



Clinical trial results:

A Phase 3, Randomized, Double-blind, Placebo-controlled, 26-week Multicenter Study with a 26-Week Extension to Evaluate the Efficacy and Safety of Ertugliflozin Monotherapy in the Treatment of Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control Despite Diet and Exercise

Summary

EudraCT number	2013-002519-90
Trial protocol	GB IT
Global end of trial date	28 July 2016

Results information

Result version number	v1 (current)
This version publication date	06 August 2017
First version publication date	06 August 2017

Trial information

Trial identification

Sponsor protocol code	MK-8835-003
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01958671
WHO universal trial number (UTN)	-
Other trial identifiers	Pfizer protocol number: B1521022

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 July 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This trial will evaluate the efficacy and safety of ertugliflozin monotherapy in the treatment of participants with type 2 diabetes mellitus (T2DM) and inadequate glycemic control on diet and exercise. This trial consists of a run-in period of 3 to 11 weeks, a 26-week placebo-controlled treatment period (Phase A), and a 26-week active-controlled treatment period (Phase B). The primary hypotheses of the trial are that at Week 26, the mean reduction from baseline in hemoglobin A1c (A1C) for 15 mg ertugliflozin is greater than that for placebo and the mean reduction from baseline in A1C for 5 mg ertugliflozin is greater than that for placebo.

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: participants were prescribed glycemic rescue therapy in the form of open-label metformin in Phase A or glimepiride in Phase B if they met, progressively more stringent, specific glycemic criteria.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 October 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	Canada: 128
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 32
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	South Africa: 20
Country: Number of subjects enrolled	United Kingdom: 86
Country: Number of subjects enrolled	United States: 180
Worldwide total number of subjects	461
EEA total number of subjects	118

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)	341
From 65 to 84 years	118
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligibility criteria included participants with T2DM and with no prior allowable oral anti-hyperglycemic agents (AHA) for at least 8 weeks prior to study participation or if on a single allowable AHA pre-study, willing to discontinue this medication at the screening visit and remain off this medication for the duration of the 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	Ertugliflozin 5 mg/Ertugliflozin 5 mg

Arm description:

Phase A: Ertugliflozin 5 mg administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Ertugliflozin 5 mg administered once daily for 26 weeks. Participants not rescued with metformin in Phase A, will receive placebo to metformin. Participants rescued with metformin in Phase A will continue to receive metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.

Arm type	Experimental
Investigational medicinal product name	Ertugliflozin 5 mg
Investigational medicinal product code	
Other name	MK-8835, PF-04971729
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg once daily in the morning

Investigational medicinal product name	Placebo to ertugliflozin 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One placebo tablet matching the ertugliflozin 10 mg tablet daily in the morning

Investigational medicinal product name	Metformin 500 mg
Investigational medicinal product code	
Other name	Glucophage XR, Carbophage SR, Riomet, Fortamet, Glumetza, Obimet, Gluformin, Dianben, Diabex, Diaformin, Siofor and Metfogamma.
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet in the morning and 1 tablet in the evening for 2 weeks, 2 tablets in the morning and 1 tablet in the evening for 2 weeks and 2 tablets in the morning and 2 tablets in the evening, thereafter.

Investigational medicinal product name	Placebo to metformin 500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet in the morning and 1 tablet in the evening for 2 weeks, 2 tablets in the morning and 1 tablet in the evening for 2 weeks and 2 tablets in the morning and 2 tablets in the evening, thereafter.

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

Dosage and administration details:

Dosing and titration of glimepiride as rescue therapy was determined by the investigator.

Arm title	Ertugliflozin 15 mg/Ertugliflozin 15 mg
------------------	---

Arm description:

Phase A: Ertugliflozin 15 mg administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Ertugliflozin 15 mg administered once daily for 26 weeks. Participants not rescued with metformin in Phase A, will receive placebo to metformin. Participants rescued with metformin in Phase A will continue to receive metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.

Arm type	Experimental
Investigational medicinal product name	Ertugliflozin 5 mg
Investigational medicinal product code	
Other name	MK-8835, PF-04971729
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg once daily in the morning

Investigational medicinal product name	Ertugliflozin 10 mg
Investigational medicinal product code	
Other name	MK-8835, PF-04971729
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg once daily in the morning

Investigational medicinal product name	Metformin 500 mg
Investigational medicinal product code	
Other name	Glucophage XR, Carbophage SR, Riomet, Fortamet, Glumetza, Obimet, Gluformin, Dianben, Diabex, Diaformin, Siofor and Metfogamma.
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet in the morning and 1 tablet in the evening for 2 weeks, 2 tablets in the morning and 1 tablet in the evening for 2 weeks and 2 tablets in the morning and 2 tablets in the evening, thereafter.

Investigational medicinal product name	Placebo to metformin 500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet in the morning and 1 tablet in the evening for 2 weeks, 2 tablets in the morning and 1 tablet in

the evening for 2 weeks and 2 tablets in the morning and 2 tablets in the evening, thereafter.

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

Dosage and administration details:

Dosing and titration of glimepiride as rescue therapy was determined by the investigator.

Arm title	Placebo/Metformin
------------------	-------------------

Arm description:

Phase A: Placebo to ertugliflozin administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Participants not rescued with open-label metformin in Phase A will also receive blinded metformin up to twice daily for 26 weeks in addition to placebo. Participants rescued with metformin in Phase A will continue to receive open-label metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.

Arm type	Placebo/Active comparator
Investigational medicinal product name	Placebo to ertugliflozin 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One placebo tablet matching the ertugliflozin 5mg tablet daily in the morning

Investigational medicinal product name	Placebo to ertugliflozin 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One placebo tablet matching the ertugliflozin 10 mg tablet daily in the morning

Investigational medicinal product name	Metformin 500 mg
Investigational medicinal product code	
Other name	Glucophage XR, Carbophage SR, Riomet, Fortamet, Glumetza, Obimet, Gluformin, Dianben, Diabex, Diaformin, Siofor and Metfogamma.
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet in the morning and 1 tablet in the evening for 2 weeks, 2 tablets in the morning and 1 tablet in the evening for 2 weeks and 2 tablets in the morning and 2 tablets in the evening, thereafter.

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

Dosage and administration details:

Dosing and titration of glimepiride as rescue therapy was determined by the investigator.

Number of subjects in period 1	Ertugliflozin 5 mg/Ertugliflozin 5 mg	Ertugliflozin 15 mg/Ertugliflozin 15 mg	Placebo/Metformin
Started	156	152	153
Completed	137	128	121
Not completed	19	24	32
Adverse event, serious fatal	1	-	-
Participant moved	-	-	1
Consent withdrawn by subject	8	10	13
Adverse event, non-fatal	1	1	5
Excluded medication	-	-	1
Pregnancy	-	-	1
Non-compliance with study drug	1	1	1
Study site terminated by sponsor	1	-	1
Lost to follow-up	7	11	7
Hyperglycemia	-	-	2
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Ertugliflozin 5 mg/Ertugliflozin 5 mg
-----------------------	---------------------------------------

Reporting group description:

Phase A: Ertugliflozin 5 mg administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Ertugliflozin 5 mg administered once daily for 26 weeks. Participants not rescued with metformin in Phase A, will receive placebo to metformin. Participants rescued with metformin in Phase A will continue to receive metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.

Reporting group title	Ertugliflozin 15 mg/Ertugliflozin 15 mg
-----------------------	---

Reporting group description:

Phase A: Ertugliflozin 15 mg administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Ertugliflozin 15 mg administered once daily for 26 weeks. Participants not rescued with metformin in Phase A, will receive placebo to metformin. Participants rescued with metformin in Phase A will continue to receive metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.

Reporting group title	Placebo/Metformin
-----------------------	-------------------

Reporting group description:

Phase A: Placebo to ertugliflozin administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Participants not rescued with open-label metformin in Phase A will also receive blinded metformin up to twice daily for 26 weeks in addition to placebo. Participants rescued with metformin in Phase A will continue to receive open-label metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.

Reporting group values	Ertugliflozin 5 mg/Ertugliflozin 5 mg	Ertugliflozin 15 mg/Ertugliflozin 15 mg	Placebo/Metformin
Number of subjects	156	152	153
Age categorical Units: Subjects			

Age Continuous Units: Years			
arithmetic mean	56.8	56.2	56.1
standard deviation	± 11.4	± 10.8	± 10.9
Gender, Male/Female Units: Subjects			
Female	67	62	71
Male	89	90	82
Study Specific Characteristic Hemoglobin A1c (A1C)			
Ertugliflozin 5 mg/Ertugliflozin 5 mg, n=155 ; Ertugliflozin 15 mg/Ertugliflozin 15 mg, n= 151; Placebo/Metformin, n=153			
Units: Percent			
arithmetic mean	8.16	8.35	8.11
standard deviation	± 0.88	± 1.12	± 0.92
Study Specific Characteristic Fasting plasma glucose (FPG)			
Ertugliflozin 5 mg/Ertugliflozin 5 mg, n=151 ; Ertugliflozin 15 mg/Ertugliflozin 15 mg, n= 149; Placebo/Metformin, n=150			
Units: mg/dL			
arithmetic mean	180.9	179.1	180.2
standard deviation	± 48.5	± 48.2	± 45.8

Study Specific Characteristic Estimated glomerular filtration rate (eGFR) Units: mL/min/1.73m ² arithmetic mean standard deviation	88.5 ± 18.4	88.3 ± 18	86.2 ± 19.4
Study Specific Characteristic Body weight (BW) Units: Kilograms arithmetic mean standard deviation	94 ± 25.4	90.6 ± 18.3	94.2 ± 25.2
2-hour post-prandial glucose (2-hr PPG) level			
Ertugliflozin 5 mg/Ertugliflozin 5 mg, n=145 ; Ertugliflozin 15 mg/Ertugliflozin 15 mg, n= 141; Placebo/Metformin, n=150			
Units: mg/dL arithmetic mean standard deviation	260.32 ± 76.11	262.91 ± 78.189	256.21 ± 76.917
Sitting systolic blood pressure (SBP)			
Ertugliflozin 5 mg/Ertugliflozin 5 mg, n=155 ; Ertugliflozin 15 mg/Ertugliflozin 15 mg, n= 152; Placebo/Metformin, n=150			
Units: mmHg arithmetic mean standard deviation	130.49 ± 13.511	129.67 ± 14.208	129.8 ± 14.464
Sitting diastolic blood pressure (DBP)			
Ertugliflozin 5 mg/Ertugliflozin 5 mg, n=155 ; Ertugliflozin 15 mg/Ertugliflozin 15 mg, n= 152; Placebo/Metformin, n=150			
Units: mmHg arithmetic mean standard deviation	78.46 ± 8.117	78.53 ± 7.714	78.13 ± 7.458

Reporting group values	Total		
Number of subjects	461		
Age categorical Units: Subjects			

Age Continuous Units: Years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	200		
Male	261		
Study Specific Characteristic Hemoglobin A1c (A1C)			
Ertugliflozin 5 mg/Ertugliflozin 5 mg, n=155 ; Ertugliflozin 15 mg/Ertugliflozin 15 mg, n= 151; Placebo/Metformin, n=153			
Units: Percent arithmetic mean standard deviation	-		
Study Specific Characteristic Fasting plasma glucose (FPG)			
Ertugliflozin 5 mg/Ertugliflozin 5 mg, n=151 ; Ertugliflozin 15 mg/Ertugliflozin 15 mg, n= 149; Placebo/Metformin, n=150			
Units: mg/dL			

arithmetic mean standard deviation	-		
Study Specific Characteristic Estimated glomerular filtration rate (eGFR) Units: mL/min/1.73m ² arithmetic mean standard deviation	-		
Study Specific Characteristic Body weight (BW) Units: Kilograms arithmetic mean standard deviation	-		
2-hour post-prandial glucose (2-hr PPG) level			
Ertugliflozin 5 mg/Ertugliflozin 5 mg, n=145 ; Ertugliflozin 15 mg/Ertugliflozin 15 mg, n= 141; Placebo/Metformin, n=150			
Units: mg/dL arithmetic mean standard deviation	-		
Sitting systolic blood pressure (SBP)			
Ertugliflozin 5 mg/Ertugliflozin 5 mg, n=155 ; Ertugliflozin 15 mg/Ertugliflozin 15 mg, n= 152; Placebo/Metformin, n=150			
Units: mmHg arithmetic mean standard deviation	-		
Sitting diastolic blood pressure (DBP)			
Ertugliflozin 5 mg/Ertugliflozin 5 mg, n=155 ; Ertugliflozin 15 mg/Ertugliflozin 15 mg, n= 152; Placebo/Metformin, n=150			
Units: mmHg arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Ertugliflozin 5 mg/Ertugliflozin 5 mg
Reporting group description: Phase A: Ertugliflozin 5 mg administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Ertugliflozin 5 mg administered once daily for 26 weeks. Participants not rescued with metformin in Phase A, will receive placebo to metformin. Participants rescued with metformin in Phase A will continue to receive metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.	
Reporting group title	Ertugliflozin 15 mg/Ertugliflozin 15 mg
Reporting group description: Phase A: Ertugliflozin 15 mg administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Ertugliflozin 15 mg administered once daily for 26 weeks. Participants not rescued with metformin in Phase A, will receive placebo to metformin. Participants rescued with metformin in Phase A will continue to receive metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.	
Reporting group title	Placebo/Metformin
Reporting group description: Phase A: Placebo to ertugliflozin administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Participants not rescued with open-label metformin in Phase A will also receive blinded metformin up to twice daily for 26 weeks in addition to placebo. Participants rescued with metformin in Phase A will continue to receive open-label metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.	
Subject analysis set title	Ertugliflozin 5 mg
Subject analysis set type	Full analysis
Subject analysis set description: Participants randomized to ertugliflozin 5 mg who received at least one dose of study medication and had at least one measurement of each of the following endpoints in Phase A: A1C, BW, SBP, DBP.	
Subject analysis set title	Ertugliflozin 15 mg
Subject analysis set type	Full analysis
Subject analysis set description: Participants randomized to ertugliflozin 15 mg who received at least one dose of study medication and had at least one measurement of the following endpoint in Phase A: A1C.	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Participants randomized to placebo who received at least one dose of study medication and had at least one measurement of each of the following endpoints in Phase A: A1C, FPG, BW.	
Subject analysis set title	Ertugliflozin 5 mg
Subject analysis set type	Full analysis
Subject analysis set description: Participants randomized to ertugliflozin 5 mg who received at least one dose of study medication and had at least one measurement of the following endpoint in Phase A: FPG.	
Subject analysis set title	Ertugliflozin 15 mg
Subject analysis set type	Full analysis
Subject analysis set description: Participants randomized to ertugliflozin 15 mg who received at least one dose of study medication and had at least one measurement of each of the following endpoints in Phase A: FPG, BW, SBP, DBP.	
Subject analysis set title	Ertugliflozin 5 mg
Subject analysis set type	Full analysis
Subject analysis set description: Participants randomized to ertugliflozin 5 mg who received at least one dose of study medication and had at least one measurement of the following endpoint in Phase A: 2-hr PPG.	
Subject analysis set title	Ertugliflozin 15 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants randomized to ertugliflozin 15 mg who received at least one dose of study medication and had at least one measurement of the following endpoint in Phase A: 2-hr PPG

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Participants randomized to placebo who received at least one dose of study medication and had at least one measurement of the following endpoint in Phase A: 2-hr PPG.

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Participants randomized to placebo who received at least one dose of study medication and had at least one measurement of each of the following endpoints in Phase A: SBP, DBP.

Primary: Change from Baseline In A1C at Week 26

End point title	Change from Baseline In A1C at Week 26
-----------------	--

End point description:

A1C is measured as percent. The change from baseline is the Week 26 A1C percent minus the Week 0 A1C percent. Data presented exclude data following the initiation of rescue therapy. Analysis population consisted of all randomized participants who received at least 1 dose of study treatment and had a baseline A1C measurement or at least 1 post-randomization A1C measurement subsequent to at least 1 dose of study treatment.

End point type	Primary
----------------	---------

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	156	151	153	
Units: Percent				
least squares mean (confidence interval 95%)	-0.79 (-0.95 to -0.63)	-0.96 (-1.12 to -0.8)	0.2 (0.02 to 0.37)	

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[1]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-0.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	-0.76

Notes:

[1] - Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[2]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	-0.93

Notes:

[2] - Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Primary: Percentage of Participants Experiencing An Adverse Event (AE)

End point title	Percentage of Participants Experiencing An Adverse Event (AE)
End point description:	
An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Data presented include data following the initiation of rescue therapy. Analysis population consisted of all randomized participants who received at least 1 dose of study treatment. Participants were classified according to randomized treatment.	
End point type	Primary
End point timeframe:	
Up to 54 weeks (including 2 weeks following last dose)	

End point values	Ertugliflozin 5 mg/Ertugliflozin 5 mg	Ertugliflozin 15 mg/Ertugliflozin 15 mg	Placebo/Metformin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	152	153	
Units: Percentage of participants				
number (not applicable)	64.1	62.5	66.7	

Statistical analyses

Statistical analysis title	Between group comparison
Statistical analysis description:	
Difference in percentage based on Miettinen & Nurminen method	
Comparison groups	Ertugliflozin 5 mg/Ertugliflozin 5 mg v Placebo/Metformin
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentage
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.1
upper limit	8.1

Statistical analysis title	Between group comparison
Statistical analysis description:	
Difference in percentage based on Miettinen & Nurminen method	
Comparison groups	Ertugliflozin 15 mg/Ertugliflozin 15 mg v Placebo/Metformin
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentage
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.8
upper limit	6.6

Primary: Percentage of Participants Discontinuing Study Treatment Due to an AE	
End point title	Percentage of Participants Discontinuing Study Treatment Due to an AE
End point description:	
An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Data presented include data following the initiation of rescue therapy. Analysis population consisted of all randomized participants who received at least 1 dose of study treatment. Participants were classified according to randomized treatment.	
End point type	Primary
End point timeframe:	
Up to 52 weeks	

End point values	Ertugliflozin 5 mg/Ertugliflozin 5 mg	Ertugliflozin 15 mg/Ertugliflozin 15 mg	Placebo/Metformin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	152	153	
Units: Percentage of participants				
number (not applicable)	4.5	3.9	6.5	

Statistical analyses

Statistical analysis title	Between group comparison
Statistical analysis description:	
Difference in percentage based on Miettinen & Nurminen method	
Comparison groups	Ertugliflozin 5 mg/Ertugliflozin 5 mg v Placebo/Metformin
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentage
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	3.3

Statistical analysis title	Between group comparison
Statistical analysis description:	
Difference in percentage based on Miettinen & Nurminen method	
Comparison groups	Ertugliflozin 15 mg/Ertugliflozin 15 mg v Placebo/Metformin
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentage
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	2.7

Secondary: Change from Baseline in FPG at Week 26

End point title	Change from Baseline in FPG at Week 26
End point description:	
The change from baseline is the Week 26 FPG minus the Week 0 FPG. Laboratory measurements were performed after an overnight fast ≥ 10 hours in duration. Data presented exclude data following the	

initiation of glycemic rescue therapy. Analysis population consisted of all randomized participants who received at least 1 dose of study treatment and had a baseline FPG measurement or at least 1 post-randomization FPG measurement subsequent to at least 1 dose of study treatment.

End point type	Secondary
End point timeframe:	
Baseline and Week 26	

End point values	Placebo	Ertugliflozin 5 mg	Ertugliflozin 15 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	153	155	152	
Units: mg/dL				
least squares mean (confidence interval 95%)	0.57 (-6.02 to 7.16)	-33.96 (-39.85 to -28.06)	-43.44 (-49.39 to -37.49)	

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[3]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-34.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.76
upper limit	-26.29

Notes:

[3] - Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[4]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-44.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.28
upper limit	-35.74

Notes:

[4] - Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Secondary: Change from Baseline in Body Weight at Week 26

End point title	Change from Baseline in Body Weight at Week 26
-----------------	--

End point description:

The change from baseline is the Week 26 body weight minus the Week 0 body weight. Data presented exclude data following the initiation of rescue therapy. Analysis population consisted of all randomized participants who received at least 1 dose of study treatment and had a baseline body weight measurement or at least 1 post-randomization body weight measurement subsequent to at least 1 dose of study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg	Placebo	Ertugliflozin 15 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	156	153	152	
Units: Kilograms				
least squares mean (confidence interval 95%)	-3.18 (-3.72 to -2.63)	-1.42 (-2.02 to -0.81)	-3.58 (-4.13 to -3.02)	

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[5]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.57
upper limit	-0.95

Notes:

[5] - Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[6]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.98
upper limit	-1.34

Notes:

[6] - Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Secondary: Percentage of Participants with A1C <7% (<53 mmol/mol) at Week 26

End point title	Percentage of Participants with A1C <7% (<53 mmol/mol) at Week 26
-----------------	---

End point description:

A1C is measured as percent. Data presented exclude data following the initiation of rescue therapy. Analysis population consisted of all randomized participants who received at least 1 dose of study treatment and had a baseline A1C measurement or at least 1 post-randomization A1C measurement subsequent to at least 1 dose of study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	156	151	153	
Units: Percentage of participants				
number (not applicable)	28.2	35.8	13.1	

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.85
upper limit	6.95

Notes:

[7] - Fixed effects for treatment, prior antihyperglycemic medication, covariates for baseline A1C and baseline eGFR.

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.46
upper limit	13.24

Notes:

[8] - Fixed effects for treatment, prior antihyperglycemic medication, covariates for baseline A1C and baseline eGFR.

Secondary: Change from Baseline in 2-hr PPG at Week 26

End point title	Change from Baseline in 2-hr PPG at Week 26
End point description:	
The change from baseline is the Week 26 2-hr PPG minus the Week 0 2-hr PPG. Laboratory measurements were performed 120 minutes following the start of the administration of the meal for the Mixed Meal Tolerance Test (MMTT). Data presented exclude data following the initiation of rescue therapy. Analysis population consisted of all randomized participants who received at least 1 dose of study treatment and had a baseline 2-hr PPG measurement or at least 1 post-randomization 2-hr PPG measurement subsequent to at least 1 dose of study treatment.	
End point type	Secondary
End point timeframe:	
Baseline and Week 26	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	153	148	151	
Units: mg/dL				
least squares mean (confidence interval 95%)	-64.15 (-74.34 to -53.96)	-62.45 (-72.91 to -51.98)	4.88 (-6.15 to 15.92)	

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[9]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-69.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.24
upper limit	-54.83

Notes:

[9] - Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[10]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-67.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-81.73
upper limit	-52.93

Notes:

[10] - Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Secondary: Change from Baseline in SBP at Week 26

End point title	Change from Baseline in SBP at Week 26
End point description:	
The change from baseline is the Week 26 SBP minus the Week 0 SBP. Sitting blood pressure was measured in triplicate and the average of the measurements taken at a single assessment time was analyzed. Data presented exclude data following the initiation of rescue therapy. Analysis population consisted of all randomized participants who received at least 1 dose of study treatment and had a baseline SBP measurement or at least 1 post-randomization SBP measurement subsequent to at least 1 dose of study treatment.	
End point type	Secondary
End point timeframe:	
Baseline and Week 26	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	156	152	152	
Units: mmHg				
least squares mean (confidence interval 95%)	-5.54 (-7.32 to -3.76)	-3.93 (-5.74 to -2.12)	-2.22 (-4.3 to -0.14)	

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 ^[11]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-3.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.98
upper limit	-0.65

Notes:

[11] - Nominal p- value. Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.213 ^[12]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	0.98

Notes:

[12] - Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Secondary: Change from Baseline in DBP at Week 26

End point title	Change from Baseline in DBP at Week 26
-----------------	--

End point description:

The change from baseline is the Week 26 DBP minus the Week 0 DBP. Sitting blood pressure was measured in triplicate and the average of the measurements taken at a single assessment time was

analyzed. Data presented exclude data following the initiation of rescue therapy. Analysis population consisted of all randomized participants who received at least 1 dose of study treatment and had a baseline DBP measurement or at least 1 post-randomization DBP measurement subsequent to at least 1 dose of study treatment.

End point type	Secondary
End point timeframe:	
Baseline and Week 26	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	156	152	152	
Units: mmHg				
least squares mean (confidence interval 95%)	-2.52 (-3.65 to -1.4)	-1.1 (-2.24 to 0.05)	-0.72 (-2.05 to 0.6)	

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039 ^[13]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.51
upper limit	-0.09

Notes:

[13] - Nominal p- value. Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.669 ^[14]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-0.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.09
upper limit	1.35

Notes:

[14] - Nominal p- value. Fixed effects for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 54 weeks (+/- 3 days)

Adverse event reporting additional description:

Data presented below include data following the initiation of rescue therapy for the entire study (ie, all data after randomization, with no upper limit on the follow-up window for participants who discontinued study drug).

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19.0
--------------------	------

Reporting groups

Reporting group title	Ertugliflozin 5 mg/Ertugliflozin 5 mg
-----------------------	---------------------------------------

Reporting group description:

Phase A: Ertugliflozin 5 mg administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Ertugliflozin 5 mg administered once daily for 26 weeks. Participants not rescued with metformin in Phase A, will receive placebo to metformin. Participants rescued with metformin in Phase A will continue to receive open-label metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.

Reporting group title	Placebo/Metformin
-----------------------	-------------------

Reporting group description:

Phase A: Placebo to ertugliflozin administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Participants not rescued with open-label metformin in Phase A will also receive blinded metformin up to twice daily for 26 weeks in addition to placebo. Participants rescued with metformin in Phase A will continue to receive open-label metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.

Reporting group title	Ertugliflozin 15 mg/Ertugliflozin 15 mg
-----------------------	---

Reporting group description:

Phase A: Ertugliflozin 15 mg administered once daily for 26 weeks. Participants requiring rescue therapy will receive open-label metformin. Phase B: Ertugliflozin 15 mg administered once daily for 26 weeks. Participants not rescued with metformin in Phase A, will receive placebo to metformin. Participants rescued with metformin in Phase A will continue to receive open-label metformin. Participants requiring rescue therapy during Phase B will receive open-label glimepiride.

Serious adverse events	Ertugliflozin 5 mg/Ertugliflozin 5 mg	Placebo/Metformin	Ertugliflozin 15 mg/Ertugliflozin 15 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 156 (7.05%)	8 / 153 (5.23%)	6 / 152 (3.95%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 156 (0.64%)	1 / 153 (0.65%)	0 / 152 (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

Hepatic cancer metastatic			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 152 (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 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 152 (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			
Acute respiratory failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (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
Epistaxis			

subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
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 embolism			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 152 (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
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (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			
Joint injury			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ruptured cerebral aneurysm			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (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

Eye disorders			
Papilloedema			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 152 (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
Retinal artery occlusion			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (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
Ulcerative keratitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 152 (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
Blindness transient			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (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			
Bacterial infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 152 (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
Cellulitis of male external genital organ			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (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
Labyrinthitis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital abscess			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (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
Metabolism and nutrition disorders			

Diabetes mellitus inadequate control subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 152 (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
Hyperglycaemia subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 152 (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

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

Non-serious adverse events	Ertugliflozin 5 mg/Ertugliflozin 5 mg	Placebo/Metformin	Ertugliflozin 15 mg/Ertugliflozin 15 mg
Total subjects affected by non-serious adverse events subjects affected / exposed	50 / 156 (32.05%)	68 / 153 (44.44%)	48 / 152 (31.58%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	6 / 156 (3.85%) 10	9 / 153 (5.88%) 9	7 / 152 (4.61%) 9
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 11 8 / 156 (5.13%) 10 4 / 156 (2.56%) 4	4 / 153 (2.61%) 4 23 / 153 (15.03%) 26 12 / 153 (7.84%) 14	2 / 152 (1.32%) 2 5 / 152 (3.29%) 5 3 / 152 (1.97%) 4
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection	5 / 156 (3.21%) 5 8 / 156 (5.13%) 8	8 / 153 (5.23%) 9 6 / 153 (3.92%) 7	1 / 152 (0.66%) 1 11 / 152 (7.24%) 12

subjects affected / exposed occurrences (all)	9 / 156 (5.77%) 10	9 / 153 (5.88%) 15	10 / 152 (6.58%) 11
Urinary tract infection subjects affected / exposed occurrences (all)	13 / 156 (8.33%) 15	19 / 153 (12.42%) 30	10 / 152 (6.58%) 14
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	12 / 156 (7.69%) 17	2 / 153 (1.31%) 2	8 / 152 (5.26%) 11
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	2 / 156 (1.28%) 4	10 / 153 (6.54%) 23	6 / 152 (3.95%) 14

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

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28116776>