Clinical trial results:
A Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Clinical Trial to Evaluate the Efficacy and Safety of the Initial Combination of Ertugliflozin (MK-8835/PF-04971729) with Sitagliptin in the Treatment of Subjects with T2DM with Inadequate Glycemic Control on Diet and Exercise

Summary

EudraCT number	2014-001049-25
Trial protocol	HU GB CZ EE BG HR
Global end of trial date	23 February 2016

Results information

Result version number	v1 (current)
This version publication date	07 January 2017
First version publication date	07 January 2017

Trial information

Trial identification

Sponsor protocol code	MK-8835-017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02226003
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	23 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 February 2016
Global end of trial reached?	Yes
Global end of trial date	23 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study to evaluate the efficacy and safety of the ertugliflozin (MK8835/PF04971729) in combination with sitagliptin in the treatment of participants with Type 2 diabetes mellitus (T2DM) with inadequate glycemic control on diet and exercise. The primary hypothesis of the study is that ertugliflozin plus sitagliptin is more effective in lowering of hemoglobin A1C (HbA1C) than 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: Open-label glimepiride rescue therapy was initiated at 1 or 2 mg/day and may be titrated to the maximum labeled dose or maximum tolerated dose (if lower than labeled dose), as considered appropriate by the investigator, based on blood glucose measurements and in accordance with the local, approved label.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 September 2014
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	Bulgaria: 8
Country: Number of subjects enrolled	Croatia: 20
Country: Number of subjects enrolled	Czech Republic: 29
Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Serbia: 16
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	United States: 143
Country: Number of subjects enrolled	Ukraine: 37
Worldwide total number of subjects	291
EEA total number of subjects	95

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)	233
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were randomized at 66 clinical trial sites in 9 countries. This trial included an 8-week (or greater) antihyperglycemic agent (AHA) wash-off period and a 2-week single-blind placebo run-in period.

Pre-assignment

Screening details:

Male and female participants with Type 2 diabetes mellitus of at least 18 years of age were enrolled 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	Ertugliflozin 5 mg + Sitagliptin 100 mg

Arm description:

Ertugliflozin, 5 mg, administered orally, once daily for 26 weeks. Sitagliptin, 100 mg, administered orally, once daily for 26 weeks. Placebo to ertugliflozin, 10 mg, administered orally, once daily for 26 weeks.

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:

Ertugliflozin, 5 mg, administered orally, once daily for 26 weeks.

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

Dosage and administration details:

Sitagliptin, 100 mg, administered orally, once daily for 26 weeks.

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

Dosage and administration details:

Open-label glimepiride as a rescue medication, daily, dose determined per the investigator's discretion and according to the local approved label.

Investigational medicinal product name	Placebo to 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:

Placebo to ertugliflozin, 10 mg, administered orally, once daily for 26 weeks.

Arm title	Ertugliflozin 15 mg + Sitagliptin 100 mg

Arm description:

Ertugliflozin, 15 mg, administered orally, once daily for 26 weeks. Sitagliptin, 100 mg, administered orally, once daily for 26 weeks.

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:

Ertugliflozin, 5 mg, administered orally, once daily for 26 weeks.

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:

Ertugliflozin, 10 mg, administered orally, once daily for 26 weeks.

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

Dosage and administration details:

Sitagliptin, 100 mg, administered orally, once daily for 26 weeks.

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

Dosage and administration details:

Open-label glimepiride as a rescue medication, daily, dose determined per the investigator's discretion and according to the local approved label.

Arm title	Placebo

Arm description:

Placebo to ertugliflozin, 5 mg and 10 mg, administered orally, once daily for 26 weeks. Placebo to sitagliptin, 100 mg, administered orally, once daily for 26 weeks.

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

Dosage and administration details:

Placebo to ertugliflozin, 5 mg, once daily for 26 weeks

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:

Placebo to ertugliflozin, 10 mg, once daily for 26 weeks

Investigational medicinal product name	Placebo to sitagliptin 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to sitagliptin, 100 mg, once daily for 26 weeks

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

Dosage and administration details:

Open-label glimepiride as a rescue medication, daily, dose determined per the investigator's discretion and according to the local approved label.

Number of subjects in period 1	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo
Started	98	96	97
Completed	96	95	91
Not completed	2	1	6
Consent withdrawn by subject	-	-	3
Lost to follow-up	2	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Ertugliflozin 5 mg + Sitagliptin 100 mg
Reporting group description:	
Ertugliflozin, 5 mg, administered orally, once daily for 26 weeks. Sitagliptin, 100 mg, administered orally, once daily for 26 weeks. Placebo to ertugliflozin, 10 mg, administered orally, once daily for 26 weeks.	
Reporting group title	Ertugliflozin 15 mg + Sitagliptin 100 mg
Reporting group description:	
Ertugliflozin, 15 mg, administered orally, once daily for 26 weeks. Sitagliptin, 100 mg, administered orally, once daily for 26 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo to ertugliflozin, 5 mg and 10 mg, administered orally, once daily for 26 weeks. Placebo to sitagliptin, 100 mg, administered orally, once daily for 26 weeks.	

Reporting group values	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo
Number of subjects	98	96	97
Age Categorical Units: Subjects			
Adults (18-64 years)	75	75	83
From 65-84 years	23	21	14
Age Continuous Units: years			
arithmetic mean	56.4	56.1	54.3
standard deviation	± 9.3	± 10.1	± 10.3
Gender Categorical Units: Subjects			
Female	41	43	40
Male	57	53	57

Reporting group values	Total		
Number of subjects	291		
Age Categorical Units: Subjects			
Adults (18-64 years)	233		
From 65-84 years	58		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	124		
Male	167		

End points

End points reporting groups

Reporting group title	Ertugliflozin 5 mg + Sitagliptin 100 mg
Reporting group description:	
Ertugliflozin, 5 mg, administered orally, once daily for 26 weeks. Sitagliptin, 100 mg, administered orally, once daily for 26 weeks. Placebo to ertugliflozin, 10 mg, administered orally, once daily for 26 weeks.	
Reporting group title	Ertugliflozin 15 mg + Sitagliptin 100 mg
Reporting group description:	
Ertugliflozin, 15 mg, administered orally, once daily for 26 weeks. Sitagliptin, 100 mg, administered orally, once daily for 26 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo to ertugliflozin, 5 mg and 10 mg, administered orally, once daily for 26 weeks. Placebo to sitagliptin, 100 mg, administered orally, once daily for 26 weeks.	

Primary: Change from Baseline in HbA1C at Week 26 - Full Analysis Set Excluding Rescue Approach

End point title	Change from Baseline in HbA1C at Week 26 - Full Analysis Set Excluding Rescue Approach
End point description:	
HbA1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). HbA1c represents the percentage of glycated hemoglobin. A negative number indicates a reduction in HbA1c level. FAS population includes randomized participants who took at least 1 dose of study medication and had at least one assessment at or after baseline.	
End point type	Primary
End point timeframe:	
Baseline and Week 26	

End point values	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	96	96	
Units: Percentage				
least squares mean (confidence interval 95%)	-1.6 (-1.82 to -1.39)	-1.68 (-1.9 to -1.46)	-0.44 (-0.69 to -0.19)	

Statistical analyses

Statistical analysis title	Difference in the Least Squares Means
Statistical analysis description:	
Based on constrained longitudinal data analysis (cLDA) model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline estimated glomerular filtration rate (eGFR, continuous) and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Ertugliflozin 5 mg + Sitagliptin 100 mg v Placebo

Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.49
upper limit	-0.84

Statistical analysis title	Difference in the Least Squares Means

Statistical analysis description:

Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Ertugliflozin 15 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	-0.91

Primary: Percentage of Participants Who Experienced an Adverse Event (AE) - All Participants as Treated Excluding Rescue Approach

End point title	Percentage of Participants Who Experienced an Adverse Event (AE) - All Participants as Treated Excluding Rescue Approach

End point description:

An adverse event (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. All Subjects as Treated (ASaT) population consisted of all randomized participants who received at least one dose of a study drug.

End point type	Primary

End point timeframe:

Up to Week 28

End point values	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	96	97	
Units: Percentage of Participants				
number (not applicable)	44.9	44.8	42.3	

Statistical analyses

Statistical analysis title	Difference in Percentage vs Placebo
Comparison groups	Ertugliflozin 5 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage vs Placebo
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	16.4

Statistical analysis title	Difference in Percentage vs Placebo
Comparison groups	Ertugliflozin 15 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage vs Placebo
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.4
upper limit	16.4

Primary: Percentage of Participants Who Discontinued Study Medication Due to an AE - All Participants as Treated Excluding Rescue Approach

End point title	Percentage of Participants Who Discontinued Study Medication Due to an AE - All Participants as Treated Excluding Rescue Approach[1]

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. ASaT population consisted of all randomized participants who received at least one dose of a study drug.

End point type	Primary

End point timeframe:

Up to Week 26

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not planned or performed for this endpoint.

End point values	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	96	97	
Units: Percentage of Participants				
number (not applicable)	2	2.1	2.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) at Week 26 - Full Analysis Set Excluding Rescue Approach

End point title	Change from Baseline in Fasting Plasma Glucose (FPG) at Week 26 - Full Analysis Set Excluding Rescue Approach

End point description:

Blood glucose was measured after a ≥10 hour fast. 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 baseline). FAS population includes randomized participants who took at least 1 dose of study medication and had at least one assessment at or after baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	96	96	
Units: milligrams/deciliter				
least squares mean (confidence interval 95%)	-48.25 (-56.12 to -40.38)	-55.36 (-63.29 to -47.42)	-9.3 (-18.58 to -0.02)	

Statistical analyses

Statistical analysis title	Difference in the Least Squares Means

Statistical analysis description:

Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Ertugliflozin 5 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-38.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.93
upper limit	-27.96

Statistical analysis title	Difference in the Least Squares Means

Statistical analysis description:

Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Ertugliflozin 15 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-46.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.09
upper limit	-35.02

Secondary: Change from Baseline in 2-hour Post-Meal Glucose (PMG) at Week 26 - Full Analysis Set Excluding Rescue Approach

End point title	Change from Baseline in 2-hour Post-Meal Glucose (PMG) at Week 26 - Full Analysis Set Excluding Rescue Approach

End point description:

Change from baseline at Week 26 is defined as 2-hour PMG at Week 26 minus 2-hour PMG at Week 0. Two-hour post-meal glucose was measured following a standard meal. FAS population is all randomized participants who took at least 1 dose of study medication and had at least one assessment at or after baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	97	95	91	
Units: milligrams/deciliter				
least squares mean (confidence interval 95%)	-82.8 (-95.96 to -69.64)	-90.03 (-103.34 to -76.71)	-20.38 (-35.62 to -5.14)	

Statistical analyses

Statistical analysis title	Difference in the Least Squares Means

Statistical analysis description:

Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Ertugliflozin 5 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-62.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-80.47
upper limit	-44.37

Statistical analysis title	Difference in the Least Squares Means

Statistical analysis description:

Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Ertugliflozin 15 mg + Sitagliptin 100 mg v Placebo

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-69.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-87.83
upper limit	-51.46

Secondary: Percentage of Participants with HbA1C <7% (<53 mmol/mol) at Week 26

End point title	Percentage of Participants with HbA1C <7% (<53 mmol/mol) at Week 26

End point description:

HbA1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). HbA1c represents the percentage of glycated hemoglobin. FAS population includes randomized participants who took at least 1 dose of study medication and had at least one assessment at or after baseline.

End point type	Secondary

End point timeframe:

Week 26

End point values	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	96	96	
Units: Percentage of participants				
number (not applicable)	35.7	31.3	8.3	

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, antihyperglycemic medication wash-off status (yes, no). Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis.

Comparison groups	Ertugliflozin 5 mg + Sitagliptin 100 mg v Placebo

Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Odds ratio (OR)
Point estimate	6.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.81
upper limit	16.83

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, antihyperglycemic medication wash-off status (yes, no). Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis.

Comparison groups	Ertugliflozin 15 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Odds ratio (OR)
Point estimate	7.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.98
upper limit	18.31

Secondary: Change from Baseline in Body Weight at Week 26 - Full Analysis Set Excluding Rescue Approach

End point title	Change from Baseline in Body Weight at Week 26 - Full Analysis Set Excluding Rescue Approach

End point description:

Body weight was measured using a standardized, digital scale at each of the pre-defined nominal time points. Weight was taken in duplicate throughout the trial at approximately the same time of day, after voiding (i.e., forced void) and while wearing only a gown and underwear. FAS population is all randomized participants who took at least 1 dose of study medication and had at least one assessment at or after baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	96	97	
Units: Kilograms				
least squares mean (confidence interval 95%)	-2.94 (-3.6 to -2.28)	-3.04 (-3.71 to -2.38)	-0.94 (-1.7 to -0.18)	

Statistical analyses

Statistical analysis title	Difference in the Least Squares Means
Statistical analysis description:	
Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Ertugliflozin 5 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.99
upper limit	-1.01

Statistical analysis title	Difference in the Least Squares Means
Statistical analysis description:	
Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.	
Comparison groups	Ertugliflozin 15 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	-1.11

Secondary: Change from Baseline in Sitting Systolic Blood Pressure at Week 26 - Full Analysis Set Excluding Rescue Approach

End point title	Change from Baseline in Sitting Systolic Blood Pressure at Week 26 - Full Analysis Set Excluding Rescue Approach

End point description:

Blood pressure measurements were taken after at least 5 minutes of rest. Three measurements were taken approximately 2 minutes apart with the triplicate set recorded. FAS population included all randomized participants who took at least 1 dose of study medication and had at least one assessment at or after baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	96	97	
Units: millimeters of mercury				
least squares mean (confidence interval 95%)	-2.04 (-4.23 to 0.16)	-3.98 (-6.19 to -1.78)	2.41 (-0.34 to 5.15)	

Statistical analyses

Statistical analysis title	Difference in the Least Squares Means

Statistical analysis description:

Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Ertugliflozin 5 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.011
Method	Difference in the Least Squares Means
Parameter estimate	cLDA
Point estimate	-4.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.87
upper limit	-1.01

Statistical analysis title	Difference in the Least Squares Means

Statistical analysis description:

Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Ertugliflozin 15 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-6.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.83
upper limit	-2.95

Secondary: Change from Baseline in Sitting Diastolic Blood Pressure at Week 26 - Full Analysis Set Excluding Rescue Approach

End point title	Change from Baseline in Sitting Diastolic Blood Pressure at Week 26 - Full Analysis Set Excluding Rescue Approach

End point description:

Blood pressure measurements were taken after at least 5 minutes of rest. Three measurements were taken approximately 2 minutes apart with the triplicate set recorded. The FAS population included all randomized participants who took at least 1 dose of study medication and had at least one assessment at or after baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	96	97	
Units: millimeters of mercury				
least squares mean (confidence interval 95%)	-0.44 (-1.99 to 1.11)	-0.97 (-2.52 to 0.59)	1.21 (-0.73 to 3.15)	

Statistical analyses

Statistical analysis title	Difference in the Least Squares Means

Statistical analysis description:

Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off

status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Ertugliflozin 5 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.184
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.09
upper limit	0.79

Statistical analysis title	Difference in the Least Squares Means

Statistical analysis description:

Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Comparison groups	Ertugliflozin 15 mg + Sitagliptin 100 mg v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.08
Method	cLDA
Parameter estimate	Difference in the Least Squares Means
Point estimate	-2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.62
upper limit	0.26

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 28

Adverse event reporting additional description:

The serious adverse event table includes events after the initiation of glycemic rescue. The non-serious adverse event table excludes events after the initiation of glycemic rescue.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Ertugliflozin 5 mg + Sitagliptin 100 mg

Reporting group description:

Ertugliflozin, 5 mg, administered orally, once daily for 26 weeks. Sitagliptin, 100 mg, administered orally, once daily for 26 weeks. Placebo to ertugliflozin administered orally, once daily for 26 weeks.

Reporting group title	Ertugliflozin 15 mg + Sitagliptin 100 mg

Reporting group description:

Ertugliflozin, 15 mg, administered orally, once daily for 26 weeks. Sitagliptin, 100 mg, administered orally, once daily for 26 weeks.

Reporting group title	Placebo

Reporting group description:

Placebo to ertugliflozin administered orally, once daily for 26 weeks.

Serious adverse events	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 98 (2.04%)	3 / 96 (3.13%)	5 / 97 (5.15%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 98 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Injury, poisoning and procedural complications			
Multiple fractures			
subjects affected / exposed	0 / 98 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			

subjects affected / exposed	1 / 98 (1.02%)	0 / 96 (0.00%)	0 / 97 (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
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 98 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 98 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 98 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
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			
Nephrolithiasis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal column stenosis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 96 (0.00%)	0 / 97 (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			
Appendicitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis staphylococcal			

subjects affected / exposed	0 / 98 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 98 (0.00%)	1 / 96 (1.04%)	0 / 97 (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 + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 98 (8.16%)	3 / 96 (3.13%)	12 / 97 (12.37%)
Investigations			
Blood glucose increased			
subjects affected / exposed	3 / 98 (3.06%)	0 / 96 (0.00%)	7 / 97 (7.22%)
occurrences (all)	4	0	14
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 98 (5.10%)	2 / 96 (2.08%)	1 / 97 (1.03%)
occurrences (all)	6	2	1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 96 (1.04%)	6 / 97 (6.19%)
occurrences (all)	0	1	6

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