



Clinical trial results:

A Randomized, Double-Blind, 5-Arm, Parallel-Group, 26-Week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in Combination With Metformin as Initial Combination Therapy in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control With Diet and Exercise

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-000400-17
Trial protocol	HU CZ SK
Global end of trial date	01 December 2014

Results information

Result version number	v1 (current)
This version publication date	30 April 2016
First version publication date	30 April 2016

Trial information

Trial identification

Sponsor protocol code	28431754DIA3011
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01809327
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	Antwerpseweg 15-17, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group-JB BV, Janssen Research and Development, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group-JB BV, Janssen Research and Development, ClinicalTrialsEU@its.jnj.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	01 December 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study to assess the effect of the co-administration of canagliflozin and metformin extended-release (XR) compared with canagliflozin alone on hemoglobin A1c (HbA1c). To assess the effect of the co-administration of canagliflozin and metformin XR compared with metformin XR alone on HbA1c. To assess the safety and tolerability of the co-administration of canagliflozin and metformin XR, canagliflozin alone, and metformin XR alone

Protection of trial subjects:

Safety evaluations included the collection of adverse events, safety laboratory tests (including chemistry, hematology, and urinalysis), vital signs (blood pressures and pulse rates), body weight, physical examinations, self-monitored blood glucose (SMBG), and collection of potential hypoglycemic episodes.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 89
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Czech Republic: 34
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Mexico: 159
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Romania: 102
Country: Number of subjects enrolled	Russian Federation: 202
Country: Number of subjects enrolled	Slovakia: 69
Country: Number of subjects enrolled	South Africa: 22
Country: Number of subjects enrolled	Ukraine: 242
Country: Number of subjects enrolled	United States: 223
Worldwide total number of subjects	1186
EEA total number of subjects	233

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)	990
From 65 to 84 years	196
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 158 centers in 12 countries from 16 May 2013 to 01 December 2014.

Pre-assignment

Screening details:

A total of 2,000 subjects were screened and a total of 1,186 subjects were randomly assigned to study treatment.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin XR

Arm description:

Subjects received metformin extended release (XR) tablets (in doses titrated over 9 weeks) once daily with the evening meal, plus one placebo capsule before the morning meal and one placebo capsule with the evening meal (to match the canagliflozin capsules administered in other treatment arms) for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo Capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One placebo capsule was taken before the morning meal and one placebo capsule was taken with evening meal for 26 weeks

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received metformin extended release (XR) tablets (in doses titrated over 9 weeks) once daily with the evening meal for 26 weeks.

Arm title	Canagliflozin 100 mg
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Arm description:

Subjects received one 100 milligram (mg) canagliflozin capsule before the morning meal and one matching placebo capsule with the evening meal plus placebo tablets with the evening meal (to match the metformin XR tablets administered in other treatment arms) for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Canagliflozin 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:	
One 100 mg capsule taken orally once daily before the morning meal	
Investigational medicinal product name	Placebo Tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
One Placebo tablet with the evening meal.	
Investigational medicinal product name	Placebo Capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
One matching placebo capsule with the evening meal.	
Arm title	Canagliflozin 300 mg
Arm description:	
Subjects received one 300 mg canagliflozin capsule before the morning meal and one matching placebo capsule with the evening meal plus placebo tablets with the evening meal (to match the metformin XR tablets administered in other treatment arms) for 26 weeks.	
Arm type	Experimental
Investigational medicinal product name	Canagliflozin 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
One 300 mg capsule taken orally (by mouth) once daily before the morning meal for 26 weeks.	
Investigational medicinal product name	Placebo Tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
One Placebo tablet with the evening meal for 26 weeks	
Investigational medicinal product name	Placebo Capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
One placebo capsule was taken before the morning meal and one placebo capsule was taken with evening meal.	
Arm title	Canagliflozin 100 mg/Metformin XR
Arm description:	
Subjects received one 100 mg canagliflozin capsule with the evening meal and one matching placebo capsule before the morning meal plus metformin XR tablets (in doses titrated over 9 weeks) once daily with the evening meal for 26 weeks.	
Arm type	Experimental

Investigational medicinal product name	Canagliflozin 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One 100 mg capsule taken orally once daily before the morning meal

Investigational medicinal product name	Placebo Capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One placebo capsule was taken before the morning meal and one placebo capsule was taken with evening meal.

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One 500 mg tablet was taken from Day 1 up to week 1 followed by two 500 mg tablets was taken from week 1 up to week 3 and three 500 mg tablets was taken from week 3 to week 6 followed by four 500 mg tablets from Week 6 to Week 9. Tablets was administered with the evening meal.

Arm title	Canagliflozin 300 mg/Metformin XR
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Arm description:

Subjects received one 300 mg canagliflozin capsule with the evening meal and one matching placebo capsule before the morning meal plus metformin XR tablets (in doses titrated over 9 weeks) once daily with the evening meal for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Canagliflozin 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One 300 mg capsule taken orally (by mouth) once daily before the morning meal for 26 weeks.

Investigational medicinal product name	Placebo Capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One placebo capsule was taken before the morning meal and one placebo capsule was taken with evening meal.

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One 500 mg tablet was taken from Day 1 up to week 1 followed by two 500 mg tablets was taken from week 1 up to week 3 and three 500 mg tablets was taken from week 3 to week 6 followed by four 500 mg tablets from Week 6 to Week 9. Tablets was administered with the evening meal.

Number of subjects in period 1	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg
Started	237	237	238
Completed	205	211	216
Not completed	32	26	22
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	18	11	7
Physician decision	1	1	-
Adverse event, non-fatal	2	2	4
Other	1	1	2
Pregnancy	1	-	-
Adverse event, serious non-fatal	2	1	3
Lost to follow-up	5	2	4
Lack of efficacy	1	6	1
Protocol deviation	-	2	1

Number of subjects in period 1	Canagliflozin 100 mg/Metformin XR	Canagliflozin 300 mg/Metformin XR
Started	237	237
Completed	225	212
Not completed	12	25
Adverse event, serious fatal	-	-
Consent withdrawn by subject	5	7
Physician decision	-	-
Adverse event, non-fatal	2	6
Other	1	2
Pregnancy	-	-
Adverse event, serious non-fatal	2	2
Lost to follow-up	2	3
Lack of efficacy	-	2
Protocol deviation	-	3

Baseline characteristics

Reporting groups

Reporting group title	Metformin XR
Reporting group description: Subjects received metformin extended release (XR) tablets (in doses titrated over 9 weeks) once daily with the evening meal, plus one placebo capsule before the morning meal and one placebo capsule with the evening meal (to match the canagliflozin capsules administered in other treatment arms) for 26 weeks.	
Reporting group title	Canagliflozin 100 mg
Reporting group description: Subjects received one 100 milligram (mg) canagliflozin capsule before the morning meal and one matching placebo capsule with the evening meal plus placebo tablets with the evening meal (to match the metformin XR tablets administered in other treatment arms) for 26 weeks.	
Reporting group title	Canagliflozin 300 mg
Reporting group description: Subjects received one 300 mg canagliflozin capsule before the morning meal and one matching placebo capsule with the evening meal plus placebo tablets with the evening meal (to match the metformin XR tablets administered in other treatment arms) for 26 weeks.	
Reporting group title	Canagliflozin 100 mg/Metformin XR
Reporting group description: Subjects received one 100 mg canagliflozin capsule with the evening meal and one matching placebo capsule before the morning meal plus metformin XR tablets (in doses titrated over 9 weeks) once daily with the evening meal for 26 weeks.	
Reporting group title	Canagliflozin 300 mg/Metformin XR
Reporting group description: Subjects received one 300 mg canagliflozin capsule with the evening meal and one matching placebo capsule before the morning meal plus metformin XR tablets (in doses titrated over 9 weeks) once daily with the evening meal for 26 weeks.	

Reporting group values	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg
Number of subjects	237	237	238
Title for AgeCategorical Units: subjects			
Children(2-11 years)	0	0	0
Adolescents(12-17 years)	0	0	0
Adults (18-64 years)	188	201	203
From 65 to 84 years	49	36	35
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	55.2	54	55.8
standard deviation	± 9.75	± 10.7	± 9.56
Title for Gender Units: subjects			
Female	121	132	113
Male	116	105	125

Reporting group values	Canagliflozin 100 mg/Metformin XR	Canagliflozin 300 mg/Metformin XR	Total
Number of subjects	237	237	1186

Title for AgeCategorical Units: subjects			
Children(2-11 years)	0	0	0
Adolescents(12-17 years)	0	0	0
Adults (18-64 years)	204	194	990
From 65 to 84 years	33	43	196
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	54.2	55.4	
standard deviation	± 9.58	± 9.84	-
Title for Gender Units: subjects			
Female	129	122	617
Male	108	115	569

End points

End points reporting groups

Reporting group title	Metformin XR
Reporting group description: Subjects received metformin extended release (XR) tablets (in doses titrated over 9 weeks) once daily with the evening meal, plus one placebo capsule before the morning meal and one placebo capsule with the evening meal (to match the canagliflozin capsules administered in other treatment arms) for 26 weeks.	
Reporting group title	Canagliflozin 100 mg
Reporting group description: Subjects received one 100 milligram (mg) canagliflozin capsule before the morning meal and one matching placebo capsule with the evening meal plus placebo tablets with the evening meal (to match the metformin XR tablets administered in other treatment arms) for 26 weeks.	
Reporting group title	Canagliflozin 300 mg
Reporting group description: Subjects received one 300 mg canagliflozin capsule before the morning meal and one matching placebo capsule with the evening meal plus placebo tablets with the evening meal (to match the metformin XR tablets administered in other treatment arms) for 26 weeks.	
Reporting group title	Canagliflozin 100 mg/Metformin XR
Reporting group description: Subjects received one 100 mg canagliflozin capsule with the evening meal and one matching placebo capsule before the morning meal plus metformin XR tablets (in doses titrated over 9 weeks) once daily with the evening meal for 26 weeks.	
Reporting group title	Canagliflozin 300 mg/Metformin XR
Reporting group description: Subjects received one 300 mg canagliflozin capsule with the evening meal and one matching placebo capsule before the morning meal plus metformin XR tablets (in doses titrated over 9 weeks) once daily with the evening meal for 26 weeks.	

Primary: Change in glycated hemoglobin (HbA1c) from baseline to Week 26

End point title	Change in glycated hemoglobin (HbA1c) from baseline to Week 26
End point description: The change from baseline in HbA1c was compared at 26 week between the different treatment groups. Here 'N' signifies number of subjects who were analysed for this outcome measure.	
End point type	Primary
End point timeframe: Day 1 (Baseline) and Week 26	

End point values	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg	Canagliflozin 100 mg/Metformin XR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	230	230	234	235
Units: percentage of HbA1c				
least squares mean (standard error)	-1.3 ($\pm$ 0.071)	-1.37 ($\pm$ 0.071)	-1.42 ($\pm$ 0.07)	-1.77 ($\pm$ 0.069)

End point values	Canagliflozin 300 mg/Metformin XR			
Subject group type	Reporting group			
Number of subjects analysed	236			
Units: percentage of HbA1c				
least squares mean (standard error)	-1.78 ($\pm$ 0.07)			

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Canagliflozin 100 mg/Metformin XR v Metformin XR
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.657
upper limit	-0.269
Variability estimate	Standard error of the mean
Dispersion value	0.099

Statistical analysis title	Statistical analysis 2
Comparison groups	Canagliflozin 300 mg/Metformin XR v Metformin XR
Number of subjects included in analysis	466
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	-0.28
Variability estimate	Standard error of the mean
Dispersion value	0.099

Statistical analysis title	Statistical analysis 3
Comparison groups	Canagliflozin 100 mg/Metformin XR v Canagliflozin 100 mg
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.594
upper limit	-0.207
Variability estimate	Standard error of the mean
Dispersion value	0.099

Statistical analysis title	Statistical analysis 4
Comparison groups	Canagliflozin 300 mg/Metformin XR v Canagliflozin 300 mg
Number of subjects included in analysis	470
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.557
upper limit	-0.169
Variability estimate	Standard error of the mean
Dispersion value	0.099

Statistical analysis title	Statistical analysis 5
Comparison groups	Canagliflozin 100 mg v Metformin XR
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.258
upper limit	0.133
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Statistical analysis 6
Comparison groups	Canagliflozin 300 mg v Metformin XR
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.307
upper limit	0.082
Variability estimate	Standard error of the mean
Dispersion value	0.099

Secondary: Percent Change From Baseline in Body Weight at Week 26

End point title	Percent Change From Baseline in Body Weight at Week 26
End point description:	
The percent change in body weight from baseline to week 26 was compared between the different treatment groups. Here 'N' signifies number of subjects who were analysed for this outcome measure.	
End point type	Secondary
End point timeframe:	
Day 1 (Baseline) and Week 26	

End point values	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg	Canagliflozin 100 mg/Metformin XR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	237	236	236	237
Units: percent change				
least squares mean (standard error)	-2.1 (± 0.3)	-3 (± 0.3)	-3.9 (± 0.3)	-3.5 (± 0.3)

End point values	Canagliflozin 300 mg/Metformin XR			
Subject group type	Reporting group			
Number of subjects analysed	236			
Units: percent change				
least squares mean (standard error)	-4.2 (± 0.3)			

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Canagliflozin 100 mg/Metformin XR v Metformin XR
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	0.4

Statistical analysis title	Statistical analysis 2
Comparison groups	Canagliflozin 300 mg/Metformin XR v Metformin XR
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-1.4
Variability estimate	Standard error of the mean
Dispersion value	0.4

Statistical analysis title	Statistical analysis 3
Comparison groups	Canagliflozin 100 mg v Metformin XR
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.4

Statistical analysis title	Statistical analysis 4
Comparison groups	Canagliflozin 300 mg v Metformin XR
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	-1.1
Variability estimate	Standard error of the mean
Dispersion value	0.4

Secondary: Percentage of Subjects With Glycated Hemoglobin (HbA1c) Less Than 7 Percent at Week 26

End point title	Percentage of Subjects With Glycated Hemoglobin (HbA1c) Less Than 7 Percent at Week 26
End point description: The percentage of subjects achieved HbA1c less than 7 percent at Week 26 was compared between the different treatment groups. Here 'N' signifies number of subjects who were analysed for this outcome measure.	
End point type	Secondary

End point timeframe:

Week 26

End point values	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg	Canagliflozin 100 mg/Metformin XR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	207 ^[1]	206 ^[2]	215 ^[3]	224 ^[4]
Units: percentage of subjects				
number (not applicable)	43	38.8	42.8	49.6

Notes:

[1] - mITT population

[2] - mITT population

[3] - mITT population

[4] - mITT population

End point values	Canagliflozin 300 mg/Metformin XR			
Subject group type	Reporting group			
Number of subjects analysed	213 ^[5]			
Units: percentage of subjects				
number (not applicable)	56.8			

Notes:

[5] - mITT population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Canagliflozin 100 mg/Metformin XR v Metformin XR
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	2.37

Statistical analysis title	Statistical analysis 2
Comparison groups	Canagliflozin 300 mg/Metformin XR v Metformin XR

Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.52
upper limit	3.77

Secondary: Change in Systolic Blood Pressure From Baseline at Week 26

End point title	Change in Systolic Blood Pressure From Baseline at Week 26
End point description:	The change in systolic blood pressure from baseline at Week 26 was compared between the different treatment groups. Here 'N' signifies number of subjects who were analysed for this outcome measure.
End point type	Secondary
End point timeframe:	Day 1 (Baseline) and Week 26

End point values	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg	Canagliflozin 100 mg/Metformin XR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	237	236	236	237
Units: percent Change				
least squares mean (standard error)	-0.33 (± 0.633)	-2.24 (± 0.627)	-2.36 (± 0.622)	-2.24 (± 0.613)

End point values	Canagliflozin 300 mg/Metformin XR			
Subject group type	Reporting group			
Number of subjects analysed	236			
Units: percent Change				
least squares mean (standard error)	-1.65 (± 0.624)			

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Canagliflozin 100 mg/Metformin XR v Metformin XR
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.641
upper limit	-0.182
Variability estimate	Standard error of the mean
Dispersion value	0.882

Statistical analysis title	Statistical analysis 2
Comparison groups	Canagliflozin 300 mg/Metformin XR v Metformin XR
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.147
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.058
upper limit	0.431
Variability estimate	Standard error of the mean
Dispersion value	0.889

Secondary: Percent Change in Fasting High-Density Lipoprotein Cholesterol (HDL-C) From Baseline to Week 26

End point title	Percent Change in Fasting High-Density Lipoprotein Cholesterol (HDL-C) From Baseline to Week 26
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End point description:

The percentage change in Fasting High-Density Lipoprotein Cholesterol (HDL-C) from baseline to Week 26 was compared between the different treatment groups. Here 'N' signifies number of subjects who were analysed for this outcome measure.

End point type	Secondary
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End point timeframe:

Day 1 (Baseline) and Week 26

End point values	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg	Canagliflozin 100 mg/Metformin XR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	222	225	228	227
Units: Percent Change				
least squares mean (standard error)	10.2 (± 1.5)	17.6 (± 1.5)	16.6 (± 1.5)	15.5 (± 1.5)

End point values	Canagliflozin 300 mg/Metformin XR			
Subject group type	Reporting group			
Number of subjects analysed	225			
Units: Percent Change				
least squares mean (standard error)	14.5 (± 1.5)			

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Canagliflozin 100 mg/Metformin XR v Metformin XR
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.147
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	9.5
Variability estimate	Standard error of the mean
Dispersion value	2.1

Statistical analysis title	Statistical analysis 2
Comparison groups	Canagliflozin 300 mg/Metformin XR v Metformin XR

Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.147
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	8.5
Variability estimate	Standard error of the mean
Dispersion value	2.1

Secondary: Percent Change in Triglycerides From Baseline to Week 26

End point title	Percent Change in Triglycerides From Baseline to Week 26
End point description:	The percentage change in triglycerides from baseline to Week 26 was compared between the different treatment groups. Here 'N' signifies number of subjects who were analysed for this outcome measure.
End point type	Secondary
End point timeframe:	Day 1 (Baseline) and Week 26

End point values	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg	Canagliflozin 100 mg/Metformin XR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	223 ^[6]	225 ^[7]	229 ^[8]	229 ^[9]
Units: percent change				
arithmetic mean (standard deviation)	13.6 (± 51.8)	1.7 (± 50.5)	2.8 (± 60.3)	13 (± 81.9)

Notes:

[6] - mITT population

[7] - mITT population

[8] - mITT population

[9] - mITT population

End point values	Canagliflozin 300 mg/Metformin XR			
Subject group type	Reporting group			
Number of subjects analysed	225 ^[10]			
Units: percent change				
arithmetic mean (standard deviation)	21.2 (± 71.1)			

Notes:

[10] - mITT population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Canagliflozin 100 mg/Metformin XR v Metformin XR
Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.608
Method	Wilcoxon rank sum test
Parameter estimate	Hodges-Lehman Estimate
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	3.4

Statistical analysis title	Statistical analysis 2
Comparison groups	Canagliflozin 300 mg/Metformin XR v Metformin XR
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.806
Method	Wilcoxon rank sum test
Parameter estimate	Hodges-Lehman Estimate
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	10

Secondary: Number of Subjects With Treatment Emergent Adverse Events (AEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (AEs)
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End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between administration of study drug and up to 30 days after last dose of study drug that were absent before treatment or that

worsened relative to pre-treatment state.

End point type	Secondary
End point timeframe:	
Up to 30 weeks of last study drug administration	

End point values	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg	Canagliflozin 100 mg/Metformin XR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	237 ^[11]	237 ^[12]	238 ^[13]	237 ^[14]
Units: subjects				
number (not applicable)	89	88	95	99

Notes:

[11] - mITT population

[12] - mITT population

[13] - mITT population

[14] - mITT population

End point values	Canagliflozin 300 mg/Metformin XR			
Subject group type	Reporting group			
Number of subjects analysed	237 ^[15]			
Units: subjects				
number (not applicable)	105			

Notes:

[15] - mITT population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 weeks of last study drug administration

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Metformin XR
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Reporting group description:

One 500 mg tablet was taken from Day 1 up to week 1 followed by two 500 mg tablets was taken from week 1 up to week 3 and three 500 mg tablets was taken from week 3 to week 6 followed by four 500 mg tablets from Week 6 to Week 9. Tablets will be administered with the evening meal.

Reporting group title	Canagliflozin 100 mg
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Reporting group description:

Subjects received one 100 milligram (mg) canagliflozin capsule before the morning meal and one matching placebo capsule with the evening meal plus placebo tablets with the evening meal (to match the metformin XR tablets administered in other treatment arms) for 26 weeks.

Reporting group title	Canagliflozin 300 mg
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Reporting group description:

Subjects received one 300 mg canagliflozin capsule before the morning meal and one matching placebo capsule with the evening meal plus placebo tablets with the evening meal (to match the metformin XR tablets administered in other treatment arms) for 26 weeks.

Reporting group title	Canagliflozin 100 mg/Metformin XR
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Reporting group description:

Subjects received one 100 mg canagliflozin capsule with the evening meal and one matching placebo capsule before the morning meal plus metformin XR tablets (in doses titrated over 9 weeks) once daily with the evening meal for 26 weeks.

Reporting group title	Canagliflozin 300 mg/Metformin XR
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Reporting group description:

Co-administration of Canagliflozin 300 mg and Metformin XR

Serious adverse events	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 237 (2.95%)	4 / 237 (1.69%)	7 / 238 (2.94%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial Adenocarcinoma			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	0 / 238 (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
Medullary Thyroid Cancer			

subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic Carcinoma			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial Occlusive Disease			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	0 / 238 (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
Deep Vein Thrombosis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Cardiac Death			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 237 (0.00%)	1 / 237 (0.42%)	0 / 238 (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			
Extradural Haematoma			

subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Laminectomy Syndrome			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	2 / 238 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 237 (0.00%)	1 / 237 (0.42%)	0 / 238 (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
Atrial Fibrillation			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	0 / 237 (0.00%)	1 / 237 (0.42%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicobrachial Syndrome			

subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	2 / 238 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 237 (0.00%)	1 / 237 (0.42%)	0 / 238 (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
Immune Thrombocytopenic Purpura			
subjects affected / exposed	0 / 237 (0.00%)	1 / 237 (0.42%)	0 / 238 (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			
Diverticulum			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	0 / 238 (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
Eiploic Appendagitis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	0 / 238 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	0 / 238 (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 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar Pneumonia			
subjects affected / exposed	0 / 237 (0.00%)	1 / 237 (0.42%)	0 / 238 (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
Ophthalmic Herpes Simplex			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Ketoacidosis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Canagliflozin 100 mg/Metformin XR	Canagliflozin 300 mg/Metformin XR	
Total subjects affected by serious adverse events			

subjects affected / exposed	7 / 237 (2.95%)	4 / 237 (1.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial Adenocarcinoma			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medullary Thyroid Cancer			
subjects affected / exposed	0 / 237 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Carcinoma			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial Occlusive Disease			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cardiac Death			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Extradural Haematoma			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Laminectomy Syndrome			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			

subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial Syndrome			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	0 / 237 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune Thrombocytopenic Purpura			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epiplonic Appendagitis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 237 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic Herpes Simplex			
subjects affected / exposed	0 / 237 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			

subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Ketoacidosis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Metformin XR	Canagliflozin 100 mg	Canagliflozin 300 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 237 (15.61%)	38 / 237 (16.03%)	38 / 238 (15.97%)
Investigations			
Glomerular Filtration Rate Decreased			
subjects affected / exposed	0 / 237 (0.00%)	6 / 237 (2.53%)	3 / 238 (1.26%)
occurrences (all)	0	7	3
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 237 (0.42%)	2 / 237 (0.84%)	2 / 238 (0.84%)
occurrences (all)	1	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 237 (3.38%)	4 / 237 (1.69%)	4 / 238 (1.68%)
occurrences (all)	10	4	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 237 (1.27%)	3 / 237 (1.27%)	4 / 238 (1.68%)
occurrences (all)	7	4	4
Nausea			
subjects affected / exposed	6 / 237 (2.53%)	1 / 237 (0.42%)	2 / 238 (0.84%)
occurrences (all)	6	1	2
Vomiting			
subjects affected / exposed	5 / 237 (2.11%)	2 / 237 (0.84%)	1 / 238 (0.42%)
occurrences (all)	6	3	1

Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	4 / 237 (1.69%)	3 / 237 (1.27%)	5 / 238 (2.10%)
occurrences (all)	6	4	5
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 237 (1.27%)	0 / 237 (0.00%)	1 / 238 (0.42%)
occurrences (all)	3	0	1
Influenza			
subjects affected / exposed	5 / 237 (2.11%)	6 / 237 (2.53%)	5 / 238 (2.10%)
occurrences (all)	5	6	6
Nasopharyngitis			
subjects affected / exposed	3 / 237 (1.27%)	9 / 237 (3.80%)	9 / 238 (3.78%)
occurrences (all)	3	9	9
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 237 (2.53%)	2 / 237 (0.84%)	6 / 238 (2.52%)
occurrences (all)	7	2	10
Urinary Tract Infection			
subjects affected / exposed	3 / 237 (1.27%)	3 / 237 (1.27%)	3 / 238 (1.26%)
occurrences (all)	3	3	3
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	6 / 237 (2.53%)	5 / 237 (2.11%)	1 / 238 (0.42%)
occurrences (all)	6	5	1

Non-serious adverse events	Canagliflozin 100 mg/Metformin XR	Canagliflozin 300 mg/Metformin XR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 237 (17.72%)	43 / 237 (18.14%)	
Investigations			
Glomerular Filtration Rate Decreased			
subjects affected / exposed	1 / 237 (0.42%)	2 / 237 (0.84%)	
occurrences (all)	1	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 237 (2.11%)	1 / 237 (0.42%)	
occurrences (all)	5	1	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	9 / 237 (3.80%) 11	7 / 237 (2.95%) 9	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	10 / 237 (4.22%) 11	10 / 237 (4.22%) 13	
Nausea subjects affected / exposed occurrences (all)	1 / 237 (0.42%) 1	2 / 237 (0.84%) 2	
Vomiting subjects affected / exposed occurrences (all)	2 / 237 (0.84%) 2	0 / 237 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Back Pain subjects affected / exposed occurrences (all)	6 / 237 (2.53%) 7	5 / 237 (2.11%) 5	
Infections and infestations			
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 237 (0.42%) 1	5 / 237 (2.11%) 6	
Influenza subjects affected / exposed occurrences (all)	8 / 237 (3.38%) 9	7 / 237 (2.95%) 7	
Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 237 (2.53%) 8	3 / 237 (1.27%) 3	
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	3 / 237 (1.27%) 3	4 / 237 (1.69%) 4	
Urinary Tract Infection subjects affected / exposed occurrences (all)	2 / 237 (0.84%) 2	7 / 237 (2.95%) 10	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 237 (0.00%)	2 / 237 (0.84%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2013	Changes was implemented before the start of any study-related procedures and the overall reason was to update the study based on the results from completed studies in the Phase 3 program and feedback obtained from Health Authority review
04 February 2014	The overall reason was to remove adjudication of cardiovascular (CV) and renal events (as dedicated studies were conducted and designed to assess the effects of canagliflozin on CV and renal and outcomes)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported