mellitus And Inadequate Glycemic Control On Metformin Monotherapy

Summary

EudraCT number	2013-003290-95
Trial protocol	HU SK CZ PL RO
Global end of trial date	03 August 2017

Results information

Result version number	v2 (current)
This version publication date	30 December 2018
First version publication date	03 August 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	8835-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02033889
WHO universal trial number (UTN)	-

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	03 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an efficacy and safety study of ertugliflozin in participants with type 2 diabetes mellitus and inadequate glycemic control on metformin monotherapy. The primary study hypothesis is that at Week 26, the mean reduction from baseline in hemoglobin A1c (HbA1c) for ertugliflozin is equal or above that for placebo.

The trial included a 1-week screening period, a variable interval for metformin titration (if needed), and at least an 8-week metformin stable dose period when participants discontinued and remained off any previous allowable background diabetes therapy (except for metformin), a 2-week single-blind placebo run-in period prior to randomization, and a 26-week, double-blind, placebo-controlled treatment period followed by a 78-week double-blind, extension period.

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 subjects: Glycemic rescue therapy with glimepiride and basal insulin was initiated in participants with glucose values exceeding protocol-specified values. Dosing and titration of open-label glimepiride rescue therapy were at the discretion of the Investigator. After the 26-week treatment period, participants randomized to the placebo arm received glimepiride, if their fingerstick fasting glucose was ≥110 mg/dL.

Background therapy:

The trial included a variable interval for metformin titration (if needed), and at least an 8-week metformin stable dose period when participants discontinued and remained off any previous allowable background diabetes therapy (except for metformin). Participants received metformin ≥1500 mg/day, orally, once a day, through-out the remainder of trial.

Evidence for comparator: -

Actual start date of recruitment	13 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	Australia: 11
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	Hong Kong: 36
Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Mexico: 21

Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Romania: 59
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Slovakia: 50
Country: Number of subjects enrolled	South Africa: 111
Country: Number of subjects enrolled	Taiwan: 33
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 169
Worldwide total number of subjects	621
EEA total number of subjects	202

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)	523
From 65 to 84 years	98
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

1535 participants were screened and 621 participants were randomized at clinical trial sites in 14 countries.

Pre-assignment

Screening details:

Male and female participants 18 years of age at the time of the initial Screening Visit with a diagnosis of Type 2 diabetes mellitus (T2DM) in accordance with American Diabetes Association (ADA) guidelines were eligible to participate in this trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Glimepiride

Arm description:

Placebo to ertugliflozin, orally once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the placebo ertugliflozin arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded glimepiride. Participants in the placebo ertugliflozin arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open label or blinded, received open-label basal insulin.

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

Dosage and administration details:

Placebo to ertugliflozin, (1 placebo ertugliflozin 5 mg tablet and 1 placebo ertugliflozin 10 mg tablet), orally once daily from Day 1 to Week 104.

Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	Amaryl; GLIMPID; GLIMY
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride). After Week 26, participants in the placebo ertugliflozin arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded glimepiride. Dosing and titration of glimepiride was at the discretion of the investigator.

Investigational medicinal product name	Basal insulin
Investigational medicinal product code	
Other name	Insulin glargine; Insulin Detemir; NPH Insulin; Insulin Degludec

Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Up to 26 weeks, participants meeting glycemic rescue criteria were rescued with glimepiride, and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of glimepiride, they received basal insulin. If a participant met glycemic rescue criteria from Week 26 onward, and they were on maximal tolerated dose of glimepiride, then rescue with basal insulin was initiated.

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	Glucophage XR; Carbophage SR Riomet; Fortamet Glumetza Obimet; Gluformin Dianben; Diabex Diaformin Siofor; Metfogamma
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin ≥1500 mg/day, orally, once a day

Arm title	Ertugliflozin 5 mg

Arm description:

Ertugliflozin 5 mg orally, once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the ertugliflozin 5 mg arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded placebo glimepiride. Participants in the ertugliflozin 5 mg arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open-label or blinded placebo glimepiride, received open-label basal insulin.

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

Dosage and administration details:

Ertugliflozin 5 mg orally (1 ertugliflozin 5 mg tablet), once daily from Day 1 to Week 104.

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

Dosage and administration details:

Placebo to ertugliflozin, (1 placebo ertugliflozin 10 mg tablet), orally once daily from Day 1 to Week 104.

Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	Amaryl; GLIMPID; GLIMY
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride). Dosing and titration of glimepiride was at the discretion of the investigator.

Investigational medicinal product name	Basal insulin
Investigational medicinal product code	
Other name	Insulin glargine; Insulin Detemir; NPH insulin; Degludec
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Up to 26 weeks, participants meeting glycemic rescue criteria were rescued with glimepiride, and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of glimepiride, they received basal insulin. If a participant met glycemic rescue criteria Week 26 onward, and they were on maximal tolerated dose of glimepiride, then rescue with basal insulin was initiated.

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

Dosage and administration details:

Placebo to glimepiride was used in the 78-week extension period in participants who were not rescued with glimepiride during the 26-week initial period and who had a fingerstick fasting plasma glucose ≥110 mg/dL.

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	Glucophage XR; Carbophage SR Riomet; Fortamet Glumetza Obimet; Gluformin Dianben Diabex; Diaformin Siofor; Metfogamma
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin ≥1500 mg/day, orally, once a day

Arm title	Ertugliflozin 15 mg

Arm description:

Ertugliflozin 15 mg orally, once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the ertugliflozin 15 mg arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded placebo glimepiride. Participants in the ertugliflozin 15 mg arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open-label or blinded placebo glimepiride, received open-label basal insulin.

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

Dosage and administration details:

Ertugliflozin 15 mg orally (1 ertugliflozin 5 mg tablet and 1 ertugliflozin 10 mg tablet), once daily from Day 1 to Week 104.

Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	Amaryl; GLIMPID; GLIMY
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Glimepiride was used for glycemic rescue therapy (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) up to 26 weeks. Glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride was used in the 78-week extension period in participants who were not rescued with glimepiride up to 26 weeks and who had a fingerstick fasting plasma glucose ≥110 mg/dL. Dosing and titration of glimepiride was at the discretion of the investigator.

Investigational medicinal product name	Basal insulin
Investigational medicinal product code	
Other name	Insulin glargine; Insulin Detemir; NPH insulin; Degludec

Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Up to 26 weeks, participants meeting glycemic rescue criteria were rescued with glimepiride, and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of glimepiride, they received basal insulin. If a participant met glycemic rescue criteria after Week 26 onward, and they were on maximal tolerated dose of glimepiride, then rescue with basal insulin was initiated.

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

Dosage and administration details:

Placebo to glimepiride was used in the 78-week extension period in participants who were not rescued with glimepiride during the 26-week initial period and who had a fingerstick fasting plasma glucose ≥110 mg/dL. Dosing and titration of placebo to glimepiride was at the discretion of the investigator.

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	Glucophage XR; Carbophage SR Riomet; Fortamet Glumetza Obimet; Gluformin Dianben Diabex; Diaformin Siofor; Metfogamma
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin ≥1500 mg/day, orally, once a day

Number of subjects in period 1	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Started	209	207	205
Completed	175	187	180
Not completed	34	20	25
Participant moved	-	1	-
Consent withdrawn by subject	18	10	13
Physician decision	-	1	1
Excluded Medication	1	1	-
Adverse event, non-fatal	3	1	3
Death	3	1	2
Non-Compliance With Study Drug	1	-	-
Lost to follow-up	8	5	6

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/Glimepiride

Reporting group description:

Placebo to ertugliflozin, orally once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the placebo ertugliflozin arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded glimepiride. Participants in the placebo ertugliflozin arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open label or blinded, received open-label basal insulin.

Reporting group title	Ertugliflozin 5 mg

Reporting group description:

Ertugliflozin 5 mg orally, once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the ertugliflozin 5 mg arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded placebo glimepiride. Participants in the ertugliflozin 5 mg arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open-label or blinded placebo glimepiride, received open-label basal insulin.

Reporting group title	Ertugliflozin 15 mg

Reporting group description:

Ertugliflozin 15 mg orally, once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the ertugliflozin 15 mg arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded placebo glimepiride. Participants in the ertugliflozin 15 mg arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open-label or blinded placebo glimepiride, received open-label basal insulin.

Reporting group values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Number of subjects	209	207	205
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)	174	180	169
From 65-84 years	35	27	36
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	56.5	56.6	56.9
standard deviation	± 8.7	± 8.2	± 9.4

Sex: Female, Male Units: Subjects			
Female	111	110	112
Male	98	97	93
Menopausal Status			
Menopausal status includes men, premenopausal women, women who are perimenopausal or <3 years postmenopausal, women who are ≥3 years postmenopausal.			
Units: Subjects			
Male	98	97	93
Premenopausal Women	16	17	16
Perimenopausal or <3 yrs. postmenopausal	9	10	11
Women ≥3 years postmenopausal	86	83	85
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	31	34	35
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	19	22	23
White	144	134	133
More than one race	15	17	14
Unknown or Not Reported	0	0	0
Baseline Hemoglobin A1C (A1C)			
Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. N=209, 207, 205			
Units: Percentage A1C			
arithmetic mean	8.17	8.06	8.13
standard deviation	± 0.90	± 0.89	± 0.93
Fasting Plasma Glucose (FPG)			
N=202, 199, 203			
Units: mg/dL			
arithmetic mean	169.1	168.1	167.5
standard deviation	± 41.7	± 45.5	± 44.4
Body Weight			
N=209, 207, 205			
Units: Kilograms			
arithmetic mean	84.5	84.8	85.3
standard deviation	± 17.1	± 17.2	± 16.5
Sitting Systolic Blood Pressure (SBP)			
N=201, 201, 198			
Units: mmHg			
arithmetic mean	129.30	130.48	130.37
standard deviation	± 15.43	± 13.77	± 12.00
Sitting Diastolic Blood Pressure (DBP)			
N=201, 201, 198			
Units: mmHg			
arithmetic mean	77.45	78.45	78.08
standard deviation	± 7.55	± 8.32	± 7.45
Bone Mineral Density (BMD) as Measured by Dual Energy X-Ray Absorptiometry (DXA) of the Femoral Neck			
BMD at the femoral neck was assessed by DXA at baseline.			

N=209, 207, 205			
Units: g/cm^2			
arithmetic mean	0.92	0.92	0.89
standard deviation	± 0.17	± 0.16	± 0.15
BMD as Measured by DXA of the Lumbar Spine (L1-L4)			
BMD at the lumbar spine (L1-L4) was assessed by DXA at baseline. N=209, 207, 204			
Units: g/cm^2			
arithmetic mean	1.15	1.13	1.10
standard deviation	± 0.18	± 0.18	± 0.17
BMD as Measured by DXA of the Total Hip			
BMD at the total hip was assessed by DXA at baseline. N=209, 207, 205			
Units: g/cm^2			
arithmetic mean	1.06	1.07	1.04
standard deviation	± 0.15	± 0.15	± 0.14
BMD as Measured by DXA at the Distal Forearm			
BMD at the distal forearm was assessed by DXA at baseline. N=209, 205, 205			
Units: g/cm^2			
arithmetic mean	0.81	0.81	0.79
standard deviation	± 0.14	± 0.14	± 0.13
Bone Biomarker Carboxy-Terminal Cross-Linking Telopeptides of Type I Collagen (CTX)			
CTX is a biochemical marker of bone resorption. N=200, 196, 195			
Units: ng/L			
arithmetic mean	268.3	266.9	273.0
standard deviation	± 132.9	± 129.9	± 135.2
Bone Biomarker Procollagen Type I N-terminal Propeptide (P1NP)			
P1NP is a biochemical marker of bone resorption. N=200, 198, 198			
Units: microgm/L			
arithmetic mean	32.0	32.8	31.6
standard deviation	± 15.0	± 14.5	± 16.5
Bone Biomarker Parathyroid Hormone (PTH)			
PTH is a biochemical marker of bone resorption. N=202, 194, 200			
Units: ng/L			
arithmetic mean	19.29	19.52	19.97
standard deviation	± 8.17	± 6.91	± 7.73
Estimated Glomerular Filtration Rate (eGFR)			
N=209, 207, 205			
Units: mL/min/1.73 m^2			
arithmetic mean	91.6	88.9	91.1
standard deviation	± 19.8	± 17.5	± 20.6

Reporting group values	Total		
Number of subjects	621		

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)	523		
From 65-84 years	98		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	333		
Male	288		
Menopausal Status			
Menopausal status includes men, premenopausal women, women who are perimenopausal or <3 years postmenopausal, women who are ≥3 years postmenopausal.			
Units: Subjects			
Male	288		
Premenopausal Women	49		
Perimenopausal or <3 yrs. postmenopausal	30		
Women ≥3 years postmenopausal	254		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	100		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	64		
White	411		
More than one race	46		
Unknown or Not Reported	0		
Baseline Hemoglobin A1C (A1C)			
Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. N=209, 207, 205			
Units: Percentage A1C			
arithmetic mean			
standard deviation	-		
Fasting Plasma Glucose (FPG)			
N=202, 199, 203			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
Body Weight			
N=209, 207, 205			

Units: Kilograms arithmetic mean standard deviation	- -		
Sitting Systolic Blood Pressure (SBP)			
N=201, 201, 198			
Units: mmHg arithmetic mean standard deviation	- -		
Sitting Diastolic Blood Pressure (DBP)			
N=201, 201, 198			
Units: mmHg arithmetic mean standard deviation	- -		
Bone Mineral Density (BMD) as Measured by Dual Energy X-Ray Absorptiometry (DXA) of the Femoral Neck			
BMD at the femoral neck was assessed by DXA at baseline. N=209, 207, 205			
Units: g/cm^2 arithmetic mean standard deviation	- -		
BMD as Measured by DXA of the Lumbar Spine (L1-L4)			
BMD at the lumbar spine (L1-L4) was assessed by DXA at baseline. N=209, 207, 204			
Units: g/cm^2 arithmetic mean standard deviation	- -		
BMD as Measured by DXA of the Total Hip			
BMD at the total hip was assessed by DXA at baseline. N=209, 207, 205			
Units: g/cm^2 arithmetic mean standard deviation	- -		
BMD as Measured by DXA at the Distal Forearm			
BMD at the distal forearm was assessed by DXA at baseline. N=209, 205, 205			
Units: g/cm^2 arithmetic mean standard deviation	- -		
Bone Biomarker Carboxy-Terminal Cross-Linking Telopeptides of Type I Collagen (CTX)			
CTX is a biochemical marker of bone resorption. N=200, 196, 195			
Units: ng/L arithmetic mean standard deviation	- -		
Bone Biomarker Procollagen Type I N-terminal Propeptide (P1NP)			
P1NP is a biochemical marker of bone resorption. N=200, 198, 198			
Units: microgm/L			

arithmetic mean standard deviation	- -		
Bone Biomarker Parathyroid Hormone (PTH)			
PTH is a biochemical marker of bone resorption. N=202, 194, 200			
Units: ng/L arithmetic mean standard deviation	 -		
Estimated Glomerular Filtration Rate (eGFR)			
N=209, 207, 205			
Units: mL/min/1.73 m^2 arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Placebo/Glimepiride

Reporting group description:

Placebo to ertugliflozin, orally once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the placebo ertugliflozin arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded glimepiride. Participants in the placebo ertugliflozin arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open label or blinded, received open-label basal insulin.

Reporting group title	Ertugliflozin 5 mg

Reporting group description:

Ertugliflozin 5 mg orally, once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the ertugliflozin 5 mg arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded placebo glimepiride. Participants in the ertugliflozin 5 mg arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open-label or blinded placebo glimepiride, received open-label basal insulin.

Reporting group title	Ertugliflozin 15 mg

Reporting group description:

Ertugliflozin 15 mg orally, once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the ertugliflozin 15 mg arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded placebo glimepiride. Participants in the ertugliflozin 15 mg arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open-label or blinded placebo glimepiride, received open-label basal insulin.

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:

Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100 and reflects the average blood glucose levels over prolonged periods of time. This change from baseline reflects the Week 26 A1C minus the Week 0 A1C (which is estimated on average for each treatment group using a constrained longitudinal data analysis model, which allows for participants with missing data to be included in the analysis). Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had at least one measurement of the respective endpoint at baseline or post-baseline up to Week 26.

End point type	Primary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percent A1C				
least squares mean (confidence interval 95%)	-0.03 (-0.15 to 0.10)	-0.73 (-0.85 to -0.61)	-0.91 (-1.03 to -0.78)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Means

Statistical analysis description:

Based on Constrained Longitudinal Data Analysis (cLDA) model with fixed effects for treatment, time, prior anti hyperglycemic medication (metformin monotherapy or metformin + another anti-hyperglycemic agent, AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	-0.71

Statistical analysis title	Difference in Least Squares Means

Statistical analysis description:

Based on Constrained Longitudinal Data Analysis (cLDA) model with fixed effects for treatment, time, prior anti hyperglycemic medication (metformin monotherapy or metformin + another anti-hyperglycemic agent, AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.53

Primary: Percentage of Participants Experiencing An Adverse Event (AE) (Including Rescue Approach)	
End point title	Percentage of Participants Experiencing An Adverse Event (AE) (Including Rescue Approach)

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. Per protocol, participants who met pre-specified glycemic criteria were rescued with glimepiride up to Week 26 or basal insulin according to Investigator judgment. Per protocol, this data set includes data regardless of glycemic rescue therapy initiation (including rescue approach). The analysis population included all participants who received at least one dose of investigational product.

End point type	Primary

End point timeframe:

Up to Week 106

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of Participants				
number (not applicable)	76.1	70.5	75.6	

Statistical analyses

Statistical analysis title	Difference in % vs Placebo/Glimepiride

Statistical analysis description:

Miettinen & Nurminen method was used to construct the 95% CI

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs Placebo/Glimepiride
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	7.8

Statistical analysis title	Difference in % vs Placebo/Glimepiride

Statistical analysis description:

Miettinen & Nurminen method was used to construct the 95% CI

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs Placebo/Glimepiride
Point estimate	-5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	3

Primary: Percentage of Participants Discontinuing Study Treatment Due to an AE (Including Rescue Approach)

End point title	Percentage of Participants Discontinuing Study Treatment Due to an AE (Including Rescue Approach)

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. Per protocol, participants who met pre-specified glycemic criteria were rescued with glimepiride up to Week 26 or basal insulin according to Investigator judgment. Per protocol, this data set includes data regardless of glycemic rescue therapy initiation (including rescue approach). The analysis population included all participants who received at least one dose of investigational product.

End point type	Primary

End point timeframe:

Up to Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of Participants				
number (not applicable)	2.4	3.4	3.9	

Statistical analyses

Statistical analysis title	Difference in % vs Placebo/Glimepiride

Statistical analysis description:

Miettinen & Nurminen method was used to construct the 95% CI

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg

Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs Placebo/Glimepiride
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	5.4

Statistical analysis title	Difference in % vs Placebo/Glimepiride
Statistical analysis description:	
Miettinen & Nurminen method was used to construct the 95% CI	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs Placebo/Glimepiride
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	4.7

Secondary: Change from Baseline in Fasting Plasma Glucose at Week 26 (Excluding Rescue Approach)

End point title	Change from Baseline in Fasting Plasma Glucose at Week 26 (Excluding Rescue Approach)

End point description:

Blood glucose was measured on a fasting basis. Blood was drawn at predose on Day 1 and after 26 weeks of treatment to determine change in plasma glucose levels (i.e., FPG at Week 26 minus FPG at Week 0) (which is estimated on average for each treatment group using a constrained longitudinal data analysis model, which allows for participants with missing data to be included in the analysis). Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at baseline or post-baseline up to Week 26.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: mg/dL				
least squares mean (confidence interval 95%)	-0.85 (-5.93 to 4.23)	-27.54 (-32.36 to -22.73)	-39.10 (-43.96 to -34.23)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Means
Statistical analysis description:	
Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-38.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.5
upper limit	-31.99

Statistical analysis title	Difference in Least Squares Means
Statistical analysis description:	
Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in the Least Squares Means
Point estimate	-26.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.9
upper limit	-20.48

Secondary: Change from Baseline in Body Weight at Week 26 (Excluding Rescue Approach)

End point title	Change from Baseline in Body Weight at Week 26 (Excluding Rescue Approach)

End point description:

The change in body weight from baseline reflects the Week 26 body weight minus the Week 0 body weight (which is estimated on average for each treatment group using a constrained longitudinal data analysis model, which allows for participants with missing data to be included in the analysis). Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who took at least one dose of study medication and had at least one assessment of the respective endpoint at baseline or post-baseline up to Week 26.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Kilograms				
least squares mean (confidence interval 95%)	-1.33 (-1.74 to -0.92)	-3.01 (-3.40 to -2.62)	-2.93 (-3.33 to -2.53)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Means

Statistical analysis description:

Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.16
upper limit	-1.03

Statistical analysis title	Difference in Least Squares Means

Statistical analysis description:

Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.24
upper limit	-1.11

Secondary: Percentage of Participants with an A1C of <7% (53 mmol/mol) at Week 26 (Logistic Regression using Multiple Imputation: Excluding Rescue Approach)

End point title	Percentage of Participants with an A1C of <7% (53 mmol/mol) at Week 26 (Logistic Regression using Multiple Imputation: 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 (%). Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had at least one assessment of the respective endpoint at baseline or post-baseline up to Week 26.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of Participants				
number (not applicable)	15.8	35.3	40.0	

Statistical analyses

Statistical analysis title	Adjusted Odds Ratio Relative to Placebo

Statistical analysis description:

Adjusted odds ratio based on a logistic regression model fitted with fixed effects for treatment, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), menopausal status, covariates for baseline A1C and baseline eGFR (continuous). Missing data imputed using a multiple imputation procedure based on cLDA prediction modeling with fixed effects as in the primary analysis, which allows for participants with missing data to be included in the analysis.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio Relative to Placebo
Point estimate	4.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.64
upper limit	7.62

Statistical analysis title	Adjusted Odds Ratio Relative to Placebo

Statistical analysis description:

Adjusted odds ratio based on a logistic regression model fitted with fixed effects for treatment, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), menopausal status, covariates for baseline A1C and baseline eGFR (continuous). Missing data imputed using a multiple imputation procedure based on cLDA prediction modeling with fixed effects as in the primary analysis, which allows for participants with missing data to be included in the analysis.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio Relative to Placebo
Point estimate	3.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.81
upper limit	5.06

Secondary: Change from Baseline in Sitting Systolic Blood Pressure at Week 26 (Excluding Rescue Approach)

End point title	Change from Baseline in Sitting Systolic Blood Pressure at Week 26 (Excluding Rescue Approach)

End point description:

This change from baseline reflects the Week 26 sitting systolic blood pressure (SBP) minus the Week 0 sitting SBP (which is estimated on average for each treatment group using a constrained longitudinal data analysis model, which allows for participants with missing data to be included in the analysis). Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who took at least one dose of study medication and had at least one assessment of the respective endpoint at baseline or post-baseline up to Week 26.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	204	
Units: mmHg				
least squares mean (confidence interval 95%)	-0.70 (-2.46 to 1.06)	-4.38 (-6.01 to -2.75)	-5.20 (-6.87 to -3.54)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Means

Statistical analysis description:

Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was
treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.81
upper limit	-2.19

Statistical analysis title	Difference in Least Squares Means

Statistical analysis description:

Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal

status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-3.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.96
upper limit	-1.39

Secondary: Change from Baseline in Sitting Diastolic Blood Pressure at Week 26 (Excluding Rescue Approach)

End point title	Change from Baseline in Sitting Diastolic Blood Pressure at Week 26 (Excluding Rescue Approach)

End point description:

This change from baseline reflects the Week 26 sitting diastolic blood pressure (DBP) minus the Week 0 sitting DBP (which is estimated on average for each treatment group using a constrained longitudinal data analysis model, which allows for participants with missing data to be included in the analysis). Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who took at least one dose of study medication and had at least one assessment of the respective endpoint at baseline or post-baseline up to Week 26.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	204	
Units: mmHg				
least squares mean (confidence interval 95%)	0.23 (-0.85 to 1.31)	-1.59 (-2.59 to -0.59)	-2.19 (-3.21 to -1.17)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Means

Statistical analysis description:

Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was

treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-2.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.86
upper limit	-0.98

Statistical analysis title	Difference in Least Squares Means

Statistical analysis description:

Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was
treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	-0.39

Secondary: Percentage of Participants with an A1C of <6.5% (48 mmol/mol) at Week 26 (Logistic Regression using Multiple Imputation: Excluding Rescue Approach)

End point title	Percentage of Participants with an A1C of <6.5% (48 mmol/mol) at Week 26 (Logistic Regression using Multiple Imputation: 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 (%). Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had at least one assessment of the respective endpoint at baseline or post-baseline up to Week 26

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of Participants				
number (not applicable)	2.9	8.7	12.2	

Statistical analyses

Statistical analysis title	Adjusted Odds Ratio

Statistical analysis description:

Adjusted odds ratio based on a logistic regression model fitted with fixed effects for treatment, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), menopausal status, covariates for baseline A1C and baseline eGFR (continuous). Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	5.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	13.9

Statistical analysis title	Adjusted Odds Ratio

Statistical analysis description:

Adjusted odds ratio based on a logistic regression model fitted with fixed effects for treatment, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), menopausal status, covariates for baseline A1C and baseline eGFR (continuous). Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	8.22

Secondary: Percentage of Participants Receiving Glycemic Rescue Therapy up to Week 26

End point title	Percentage of Participants Receiving Glycemic Rescue Therapy up to Week 26

End point description:

Per protocol, participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. The analysis population included all participants who received at least one dose of investigational product.

End point type	Secondary

End point timeframe:

Up to Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of Participants				
number (not applicable)	17.7	2.9	1.5	

Statistical analyses

Statistical analysis title	Difference in % vs Placebo

Statistical analysis description:

Miettinen & Nurminen method was used to construct both the 95% CI and derive p-value for the difference between the proportions (i.e. percentages).

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg

Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Miettinen & Nurminen method
Parameter estimate	Difference in % vs Placebo
Point estimate	-16.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.2
upper limit	-11.2

Statistical analysis title	Difference in % vs Placebo
Statistical analysis description:	
Miettinen & Nurminen method was used to construct both the 95% CI and derive p-value for the difference between the proportions (i.e. percentages).	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Miettinen & Nurminen method.
Parameter estimate	Difference in % vs Placebo
Point estimate	-14.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.9
upper limit	-9.4

Secondary: Time to Glycemic Rescue Therapy at Week 26

End point title	Time to Glycemic Rescue Therapy at Week 26
End point description:	
Per protocol, participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. The analysis population included all participants who received at least one dose of investigational product and received glycemic rescue through Week 26.	
End point type	Secondary
End point timeframe:	
Week 26	

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	6	3	
Units: Days				
median (full range (min-max))	105 (15 to 183)	112 (23 to 151)	139 (127 to 145)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from Baseline in A1C at Week 52 (Excluding Rescue Approach)

End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Thus, this change from baseline reflects the Week 52 A1C minus the Week 0 A1C. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	179	173	
Units: Percent A1C				
arithmetic mean (standard deviation)	-0.68 (± 0.99)	-0.72 (± 0.95)	-0.96 (± 0.88)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Plasma Glucose at Week 52 (Excluding Rescue Therapy)

End point title	Change from Baseline in Fasting Plasma Glucose at Week 52 (Excluding Rescue Therapy)

End point description:

Blood glucose was measured on a fasting basis. Blood was drawn at predose on Day 1 and after 52 weeks of treatment to determine change in plasma glucose levels (i.e., FPG at Week 52 minus FPG at Week 0). Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic

rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136	173	173	
Units: mg/dL				
arithmetic mean (standard deviation)	-12.0 (± 40.0)	-22.4 (± 39.3)	-35.2 (± 40.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an A1C of <7% (53 mmol/mol) at Week 52 (Excluding Rescue Approach)

End point title	Percentage of Participants with an A1C of <7% (53 mmol/mol) at Week 52 (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 (%). Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product. Any participant without post-baseline data at Week 52 is assumed to be "not at goal" (where "at goal" is A1C <7%) for the calculation of the percentages.

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of Participants				
number (not applicable)	30.6	34.8	36.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an A1C of <6.5% (48 mmol/mol) at Week 52 (Excluding Rescue Approach)

End point title	Percentage of Participants with an A1C of <6.5% (48 mmol/mol) at Week 52 (Excluding Rescue Approach)

End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product. Any participant without post-baseline data at Week 52 is assumed to be "not at goal" (where "at goal" is A1C <6.5%) for the calculation of the percentages.

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of Participants				
number (not applicable)	11.0	10.6	14.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Receiving Glycemic Rescue Therapy up to Week 52

End point title	Percentage of Participants Receiving Glycemic Rescue Therapy up to Week 52

End point description:

Per protocol, participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. The analysis population included all participants who received at least one dose of investigational product.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of Participants				
number (confidence interval 95%)	17.2 (12.37 to 23.04)	4.3 (2.01 to 8.09)	1.5 (0.3 to 4.22)	

Statistical analyses

No statistical analyses for this end point

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:

The change in body weight from baseline reflects the Week 52 body weight minus the Week 0 body weight. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	181	178	
Units: Kilograms				
arithmetic mean (standard deviation)	0.07 (± 2.85)	-3.23 (± 3.68)	-3.35 (± 3.27)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

This change from baseline reflects the Week 52 sitting SBP minus the Week 0 sitting SBP. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	177	173	
Units: mmHg				
arithmetic mean (standard deviation)	0.65 (± 13.38)	-2.63 (± 14.40)	-4.28 (± 13.28)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

This change from baseline reflects the Week 52 sitting DBP minus the Week 0 sitting DBP. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	177	173	
Units: mmHg				
arithmetic mean (standard deviation)	0.38 (± 8.16)	-1.40 (± 9.60)	-1.19 (± 7.74)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in A1C at Week 104 (Excluding Rescue Approach)

End point title	Change from Baseline in A1C at Week 104 (Excluding Rescue

	Approach)

End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Thus, this change from baseline reflects the Week 104 A1C minus the Week 0 A1C. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who had received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 104.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	147	142	
Units: Percent A1C				
arithmetic mean (standard deviation)	-0.58 (± 0.93)	-0.60 (± 0.97)	-0.89 (± 0.90)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Plasma Glucose at Week 104 (Excluding Rescue Approach)

End point title	Change from Baseline in Fasting Plasma Glucose at Week 104 (Excluding Rescue Approach)

End point description:

Blood glucose was measured on a fasting basis. Blood was drawn at predose on Day 1 and after 104 weeks of treatment to determine change in plasma glucose levels (i.e., FPG at Week 104 minus FPG at Week 0). Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 104.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	143	144	
Units: mg/dL				
arithmetic mean (standard deviation)	-10.9 (± 44.3)	-18.2 (± 43.5)	-28.2 (± 44.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an A1C of <7% (53 mmol/mol) at Week 104 (Excluding Rescue approach)

End point title	Percentage of Participants with an A1C of <7% (53 mmol/mol) at Week 104 (Excluding Rescue approach)

End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product. Any participant without post-baseline data at Week 104 is assumed to be "not at goal" (where "at goal" is A1C <7%) for the calculation of the percentages.

End point type	Secondary

End point timeframe:

Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of Participants				
number (not applicable)	19.1	24.6	33.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an A1C of <6.5% (48 mmol/mol) at Week 104 (Excluding Rescue Approach)

End point title	Percentage of Participants with an A1C of <6.5% (48 mmol/mol) at Week 104 (Excluding Rescue Approach)

End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data

set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product. Any participant without post-baseline data at Week 104 is assumed to be "not at goal" (where "at goal" is A1C <6.5%) for the calculation of the percentages..

End point type	Secondary

End point timeframe:

Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of Participants				
number (not applicable)	7.2	10.6	12.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Receiving Glycemic Rescue Therapy up to Week 104

End point title	Percentage of Participants Receiving Glycemic Rescue Therapy up to Week 104

End point description:

Per protocol participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. The analysis population included all randomized participants who received at least one dose of investigational product.

End point type	Secondary

End point timeframe:

Up to Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: Percentage of participants				
number (confidence interval 95%)	24.4 (18.74 to 30.8)	11.1 (7.18 to 16.2)	10.7 (6.85 to 15.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Weight at Week 104 (Excluding Rescue Approach)

End point title	Change from Baseline in Body Weight at Week 104 (Excluding Rescue Approach)

End point description:

The change in body weight from baseline reflects the Week 104 body weight minus the Week 0 body weight. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 104.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	148	145	
Units: Kilograms				
arithmetic mean (standard deviation)	-0.18 (± 3.38)	-3.77 (± 4.29)	-3.63 (± 3.86)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sitting Systolic Blood Pressure at Week 104 (Excluding Rescue Approach)

End point title	Change from Baseline in Sitting Systolic Blood Pressure at Week 104 (Excluding Rescue Approach)

End point description:

This change from baseline reflects the Week 104 sitting SBP minus the Week 0 sitting SBP. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 104.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	145	142	
Units: mmHg				
arithmetic mean (standard deviation)	0.05 (± 13.76)	-3.61 (± 12.78)	-3.13 (± 14.11)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sitting Diastolic Blood Pressure at Week 104 (Excluding Rescue Approach)

End point title	Change from Baseline in Sitting Diastolic Blood Pressure at Week 104 (Excluding Rescue Approach)

End point description:

This change from baseline reflects the Week 104 sitting DBP minus the Week 0 sitting DBP. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 104.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	145	142	
Units: mmHg				
arithmetic mean (standard deviation)	-0.46 (± 8.77)	-2.36 (± 9.23)	-1.52 (± 8.61)	

Statistical analyses

No statistical analyses for this end point

Secondary: Ertugliflozin Plasma Concentrations (ng/mL): Summary Statistics Over Time (Excluding Rescue Approach)

End point title	Ertugliflozin Plasma Concentrations (ng/mL): Summary Statistics Over Time (Excluding Rescue Approach)

End point description:

Pharmacokinetic samples were collected at approximately 24 hours following the prior day's dose and before administration of the current day's dose. The lower limit of quantitation (LLOQ) was 0.500 ng/mL. Participants who met pre-specified glycemic criteria were rescued with oral tablets of glimepiride up to Week 26 or basal insulin injected subcutaneously, and dosed according to Investigator judgment. Per protocol, this data set excludes data for any participant after the initiation of glycemic rescue therapy. A value of 9999 indicates that data for this field was not available as it was below the lower

limit of quantification for these assays. The analysis population included all participants as treated (including those with all concentrations below the lower limit of quantification) and was included in the calculation of the summary statistics. Numbers of participants with non-missing concentrations at the respective time points are displayed.

End point type	Secondary

End point timeframe:

Pre-dose and/or 60 minutes post-dose on Weeks 6, 12, 18, and 30

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	207	205	
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 6:Pre-dose|	9999 (± 9999)	14.89 (± 28.11)	38.38 (± 74.83)	
Week 12:Pre-dose|	9999 (± 9999)	12.34 (± 26.07)	29.23 (± 55.63)	
Week 12:60 mins post-dose|	9999 (± 9999)	74.84 (± 51.58)	228.13 (± 139.14)	
Week 18:Pre-dose|	0.01 (± 0.10)	9.91 (± 21.18)	24.46 (± 39.97)	
Week 18:60 mins post-dose|	0.01 (± 0.09)	74.39 (± 49.77)	214.96 (± 147.36)	
Week 30:Pre-dose|	0.15 (± 1.07)	12.66 (± 25.50)	30.55 (± 60.33)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in BMD at Week 26 as Measured by DXA at the Lumbar Spine (L1-L4) Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 26 as Measured by DXA at the Lumbar Spine (L1-L4) Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the femoral neck was assessed by DXA at Week 0 and Week 26. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	200	189	
Units: Percentage change				
least squares mean (confidence interval 95%)	0.22 (-0.20 to 0.65)	-0.01 (-0.42 to 0.41)	0.12 (-0.31 to 0.55)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	0.5

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	0.37

Secondary: Percent Change from Baseline in BMD at Week 26 as Measured by DXA at the Femoral Neck Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 26 as Measured by DXA at the Femoral Neck Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the femoral neck was assessed by DXA at Week 0 and Week 26. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	200	190	
Units: Percent change				
least squares mean (confidence interval 95%)	-0.40 (-0.89 to 0.09)	-0.10 (-0.57 to 0.38)	0.30 (-0.19 to 0.79)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1.39

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.99

Secondary: Percent Change from Baseline in BMD at Week 26 as Measured by DXA at the Total Hip Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 26 as Measured by DXA at the Total Hip Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the total hip was assessed by DXA at Week 0 and Week 26. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	200	190	
Units: Percent change				
least squares mean (confidence interval 95%)	-0.63 (-0.92 to -0.34)	-0.55 (-0.83 to -0.27)	-0.36 (-0.65 to -0.07)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg

Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.68

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.48

Secondary: Percent Change from Baseline in BMD at Week 26 as Measured by DXA at the Distal Forearm Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 26 as Measured by DXA at the Distal Forearm Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the distal forearm was assessed by DXA at Week 0 and Week 26. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	200	189	
Units: Percent change				
least squares mean (confidence interval 95%)	0.06 (-0.35 to 0.47)	-0.15 (-0.55 to 0.24)	-0.13 (-0.53 to 0.28)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	0.39

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	0.35

Secondary: Change from Baseline in Bone Biomarker Carboxy-Terminal Cross-Linking Telopeptides of Type I Collagen (CTX) at Week 26 (Excluding Bone Rescue

Approach)	
End point title	Change from Baseline in Bone Biomarker Carboxy-Terminal Cross-Linking Telopeptides of Type I Collagen (CTX) at Week 26 (Excluding Bone Rescue Approach)

End point description:

CTX is a biochemical marker of bone resorption. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 26.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	179	180	
Units: ng/L				
arithmetic mean (standard deviation)	10.8 (± 106.6)	51.9 (± 121.9)	80.2 (± 149.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bone Biomarker Procollagen Type I N-terminal Propeptide (P1NP) at Week 26 (Excluding Bone Rescue Approach)

End point title	Change from Baseline in Bone Biomarker Procollagen Type I N-terminal Propeptide (P1NP) at Week 26 (Excluding Bone Rescue Approach)

End point description:

P1NP is a biochemical marker of bone resorption. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 26.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	183	183	
Units: ug/L				
arithmetic mean (standard deviation)	0.5 (± 11.7)	0.8 (± 12.1)	0.5 (± 15.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bone Biomarker Parathyroid Hormone (PTH) at Week 26 (Excluding Bone Rescue Approach)

End point title	Change from Baseline in Bone Biomarker Parathyroid Hormone (PTH) at Week 26 (Excluding Bone Rescue Approach)

End point description:

PTH is a biochemical marker of bone resorption. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 26.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	182	184	
Units: ng/L				
arithmetic mean (standard deviation)	-0.98 (± 6.71)	0.28 (± 7.52)	0.14 (± 7.53)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in BMD at Week 52 as Measured by DXA at the Lumbar Spine (L1-L4) Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 52 as Measured by DXA at the Lumbar Spine (L1-L4) Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the femoral neck was assessed by DXA at Week 0 and Week 52. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least

one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	202	189	
Units: Percent change				
least squares mean (confidence interval 95%)	-0.10 (-0.60 to 0.40)	-0.28 (-0.77 to 0.20)	0.07 (-0.43 to 0.57)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.88

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.51

Secondary: Percent Change from Baseline in BMD at Week 52 as Measured by DXA at the Femoral Neck Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 52 as Measured by DXA at the Femoral Neck Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the femoral neck was assessed by DXA at Week 0 and Week 52. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	202	190	
Units: Percent change				
least squares mean (confidence interval 95%)	-0.69 (-1.25 to -0.14)	-0.49 (-1.04 to 0.06)	-0.44 (-1.06 to 0.17)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.98

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.91

Secondary: Percent Change from Baseline in BMD at Week 52 as Measured by DXA at the Total Hip Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 52 as Measured by DXA at the Total Hip Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the total hip was assessed by DXA at Week 0 and Week 52. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	202	190	
Units: Percent change				
least squares mean (confidence interval 95%)	-0.82 (-1.19 to -0.46)	-1.04 (-1.41 to -0.67)	-1.32 (-1.69 to -0.94)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	-0.04

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0.23

Secondary: Percent Change from Baseline in BMD at Week 52 as Measured by DXA at the Distal Forearm Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 52 as Measured by DXA at the Distal Forearm Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the distal forearm was assessed by DXA at Week 0 and Week 52. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	200	189	
Units: Percent change				
least squares mean (confidence interval 95%)	-0.44 (-0.95 to 0.06)	-0.59 (-1.04 to 0.14)	-0.39 (-0.90 to 0.12)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.72

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg

Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	0.49

Secondary: Percent Change from Baseline in Bone Biomarker CTX at Week 52 (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in Bone Biomarker CTX at Week 52 (Excluding Bone Rescue Approach)

End point description:

CTX is a biochemical marker of bone resorption. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	178	171	
Units: Percent change				
arithmetic mean (standard deviation)	15.54 (± 43.34)	34.36 (± 52.74)	41.57 (± 50.69)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Bone Biomarker P1NP at Week 52 (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in Bone Biomarker P1NP at Week 52 (Excluding Bone Rescue Approach)

End point description:

P1NP is a biochemical marker of bone resorption. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	179	173	
Units: Percent Change				
arithmetic mean (standard deviation)	24.50 (± 120.29)	8.41 (± 30.95)	19.79 (± 79.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Bone Biomarker PTH at Week 52 (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in Bone Biomarker PTH at Week 52 (Excluding Bone Rescue Approach)

End point description:

PTH is a biochemical marker of bone resorption. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	177	175	
Units: Percent Change				
arithmetic mean (standard deviation)	8.11 (± 52.05)	11.09 (± 41.80)	2.48 (± 36.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in BMD at Week 104 as Measured by DXA at the Lumbar Spine (L1-L4) Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 104 as

	Measured by DXA at the Lumbar Spine (L1-L4) Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the lumbar spine was assessed by DXA at Week 0 and Week 104. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	202	189	
Units: Percent change				
least squares mean (confidence interval 95%)	0.09 (-0.47 to 0.66)	-0.19 (-0.72 to 0.35)	-0.13 (-0.68 to 0.42)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.56

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg

Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	0.5

Secondary: Percent Change from Baseline in BMD at Week 104 as Measured by DXA at the Femoral Neck Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 104 as Measured by DXA at the Femoral Neck Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the femoral neck was assessed by DXA at Week 0 and Week 104. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	202	190	
Units: Percent change				
least squares mean (confidence interval 95%)	-1.23 (-1.86 to -0.61)	-1.11 (-1.74 to -0.49)	-0.96 (-1.67 to -0.26)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg

Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	1.13

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.93

Secondary: Percent Change from Baseline in BMD at Week 104 as Measured by DXA at the Total Hip Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in BMD at Week 104 as Measured by DXA at the Total Hip Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the total hip was assessed by DXA at Week 0 and Week 104. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	202	190	
Units: Percent change				
least squares mean (confidence interval 95%)	-1.18 (-1.63 to -0.73)	-1.72 (-2.19 to -1.25)	-2.02 (-2.51 to -1.53)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	-0.24

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the least Squares Means
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	0.05

Secondary: Percent Change from BMD at Week 104 as Measured by DXA at the Distal Forearm Using Raw Data (Excluding Bone Rescue Approach)

End point title	Percent Change from BMD at Week 104 as Measured by DXA at the Distal Forearm Using Raw Data (Excluding Bone Rescue Approach)

End point description:

BMD at the distal forearm was assessed by DXA at Week 0 and Week 104. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had a measurement at baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	200	189	
Units: Percent change				
least squares mean (confidence interval 95%)	-0.58 (-1.13 to -0.03)	-0.40 (-0.87 to 0.06)	-0.64 (-1.19 to -0.09)	

Statistical analyses

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 15 mg
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	0.65

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 (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status, and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Placebo/Glimepiride v Ertugliflozin 5 mg

Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the Least Squares Means
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.85

Secondary: Percent Change from Baseline in Bone Biomarker CTX at Week 104 (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in Bone Biomarker CTX at Week 104 (Excluding Bone Rescue Approach)

End point description:

CTX is a biochemical marker of bone resorption. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 104.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	160	159	
Units: Percent change				
arithmetic mean (standard deviation)	19.29 (± 71.73)	26.94 (± 58.44)	32.53 (± 59.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Bone Biomarker P1NP at Week 104 (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in Bone Biomarker P1NP at Week 104 (Excluding Bone Rescue Approach)

End point description:

P1NP is a biochemical marker of bone resorption. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and

Week 104.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	162	162	
Units: Percent change				
arithmetic mean (standard deviation)	19.38 (± 93.02)	10.11 (± 39.14)	24.21 (± 83.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Bone Biomarker PTH at Week 104 (Excluding Bone Rescue Approach)

End point title	Percent Change from Baseline in Bone Biomarker PTH at Week 104 (Excluding Bone Rescue Approach)

End point description:

PTH is a biochemical marker of bone resorption. Participants who exhibited a significant reduction in BMD according to the protocol defined criteria completed an unscheduled DXA scan and, if required, received bone-active therapy. This table excludes measurements obtained after initiation of bone rescue medications. The analysis population included all randomized participants who received at least one dose of investigational product and had measurements of the respective endpoint at both baseline and Week 104.

End point type	Secondary

End point timeframe:

Baseline and Week 104

End point values	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	158	161	
Units: Percent change				
arithmetic mean (standard deviation)	10.12 (± 60.13)	8.16 (± 40.97)	5.46 (± 38.53)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 106

Adverse event reporting additional description:

Participants who met pre-specified glycemic criteria were rescued with glimepiride up to Week 26 or basal insulin. This data set includes data regardless of glycemic rescue therapy initiation (including rescue approach). The analysis population was all participants who received at least one dose of investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo/Glimepiride

Reporting group description:

Placebo to ertugliflozin, orally once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the placebo ertugliflozin arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded glimepiride. Participants in the placebo ertugliflozin arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open label or blinded, received open-label basal insulin.

Reporting group title	Ertugliflozin 5 mg

Reporting group description:

Ertugliflozin 5 mg orally, once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the ertugliflozin 5 mg arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded placebo glimepiride. Participants in the ertugliflozin 5 mg arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open-label or blinded placebo glimepiride, received open-label basal insulin.

Reporting group title	Ertugliflozin 15 mg

Reporting group description:

Ertugliflozin 15 mg orally, once daily from Day 1 to Week 104. Participants meeting glycemic rescue criteria up to Week 26 were rescued with open-label glimepiride (up to a maximum of 6 or 8 mg per day, based on the local label of glimepiride) and if they met glycemic rescue criteria again, and they were on maximal tolerated doses of open-label glimepiride, they received open-label basal insulin. After Week 26, participants in the ertugliflozin 15 mg arm, who had not received glycemic rescue prior to Week 26 and whose fasting finger-stick glucose was 110 mg/dL or more, received blinded placebo glimepiride. Participants in the ertugliflozin 15 mg arm who met glycemic rescue criteria from Week 26 onwards, and who were on maximal tolerated doses of glimepiride, open-label or blinded placebo glimepiride, received open-label basal insulin.

Serious adverse events	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 209 (10.53%)	20 / 207 (9.66%)	20 / 205 (9.76%)
number of deaths (all causes)	3	1	2
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Bowen's disease			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Hepatic cancer			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Plasma cell myeloma			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Prostate cancer			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
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 cancer metastatic			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Hypertension			

subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	2 / 205 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Venous thrombosis limb			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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			
Cardiac death			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Chest pain			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Death			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Sleep apnoea syndrome			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Laceration			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb crushing injury			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Traumatic intracranial haemorrhage			

subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Congenital, familial and genetic disorders			
Myocardial bridging			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phimosis			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
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	1 / 209 (0.48%)	1 / 207 (0.48%)	0 / 205 (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
Angina pectoris			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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	0 / 209 (0.00%)	2 / 207 (0.97%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 209 (0.00%)	2 / 207 (0.97%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
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 failure acute			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Cardiomyopathy			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 209 (0.48%)	2 / 207 (0.97%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 209 (0.48%)	1 / 207 (0.48%)	0 / 205 (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
Loss of consciousness			

subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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 haemorrhagic			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
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			
subjects affected / exposed	2 / 209 (0.96%)	0 / 207 (0.00%)	0 / 205 (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
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
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			
Stress urinary incontinence			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Ureterolithiasis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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 disorder			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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

Necrotising myositis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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			
subjects affected / exposed	1 / 209 (0.48%)	1 / 207 (0.48%)	0 / 205 (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
Pain in extremity			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
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 osteoarthritis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Otitis media chronic			

subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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 / 209 (0.48%)	1 / 207 (0.48%)	0 / 205 (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
Urinary tract infection			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 209 (0.00%)	1 / 207 (0.48%)	0 / 205 (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
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 209 (0.48%)	0 / 207 (0.00%)	0 / 205 (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
Diabetic ketoacidosis			
subjects affected / exposed	0 / 209 (0.00%)	0 / 207 (0.00%)	1 / 205 (0.49%)
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	Placebo/Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 209 (49.28%)	79 / 207 (38.16%)	100 / 205 (48.78%)
Investigations			
Weight decreased			
subjects affected / exposed	3 / 209 (1.44%)	9 / 207 (4.35%)	15 / 205 (7.32%)
occurrences (all)	3	9	15
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 209 (4.78%)	14 / 207 (6.76%)	11 / 205 (5.37%)
occurrences (all)	15	18	15
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 209 (5.26%)	8 / 207 (3.86%)	8 / 205 (3.90%)
occurrences (all)	13	8	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 209 (3.35%)	7 / 207 (3.38%)	11 / 205 (5.37%)
occurrences (all)	7	9	12
Back pain			
subjects affected / exposed	10 / 209 (4.78%)	9 / 207 (4.35%)	20 / 205 (9.76%)
occurrences (all)	10	10	20
Infections and infestations			
Influenza			
subjects affected / exposed	12 / 209 (5.74%)	11 / 207 (5.31%)	10 / 205 (4.88%)
occurrences (all)	13	13	13
Upper respiratory tract infection			
subjects affected / exposed	33 / 209 (15.79%)	23 / 207 (11.11%)	21 / 205 (10.24%)
occurrences (all)	44	30	22
Urinary tract infection			
subjects affected / exposed	13 / 209 (6.22%)	6 / 207 (2.90%)	17 / 205 (8.29%)
occurrences (all)	18	9	22
Viral upper respiratory tract infection			
subjects affected / exposed	21 / 209 (10.05%)	12 / 207 (5.80%)	9 / 205 (4.39%)
occurrences (all)	27	16	11
Metabolism and nutrition disorders			

Hypoglycaemia subjects affected / exposed occurrences (all)	43 / 209 (20.57%) 213	14 / 207 (6.76%) 119	18 / 205 (8.78%) 66

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

None reported