



Clinical trial results:

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Clinical Trial to Evaluate the Safety and Efficacy of Ertugliflozin (MK8835/PF04971729) in the Treatment of Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin and Sitagliptin

Summary

EudraCT number	2013-003697-26
Trial protocol	CZ SK FI BG HU
Global end of trial date	06 June 2016

Results information

Result version number	v1 (current)
This version publication date	04 June 2017
First version publication date	04 June 2017

Trial information

Trial identification

Sponsor protocol code	8835-006
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02036515
WHO universal trial number (UTN)	-
Other trial identifiers	Pfizer Protocol Number: B1521015

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	06 June 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a safety and efficacy study of ertugliflozin (MK8835/PF04971729) in the treatment of participants with type 2 diabetes mellitus who have inadequate glycemic control on metformin and sitagliptin. The primary objective of the trial is to assess the hemoglobin A1C (A1C) lowering efficacy of the addition of ertugliflozin compared to the addition of placebo with an underlying hypothesis that addition of treatment with ertugliflozin provides greater reduction in A1C compared with the addition of placebo; the primary objective will be tested for both 5mg and 15mg doses of ertugliflozin.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The following additional measure(s) defined for this individual study was (were) in place for the protection of trial subjects: During the double-blind treatment period, participants who met progressively more stringent glycemic rescue criteria were to receive open-label glimepiride rescue medication. In the event that an investigator considers use of glimepiride to not be appropriate for a participant meeting protocol-specified glycemic rescue criteria, insulin glargine may have been initiated as the rescue medication.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 March 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	Argentina: 16
Country: Number of subjects enrolled	Bulgaria: 32
Country: Number of subjects enrolled	Colombia: 17
Country: Number of subjects enrolled	Czech Republic: 48
Country: Number of subjects enrolled	Finland: 27
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	Israel: 35
Country: Number of subjects enrolled	Korea, Republic of: 63
Country: Number of subjects enrolled	Malaysia: 30
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Slovakia: 36
Country: Number of subjects enrolled	United States: 94
Worldwide total number of subjects	464
EEA total number of subjects	209

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)	326
From 65 to 84 years	138
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Two participants were randomized to Ertugliflozin 15 mg, but did not receive any treatment.

Period 1

Period 1 title	Randomization period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
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Arm title	Ertugliflozin 5 mg
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Arm description:

Ertugliflozin, 5 mg, oral, once daily for 52 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, oral, 5 mg tablet once daily for 52 weeks

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

Dosage and administration details:

Participants were to remain on their stable doses of metformin (oral, ≥ 1500 mg/day) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Participants were to remain on their stable doses of sitagliptin (oral, 100 mg once daily) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Glimepiride rescue medication, oral, once daily, open-label glimepiride; dose determined per the investigator's discretion

Investigational medicinal product name	Insulin
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine rescue medication, injectable, as required. In the event that an investigator considers use of glimepiride to not be appropriate for a participant meeting protocol specified glycemic rescue criteria, insulin glargine may have been initiated as the rescue medication, and managed by the investigator according to clinical practice guidelines of the local country.

Arm title	Ertugliflozin 15 mg
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Arm description:

Ertugliflozin, 15 mg, oral, once daily for 52 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, oral, 5 mg tablet once daily for 52 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, oral, 10 mg tablet once daily for 52 weeks

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	Glucophage Glucophage XR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were to remain on their stable doses of metformin (oral, ≥ 1500 mg/day) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Participants were to remain on their stable doses of sitagliptin (oral, 100 mg once daily) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Glimepiride rescue medication, oral, once daily, open-label glimepiride; dose determined per the investigator's discretion

Investigational medicinal product name	Insulin
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine rescue medication, injectable, as required. In the event that an investigator considers use of glimepiride to not be appropriate for a participant meeting protocol specified glycemic rescue criteria, insulin glargine may have been initiated as the rescue medication, and managed by the investigator according to clinical practice guidelines of the local country.

Arm title	Placebo
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Arm description:

Matching placebo to ertugliflozin, oral, once daily for 52 weeks

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

Dosage and administration details:

Placebo to ertugliflozin 5 mg and 10 mg once daily for 52 weeks

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	Glucophage Glucophage XR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were to remain on their stable doses of metformin (oral, ≥ 1500 mg/day) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Participants were to remain on their stable doses of sitagliptin (oral, 100 mg once daily) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Glimepiride rescue medication, oral, once daily, open-label glimepiride; dose determined per the investigator's discretion

Investigational medicinal product name	Insulin
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine rescue medication, injectable, as required. In the event that an investigator considers use of glimepiride to not be appropriate for a participant meeting protocol specified glycemic rescue criteria, insulin glargine may have been initiated as the rescue medication, and managed by the

Number of subjects in period 1	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
Started	156	155	153
Completed	156	153	153
Not completed	0	2	0
Screen failure	-	2	-

Period 2

Period 2 title	52-week treatment period
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ertugliflozin 5 mg

Arm description:

Ertugliflozin, 5 mg, oral, once daily for 52 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, oral, 5 mg tablet once daily for 52 weeks

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

Dosage and administration details:

Participants were to remain on their stable doses of metformin (oral, ≥ 1500 mg/day) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Participants were to remain on their stable doses of sitagliptin (oral, 100 mg once daily) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Glimepiride rescue medication, oral, once daily, open-label glimepiride; dose determined per the investigator's discretion

Investigational medicinal product name	Insulin
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine rescue medication, injectable, as required. In the event that an investigator considers use of glimepiride to not be appropriate for a participant meeting protocol specified glycemic rescue criteria, insulin glargine may have been initiated as the rescue medication, and managed by the investigator according to clinical practice guidelines of the local country.

Arm title	Ertugliflozin 15 mg
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Arm description:

Ertugliflozin, 15 mg, oral, once daily for 52 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, oral, 5 mg tablet once daily for 52 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, oral, 10 mg tablet once daily for 52 weeks

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	Glucophage Glucophage XR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were to remain on their stable doses of metformin (oral, ≥ 1500 mg/day) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Participants were to remain on their stable doses of sitagliptin (oral, 100 mg once daily) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Glimepiride rescue medication, oral, once daily, open-label glimepiride; dose determined per the investigator's discretion

Investigational medicinal product name	Insulin
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine rescue medication, injectable, as required. In the event that an investigator considers use of glimepiride to not be appropriate for a participant meeting protocol specified glycemic rescue criteria, insulin glargine may have been initiated as the rescue medication, and managed by the investigator according to clinical practice guidelines of the local country.

Arm title	Placebo
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Arm description:

Matching placebo to ertugliflozin, oral, once daily for 52 weeks

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

Dosage and administration details:

Placebo to ertugliflozin 5 mg and 10 mg once daily for 52 weeks

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	Glucophage Glucophage XR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were to remain on their stable doses of metformin (oral, ≥ 1500 mg/day) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Participants were to remain on their stable doses of sitagliptin (oral, 100 mg once daily) while receiving blinded investigational product during the double-blind treatment period.

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

Dosage and administration details:

Glimepiride rescue medication, oral, once daily, open-label glimepiride; dose determined per the investigator's discretion

Investigational medicinal product name	Insulin
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine rescue medication, injectable, as required. In the event that an investigator considers use of glimepiride to not be appropriate for a participant meeting protocol specified glycemic rescue criteria, insulin glargine may have been initiated as the rescue medication, and managed by the investigator according to clinical practice guidelines of the local country.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The baseline period (52-week treatment period) consists of participants who received at least one dose of study medication. Period 1 includes 2 participants who were randomized but not treated.

Number of subjects in period 2^[2]	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
Started	156	153	153
Completed	151	143	139
Not completed	5	10	14
Consent withdrawn by subject	4	7	9
Adverse event, non-fatal	1	1	2
Non-compliance with study drug	-	-	2
Lost to follow-up	-	2	-
Hyperglycemia	-	-	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number of subjects enrolled in the study includes 2 participants who were randomized but not treated. The baseline period (52-week treatment period) consists of participants who received at least one dose of study medication.

Baseline characteristics

Reporting groups

Reporting group title	Ertugliflozin 5 mg
Reporting group description: Ertugliflozin, 5 mg, oral, once daily for 52 weeks	
Reporting group title	Ertugliflozin 15 mg
Reporting group description: Ertugliflozin, 15 mg, oral, once daily for 52 weeks	
Reporting group title	Placebo
Reporting group description: Matching placebo to ertugliflozin, oral, once daily for 52 weeks	

Reporting group values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
Number of subjects	156	153	153
Age categorical			
Units: Subjects			
<45 years	10	9	15
45 to 64 years	97	102	91
65 years and older	49	42	47
Age Continuous			
Units: years			
arithmetic mean	59.2	59.7	58.3
standard deviation	± 9.3	± 8.6	± 9.2
Gender, Male/Female			
Units: Subjects			
Female	75	71	53
Male	81	82	100
Study Specific Characteristic Hemoglobin A1c (A1C)			
Participants with baseline data: ertugliflozin 5 mg, n=155; ertugliflozin 15 mg, n=152; placebo, n=152; total, n=459			
Units: Percent			
arithmetic mean	8.05	8	8.03
standard deviation	± 0.86	± 0.83	± 0.93
Study Specific Characteristic Fasting plasma glucose			
Participants with baseline data: ertugliflozin 5 mg, n=156; ertugliflozin 15 mg, n=152; placebo, n=152; total, n=460			
Units: mg/dL			
arithmetic mean	167.7	171.7	169.6
standard deviation	± 37.7	± 39.1	± 37.8
Study Specific Characteristic Body weight			
Units: Kilograms			
arithmetic mean	87.6	86.6	86.4
standard deviation	± 18.6	± 19.5	± 20.8
Study Specific Characteristic Estimated glomerular filtration rate (eGFR)			
Units: mL/min/1.73m ²			
arithmetic mean	87	86.9	89.9

standard deviation	± 17.5	± 15.6	± 17.5
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Reporting group values	Total		
Number of subjects	462		
Age categorical			
Units: Subjects			
<45 years	34		
45 to 64 years	290		
65 years and older	138		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	199		
Male	263		
Study Specific Characteristic Hemoglobin A1c (A1C)			
Participants with baseline data: ertugliflozin 5 mg, n=155; ertugliflozin 15 mg, n=152; placebo, n=152; total, n=459			
Units: Percent			
arithmetic mean			
standard deviation	-		
Study Specific Characteristic Fasting plasma glucose			
Participants with baseline data: ertugliflozin 5 mg, n=156; ertugliflozin 15 mg, n=152; placebo, n=152; total, n=460			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
Study Specific Characteristic Body weight			
Units: Kilograms			
arithmetic mean			
standard deviation	-		
Study Specific Characteristic Estimated glomerular filtration rate (eGFR)			
Units: mL/min/1.73m ²			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Ertugliflozin 5 mg
Reporting group description: Ertugliflozin, 5 mg, oral, once daily for 52 weeks	
Reporting group title	Ertugliflozin 15 mg
Reporting group description: Ertugliflozin, 15 mg, oral, once daily for 52 weeks	
Reporting group title	Placebo
Reporting group description: Matching placebo to ertugliflozin, oral, once daily for 52 weeks	
Reporting group title	Ertugliflozin 5 mg
Reporting group description: Ertugliflozin, 5 mg, oral, once daily for 52 weeks	
Reporting group title	Ertugliflozin 15 mg
Reporting group description: Ertugliflozin, 15 mg, oral, once daily for 52 weeks	
Reporting group title	Placebo
Reporting group description: Matching placebo to ertugliflozin, oral, once daily for 52 weeks	

Primary: Change from baseline in hemoglobin A1C at Week 26

End point title	Change from baseline in hemoglobin A1C at Week 26
End point description: A1C is measured as percent. Thus this change from baseline reflects the Week 26 A1C percent minus the Week 0 A1C percent. Laboratory measurements were performed after an overnight fast ≥ 10 hours in duration. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one A1C measurement (baseline or post-baseline).	
End point type	Primary
End point timeframe: Baseline and Week 26	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: Percent				
least squares mean (confidence interval 95%)	-0.78 (-0.91 to -0.65)	-0.86 (-0.99 to -0.72)	-0.09 (-0.23 to -0.04)	

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	
P-value	< 0.001 ^[1]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares mean
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.5

Notes:

[1] - Model is fitted with effects for treatment, time, interaction of time by treatment, effects for baseline eGFR and prior antihyperglycemic medication

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[2]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares mean
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	-0.58

Notes:

[2] - Model is fitted with effects for treatment, time, interaction of time by treatment, effects for baseline eGFR and prior antihyperglycemic medication

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

End point title	Percentage of Participants Experiencing An Adverse Event (AE)
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End point description:

An adverse event is defined as any untoward medical occurrence in a participant 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 took at least one dose of study medication.

End point type	Primary
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End point timeframe:

Up to Week 54

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: Percentage of participants				
number (not applicable)	57.7	60.1	63.4	

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	
Parameter estimate	Difference in percentage
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	5.2

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.1
upper limit	7.6

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 adverse event is defined as any untoward medical occurrence in a participant 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 took at least one dose of study medication.	
End point type	Primary

End point timeframe:

Up to Week 52

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

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	
Parameter estimate	Difference in percentage
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	5.6

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	4.9

Secondary: Change from baseline in fasting plasma glucose (FPG) at Week 26

End point title	Change from baseline in fasting plasma glucose (FPG) at Week 26
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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 rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one FPG measurement (baseline or post-baseline).

End point type	Secondary
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End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: mg/dL				
least squares mean (confidence interval 95%)	-26.91 (-32.58 to -21.24)	-33.04 (-38.71 to -27.36)	-1.76 (-7.7 to 4.18)	

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	
P-value	< 0.001 ^[3]
Method	Constrained longitudinal data analysis
Parameter estimate	Differenc in least squares means
Point estimate	-25.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.76
upper limit	-17.54

Notes:

[3] - Model is fitted with effects for treatment, time, interaction of time by treatment, effects for baseline eGFR and prior antihyperglycemic medication

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[4]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-31.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.9
upper limit	-23.66

Notes:

[4] - Model is fitted with effects for treatment, time, interaction of time by treatment, effects for baseline eGFR and prior antihyperglycemic medication

Secondary: Change from baseline in body weight at Week 26

End point title	Change from baseline in body weight at Week 26
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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 included all randomized participants who took at least one dose of study medication and had at least one body weight measurement (baseline or post-baseline).

End point type	Secondary
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End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: kg				
least squares mean (confidence interval 95%)	-3.35 (-3.78 to -2.91)	-3.04 (-3.48 to -2.6)	-1.32 (-1.77 to -0.87)	

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	
P-value	< 0.001 ^[5]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	-1.4

Notes:

[5] - Model is fitted with effects for treatment, time, interaction of time by treatment, effects for baseline eGFR and prior antihyperglycemic medication

Statistical analysis title	Between group comparison
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Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[6]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.35
upper limit	-1.09

Notes:

[6] - Model is fitted with effects for treatment, time, interaction of time by treatment, effects for baseline eGFR and prior antihyperglycemic medication

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

End point title	Percentage of participants with an A1C <7% (53 mmol/mol) at Week 26
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End point description:

A1C is measured as percent. Laboratory measurements were performed after an overnight fast ≥ 10 hours in duration. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one A1C measurement (baseline or post-baseline).

End point type	Secondary
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End point timeframe:

Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: Percentage of participants				
number (not applicable)	32.1	39.9	17	

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	
P-value	< 0.001 ^[7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.74
upper limit	5.72

Notes:

[7] - Logistic regression model fitted with terms for treatment, baseline A1C, baseline eGFR and prior antihyperglycemic medication.

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[8]
Method	Regression, Logistic
Parameter estimate	Difference in least squares means
Point estimate	4.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.44
upper limit	8.02

Notes:

[8] - Logistic regression model fitted with terms for treatment, baseline A1C, baseline eGFR and prior antihyperglycemic medication.

Secondary: Change from baseline in sitting systolic blood pressure at Week 26

End point title	Change from baseline in sitting systolic blood pressure at Week 26
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End point description:

The change from baseline is the Week 26 systolic blood pressure minus the Week 0 systolic blood pressure. Sitting blood pressure was measured in triplicate. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one systolic blood pressure measurement (baseline or post-baseline).

End point type	Secondary
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End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: mmHg				
least squares mean (standard error)				
Baseline	130.87 (± 0.62)	130.87 (± 0.62)	130.87 (± 0.62)	
Change from baseline	-3.81 (± 0.87)	-4.82 (± 0.88)	-0.88 (± 0.93)	

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	
P-value	= 0.019 ^[9]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-2.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.36
upper limit	-0.49

Notes:

[9] - Model is fitted with effects for treatment, time, interaction of time by treatment, effects for baseline eGFR and prior antihyperglycemic medication

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002 ^[10]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-3.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.39
upper limit	-1.5

Notes:

[10] - Model is fitted with effects for treatment, time, interaction of time by treatment, effects for baseline eGFR and prior antihyperglycemic medication

Secondary: Change from baseline in hemoglobin A1C at Week 52

End point title	Change from baseline in hemoglobin A1C at Week 52
End point description:	
A1C is measured as percent. Thus this change from baseline reflects the Week 52 A1C percent minus the Week 0 A1C percent. Laboratory measurements were performed after an overnight fast ≥ 10 hours in duration. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one A1C measurement (baseline or post-baseline).	
End point type	Secondary

End point timeframe:
Baseline and Week 52

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: Percent				
least squares mean (confidence interval 95%)	-0.75 (-0.9 to -0.59)	-0.81 (-0.97 to -0.66)	0.02 (-0.15 to 0.19)	

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	
Parameter estimate	Difference in least squares means
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	-0.54

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in least squares means
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	-0.61

Secondary: Change from baseline in FPG at Week 52

End point title	Change from baseline in FPG at Week 52
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End point description:

The change from baseline is the Week 52 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 rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one FPG measurement (baseline or post-baseline).

End point type	Secondary
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End point timeframe:

Baseline and Week 52

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: mg/dL				
least squares mean (confidence interval 95%)	-25.57 (-30.91 to -20.23)	-26.38 (-31.8 to -20.97)	3.19 (-3.08 to 9.47)	

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	
Parameter estimate	Difference in least squares means
Point estimate	-28.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.44
upper limit	-21.09

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in least squares means
Point estimate	-29.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.3
upper limit	-21.85

Secondary: Change from baseline in body weight at Week 52

End point title	Change from baseline in body weight at Week 52
-----------------	--

End point description:

The change from baseline is the Week 52 body weight minus the Week 0 body weight. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one body weight measurement (baseline or post-baseline).

End point type	Secondary
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End point timeframe:

Baseline and Week 52

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: kg				
least squares mean (confidence interval 95%)	-3.46 (-4.07 to -2.85)	-2.83 (-3.45 to -2.21)	-0.95 (-1.65 to -0.26)	

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	
Parameter estimate	Difference in least squares means
Point estimate	-2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.43
upper limit	-1.59

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in least squares means
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.81
upper limit	-0.95

Secondary: Percentage of participants with an A1C <7% (53 mmol/mol) at Week 52

End point title	Percentage of participants with an A1C <7% (53 mmol/mol) at Week 52
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End point description:

A1C is measured as percent. Laboratory measurements were performed after an overnight fast ≥ 10 hours in duration. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one A1C measurement (baseline or post-baseline).

End point type	Secondary
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End point timeframe:

Week 52

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: Percentage of participants				
number (not applicable)	33.3	32.7	13.7	

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	
Parameter estimate	Odds ratio (OR)
Point estimate	3.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.98
upper limit	6.64

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	4.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.22
upper limit	7.28

Secondary: Change from baseline in sitting systolic blood pressure at Week 52

End point title	Change from baseline in sitting systolic blood pressure at Week 52
End point description:	
The change from baseline is the Week 52 systolic blood pressure minus the Week 0 systolic blood pressure. Sitting blood pressure was measured in triplicate. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one systolic blood pressure measurement (baseline or post-baseline).	
End point type	Secondary
End point timeframe:	
Baseline and Week 52	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: mmHg				
least squares mean (standard error)				
Baseline	130.92 (± 0.62)	130.92 (± 0.62)	130.92 (± 0.62)	
Change from baseline	-4.16 (± 0.95)	-4.09 (± 0.96)	0.83 (± 1.14)	

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	
Parameter estimate	Difference in least squares means
Point estimate	-4.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.82
upper limit	-2.15

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in least squares means
Point estimate	-4.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.76
upper limit	-2.07

Secondary: Change from baseline in sitting diastolic blood pressure at Week 26

End point title	Change from baseline in sitting diastolic blood pressure at Week 26
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End point description:

The change from baseline is the Week 26 diastolic blood pressure minus the Week 0 diastolic blood pressure. Sitting blood pressure was measured in triplicate. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one diastolic blood pressure measurement (baseline or post-baseline).

End point type	Secondary
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End point timeframe:

Baseline and Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: mmHg				
least squares mean (standard error)				
Baseline	78.42 (± 0.36)	78.42 (± 0.36)	78.42 (± 0.36)	
Change from baseline	-1.68 (± 0.61)	-1.81 (± 0.62)	-0.43 (± 0.65)	

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	
Parameter estimate	Difference in least squares means
Point estimate	-1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	0.48

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in least squares means
Point estimate	-1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	0.36

Secondary: Change from baseline in sitting diastolic blood pressure at Week 52

End point title	Change from baseline in sitting diastolic blood pressure at Week 52
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End point description:

The change from baseline is the Week 52 diastolic blood pressure minus the Week 0 diastolic blood pressure. Sitting blood pressure was measured in triplicate. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one diastolic blood pressure measurement (baseline or post-baseline).

End point type	Secondary
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End point timeframe:

Baseline and Week 52

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: mmHg				
least squares mean (standard error)				
Baseline	78.44 (± 0.36)	78.44 (± 0.36)	78.44 (± 0.36)	
Change from baseline	-1.52 (± 0.61)	-1.38 (± 0.62)	-0.53 (± 0.73)	

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	
Parameter estimate	Difference in least squares means
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.82
upper limit	0.84

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in least squares means
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.69
upper limit	0.99

Secondary: Percentage of participants receiving glycemic rescue medication by Week 26

End point title	Percentage of participants receiving glycemic rescue medication by Week 26
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End point description:

Glycemic rescue medication was initiated for participants who met progressively more stringent glycemic rescue criteria. Rescue medication included glimepiride (or insulin glargine if glimepiride was not considered appropriate for the participant). Analysis population included all randomized participants who took at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Week 26

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: Percentage of participants				
number (not applicable)	1.3	2	16.3	

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	
Parameter estimate	Difference in percent
Point estimate	-15.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.9
upper limit	-9.4

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percent
Point estimate	-14.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.3
upper limit	-8.5

Secondary: Percentage of participants receiving glycemic rescue medication by Week 52

End point title	Percentage of participants receiving glycemic rescue medication by Week 52
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End point description:

Glycemic rescue medication was initiated for participants who met progressively more stringent glycemic rescue criteria. Rescue medication included glimepiride (or insulin glargine if glimepiride was not considered appropriate for the participant). Analysis population included all randomized participants who took at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Week 52

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: Percentage of participants				
number (not applicable)	12.8	13.7	41.8	

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	
Parameter estimate	Difference in percentage
Point estimate	-29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.3
upper limit	-19.4

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	-28.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.5
upper limit	-18.4

Secondary: Time to initiation of glycemic rescue by Week 26

End point title	Time to initiation of glycemic rescue by Week 26
End point description: Glycemic rescue medication was initiated for participants who met progressively more stringent glycemic rescue criteria. Rescue medication included glimepiride (or insulin glargine if glimepiride was not considered appropriate for the participant). Data presented are the minimum and maximum times to the initiation of rescue therapy in days. Analysis population included all randomized participants who took at least one dose of study medication.	
End point type	Secondary
End point timeframe: Up to week 26	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: Days				
Minimum time to initiation of glycemic rescue	135	43	26	
Maximum time to initiation of glycemic rescue	141	147	212	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to initiation of glycemic rescue by Week 52

End point title	Time to initiation of glycemic rescue by Week 52
End point description: Glycemic rescue medication was initiated for participants who met progressively more stringent glycemic rescue criteria. Rescue medication included glimepiride (or insulin glargine if glimepiride was not considered appropriate for the participant). Data presented are the minimum and maximum times to the initiation of rescue therapy in days. Analysis population included all randomized participants who took at least one dose of study medication.	
End point type	Secondary

End point timeframe:

Up to week 52

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	153	153	
Units: Days				
Minimum time to initiation of glycemic rescue	135	43	26	
Maximum time to initiation of glycemic rescue	295	299	327	

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline homeostasis model assessment of β -cell function (HOMA-% β) value

End point title	Baseline homeostasis model assessment of β -cell function (HOMA-% β) value
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End point description:

HOMA-% β is a well-accepted means of assessing fasting β -cell function, and is calculated using measured C-peptide and glucose levels and is measured as a percentage of a normal reference population. $\text{HOMA-\%}\beta = [20 \times \text{fasting insulin } (\mu\text{U/mL})] / [\text{fasting plasma glucose (mmol/L)} - 3.5]$. Analysis population included all randomized participants who took at least one dose of study medication and had HOMA-% β measurement at baseline.

End point type	Secondary
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End point timeframe:

Baseline

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	131	127	
Units: Percentage				
arithmetic mean (standard deviation)	47.99 (\pm 23.89)	48.54 (\pm 34.782)	48.04 (\pm 30.733)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in HOMA-% β at Week 26

End point title	Change from baseline in HOMA-%β at Week 26
End point description:	
HOMA-%β is a well-accepted means of assessing fasting β-cell function, and is calculated using measured C-peptide and glucose levels and is measured as a percentage of a normal reference population. $HOMA\text{-}\% \beta = [20 \times \text{fasting insulin } (\mu\text{U/mL})] / [\text{fasting plasma glucose (mmol/L)} - 3.5]$. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one HOMA-%β measurement (baseline or post-baseline).	
End point type	Secondary
End point timeframe:	
Baseline and Week 26	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	151	147	
Units: Percentage				
least squares mean (confidence interval 95%)	13.28 (8.87 to 17.68)	12.43 (7.94 to 16.93)	0.52 (-4.08 to 5.12)	

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in least squares means
Point estimate	12.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.83
upper limit	18.68

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in least squares means
Point estimate	11.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	5.94
upper limit	17.88

Secondary: Change from baseline in HOMA-%β at Week 52

End point title	Change from baseline in HOMA-%β at Week 52
End point description:	
HOMA-%β is a well-accepted means of assessing fasting β-cell function, and is calculated using measured C-peptide and glucose levels and is measured as a percentage of a normal reference population. $HOMA\text{-}\% \beta = [20 \times \text{fasting insulin } (\mu\text{U/mL})] / [\text{fasting plasma glucose (mmol/L)} - 3.5]$. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one HOMA-%β measurement (baseline or post-baseline).	
End point type	Secondary
End point timeframe:	
Baseline and Week 52	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155	152	152	
Units: Percentage				
least squares mean (confidence interval 95%)	10.85 (6.29 to 15.41)	10.93 (6.24 to 15.61)	-1.93 (-6.88 to 3.02)	

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Ertugliflozin 5 mg v Placebo
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in least squares means
Point estimate	12.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.54
upper limit	19.03

Statistical analysis title	Between group comparison
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Comparison groups	Ertugliflozin 15 mg v Placebo
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in least squares means
Point estimate	12.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.54
upper limit	19.18

Secondary: Baseline EQ-5D 3-level version (EQ-5D-3L) Questionnaire Score

End point title	Baseline EQ-5D 3-level version (EQ-5D-3L) Questionnaire Score
End point description: The EQ-5D-3L is a health profile questionnaire that assesses quality of life along 5 dimensions. Participants rate 5 aspects of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by choosing from 3 answering options (1=no problems; 2=some problems; 3=extreme problems). The summed score ranges from 1-15 with "3" corresponding to no problems and "15" corresponding to severe problems in the 5 dimensions. EQ-5D-3L also includes an EQ visual analogue score (VAS) that ranges between 100 (best imaginable health) and 0 (worst imaginable health). Total index summary score is weighted with a range of -0.594 (worst) to 1.0 (best). Analysis population included all randomized participants who took at least one dose of study medication and had a baseline EQ-5D-3L measurement.	
End point type	Secondary
End point timeframe: Baseline	

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	150	152	
Units: Score on a scale				
arithmetic mean (standard deviation)	0.88 (± 0.166)	0.89 (± 0.182)	0.9 (± 0.144)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EQ-5D-3L Questionnaire Score at Week 26

End point title	Change from baseline in EQ-5D-3L Questionnaire Score at Week 26
End point description: The EQ-5D-3L is a health profile questionnaire that assesses quality of life along 5 dimensions. Participants rate 5 aspects of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by choosing from 3 answering options (1=no problems; 2=some problems; 3=extreme problems). The summed score ranges from 3-15 with "3" corresponding to no problems and	

"15" corresponding to severe problems in the 5 dimensions. EQ-5D-3L also includes an EQ VAS that ranges between 100 (best imaginable health) and 0 (worst imaginable health). Total index summary score is weighted with a range of -0.594 (worst) to 1.0 (best). Decrease from baseline in EQ-5D-3L signifies improvement. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one EQ-5D-3L measurement (baseline or post-baseline).

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

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155	151	153	
Units: Score on a scale				
least squares mean (confidence interval 95%)	0 (-0.02 to 0.03)	0.02 (0 to 0.04)	0.01 (-0.01 to 0.04)	

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	
Parameter estimate	Difference in least squares means
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.02

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	
Parameter estimate	Difference in least squares means
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.04

Secondary: Change from baseline in EQ-5D-3L score at Week 52

End point title	Change from baseline in EQ-5D-3L score at Week 52
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End point description:

The EQ-5D-3L is a health profile questionnaire that assesses quality of life along 5 dimensions. Participants rate 5 aspects of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by choosing from 3 answering options (1=no problems; 2=some problems; 3=extreme problems). The summed score ranges from 3-15 with "3" corresponding to no problems and "15" corresponding to severe problems in the 5 dimensions. EQ-5D-3L also includes an EQ VAS that ranges between 100 (best imaginable health) and 0 (worst imaginable health). Total index summary score is weighted with a range of -0.594 (worst) to 1.0 (best). Decrease from baseline in EQ-5D-3L signifies improvement. Data presented exclude data following the initiation of rescue therapy. Analysis population included all randomized participants who took at least one dose of study medication and had at least one EQ-5D-3L measurement (baseline or post-baseline).

End point type	Secondary
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End point timeframe:

Baseline and Week 52

End point values	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155	151	153	
Units: Score on a scale				
least squares mean (confidence interval 95%)	0.03 (0 to 0.05)	0 (-0.03 to 0.03)	0.02 (-0.01 to 0.06)	

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	
Parameter estimate	Difference in least squares means
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.04

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	
Parameter estimate	Difference in least squares means
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.02

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 54 weeks

Adverse event reporting additional description:

Data presented below includes 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). Two participants randomized to ertugliflozin 15 mg didn't receive any study medication & aren't included in the below tables

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Ertugliflozin 5 mg (Phase A+B)
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Reporting group description:

Ertugliflozin, 5 mg, oral, once daily for 52 weeks

Reporting group title	Placebo (Phase A+B)
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Reporting group description:

Matching placebo to ertugliflozin, oral, once daily for 52 weeks

Reporting group title	Ertugliflozin 15 mg (Phase A+B)
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Reporting group description:

Ertugliflozin, 15 mg, oral, once daily for 52 weeks

Serious adverse events	Ertugliflozin 5 mg (Phase A+B)	Placebo (Phase A+B)	Ertugliflozin 15 mg (Phase A+B)
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 156 (8.33%)	8 / 153 (5.23%)	3 / 153 (1.96%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign ear neoplasm			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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
Bladder cancer			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 153 (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
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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			
Femur fracture			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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
Spinal compression fracture			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 153 (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
Angina pectoris			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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
Coronary artery disease			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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			
Cerebral haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 153 (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			
Cholelithiasis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 153 (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
Liver disorder			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Urge incontinence			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 156 (0.00%)	0 / 153 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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
Bone tuberculosis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 153 (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
Gastroenteritis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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
Lymphangitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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
Meningitis tuberculous			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 153 (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

Osteomyelitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 156 (0.64%)	0 / 153 (0.00%)	0 / 153 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 156 (0.00%)	1 / 153 (0.65%)	0 / 153 (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 (Phase A+B)	Placebo (Phase A+B)	Ertugliflozin 15 mg (Phase A+B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 156 (15.38%)	29 / 153 (18.95%)	18 / 153 (11.76%)
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 156 (5.13%)	6 / 153 (3.92%)	3 / 153 (1.96%)
occurrences (all)	8	6	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 156 (5.13%)	5 / 153 (3.27%)	6 / 153 (3.92%)
occurrences (all)	8	6	6
Urinary tract infection			
subjects affected / exposed	2 / 156 (1.28%)	8 / 153 (5.23%)	5 / 153 (3.27%)
occurrences (all)	2	9	5
Metabolism and nutrition disorders			

Hypoglycaemia subjects affected / exposed occurrences (all)	7 / 156 (4.49%) 16	11 / 153 (7.19%) 18	5 / 153 (3.27%) 11
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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