Clinical trial results:
A Randomized, Multicenter, Double-Blind, Parallel-Group, Placebo-Controlled Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (>=10 to <18 years) with Type 2 Diabetes Mellitus

Summary

EudraCT number	2016-005223-88
Trial protocol	GR PL Outside EU/EEA
Global end of trial date	20 September 2023

Results information

Result version number	v1 (current)
This version publication date	31 March 2024
First version publication date	31 March 2024

Trial information

Trial identification

Sponsor protocol code	28431754DIA3018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03170518
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, NJ 08869, United States, 300
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001030-PIP01-10
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 September 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to assess the effect of canagliflozin relative to placebo on glycated hemoglobin (HbA1c) after 26 weeks of treatment, and to assess the overall safety and tolerability of canagliflozin.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 July 2017
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	Brazil: 12
Country: Number of subjects enrolled	China: 4
Country: Number of subjects enrolled	India: 9
Country: Number of subjects enrolled	Mexico: 36
Country: Number of subjects enrolled	Malaysia: 30
Country: Number of subjects enrolled	Philippines: 23
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	171
EEA total number of subjects	6

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)	19
Adolescents (12-17 years)	152
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 171 subjects (87 received placebo and 84 received Canagliflozin) were enrolled. Of the 84 subjects on canagliflozin, 33 subjects were re-randomised (1:1 ratio) at Week 13 based on Week 12 HbA1c (>=7%) and eGFR (>=60 mL/min/1.73 m^2): 16 subjects remained on 100 milligrams (mg) and 17 subjects were up-titrated to receive 300 mg.

Pre-assignment

Screening details:

Randomisation was stratified by antihyperglycemic agent (AHA) background (that is, diet and exercise only; metformin monotherapy; insulin monotherapy; or combination of insulin and metformin) and age group (greater than or equal to [>=]10 to less than [<]15 years old; >=15 to <18 years old).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received orally 1 placebo tablet matching to canagliflozin 100/300 milligrams (mg) once-daily from Day 1 till Week 52. At Week 13, subjects who met re-randomisation criteria (glycated hemoglobin [HbA1c] of >=7.0 percent [%], estimated glomerular filtration rate [eGFR] >=60 millilitre per minute per 1.73 metre square [mL/min/1.73 m^2]) at Week 12 were alone re-randomized to receive orally 1 tablet of placebo matching canagliflozin 100 mg and 1 tablet of placebo matching canagliflozin 300 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of placebo matching to canagliflozin 100 mg once daily till Week 52.

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

Dosage and administration details:

Subjects received 1 placebo matching to canagliflozin 100/300 milligrams (mg) once-daily from Day 1 till Week 52. At Week 13, subjects who met re-randomisation criteria (HbA1c] of >=7.0%, eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised to receive orally 1 placebo matching canagliflozin 100 mg and 1 placebo matching canagliflozin 300 mg once daily till Week 52.

Arm title	Canagliflozin 100 mg

Arm description:

Subjects received orally canagliflozin 100 mg tablet once daily from Day 1 till Week 12. At Week 13, subjects who met re-randomisation criteria (HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised at 1:1 ratio to receive orally 1 tablet of canagliflozin 100 mg tablet and 1 tablet of placebo matching canagliflozin 300 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of canagliflozin 100 mg once daily till Week 52.

Arm type	Experimental

Investigational medicinal product name	Canagliflozin
Investigational medicinal product code	
Other name	JNJ-28431754
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received canagliflozin 100 mg once daily from Day 1 till Week 12. At week 13, subjects who had HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2 were re-randomised at 1:1 ratio to continue receiving canagliflozin 100 mg and 1 added placebo matching to canagliflozin 300 mg once daily for the remainder of the double-blind treatment period till Week 52.

Arm title	Canagliflozin 300 mg

Arm description:

Subjects received orally canagliflozin 100 mg tablet once daily from Day 1 till Week 12. At Week 13, subjects who met re-randomisation criteria (HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised at 1:1 ratio to receive orally 1 tablet of canagliflozin 300 mg tablet and 1 tablet of placebo matching canagliflozin 100 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of canagliflozin 100 mg once daily till Week 52.

Arm type	Experimental
Investigational medicinal product name	Canagliflozin
Investigational medicinal product code	
Other name	JNJ-28431754
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

At Week 13, subjects who met re-randomisation criteria (HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised at 1:1 ratio to receive 1 canagliflozin 300 mg and 1 placebo matching canagliflozin 100 mg once daily till Week 52.

Number of subjects in period 1	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg
Started	87	67	17
Subjects not re-randomized at Week 13	27 [1]	51 [2]	0 [3]
Subjects Re-randomized at Week 13	60 [4]	16 [5]	17
Subjects treated from Week13 till Week52	87	67	17
Completed	75	60	14
Not completed	12	7	3
Physician decision	1	-	-
Site terminated by sponsor	-	1	-
Non-compliance with study drug	1	-	1
Lost to follow-up	4	1	-
Withdrawal by parent/guardian	2	-	-
Withdrawal by subject	4	5	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only reported subjects were planned to be included in the respective milestone.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only reported subjects were planned to be included in the respective milestone.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only reported subjects were planned to be included in the respective milestone.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only reported subjects were planned to be included in the respective milestone.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only reported subjects were planned to be included in the respective milestone.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Subjects received orally 1 placebo tablet matching to canagliflozin 100/300 milligrams (mg) once-daily from Day 1 till Week 52. At Week 13, subjects who met re-randomisation criteria (glycated hemoglobin [HbA1c] of >=7.0 percent [%], estimated glomerular filtration rate [eGFR] >=60 millilitre per minute per 1.73 metre square [mL/min/1.73 m^2]) at Week 12 were alone re-randomized to receive orally 1 tablet of placebo matching canagliflozin 100 mg and 1 tablet of placebo matching canagliflozin 300 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of placebo matching to canagliflozin 100 mg once daily till Week 52.

Reporting group title	Canagliflozin 100 mg

Reporting group description:

Subjects received orally canagliflozin 100 mg tablet once daily from Day 1 till Week 12. At Week 13, subjects who met re-randomisation criteria (HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised at 1:1 ratio to receive orally 1 tablet of canagliflozin 100 mg tablet and 1 tablet of placebo matching canagliflozin 300 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of canagliflozin 100 mg once daily till Week 52.

Reporting group title	Canagliflozin 300 mg

Reporting group description:

Subjects received orally canagliflozin 100 mg tablet once daily from Day 1 till Week 12. At Week 13, subjects who met re-randomisation criteria (HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised at 1:1 ratio to receive orally 1 tablet of canagliflozin 300 mg tablet and 1 tablet of placebo matching canagliflozin 100 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of canagliflozin 100 mg once daily till Week 52.

Reporting group values	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg
Number of subjects	87	67	17
Title for AgeCategorical Units: subjects			
Children (2-11 years)	10	7	2
Adolescents (12-17 years)	77	60	15
Adults (18-64 years)	0	0	0
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	14.4	14.2	14.5
standard deviation	± 2.04	± 2	± 2.07
Title for Gender Units: subjects			
Female	60	49	8
Male	27	18	9

Reporting group values	Total		
Number of subjects	171		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	19		
Adolescents (12-17 years)	152		

Adults (18-64 years)	0		
From 65 to 84 years	0		
85 years and over	0		
Title for AgeContinuous			
Units: years			
arithmetic mean			
standard deviation	-		
Title for Gender			
Units: subjects			
Female	117		
Male	54		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received orally 1 placebo tablet matching to canagliflozin 100/300 milligrams (mg) once-daily from Day 1 till Week 52. At Week 13, subjects who met re-randomisation criteria (glycated hemoglobin [HbA1c] of >=7.0 percent [%], estimated glomerular filtration rate [eGFR] >=60 millilitre per minute per 1.73 metre square [mL/min/1.73 m^2]) at Week 12 were alone re-randomized to receive orally 1 tablet of placebo matching canagliflozin 100 mg and 1 tablet of placebo matching canagliflozin 300 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of placebo matching to canagliflozin 100 mg once daily till Week 52.

Reporting group title	Canagliflozin 100 mg

Reporting group description:

Subjects received orally canagliflozin 100 mg tablet once daily from Day 1 till Week 12. At Week 13, subjects who met re-randomisation criteria (HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised at 1:1 ratio to receive orally 1 tablet of canagliflozin 100 mg tablet and 1 tablet of placebo matching canagliflozin 300 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of canagliflozin 100 mg once daily till Week 52.

Reporting group title	Canagliflozin 300 mg

Reporting group description:

Subjects received orally canagliflozin 100 mg tablet once daily from Day 1 till Week 12. At Week 13, subjects who met re-randomisation criteria (HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised at 1:1 ratio to receive orally 1 tablet of canagliflozin 300 mg tablet and 1 tablet of placebo matching canagliflozin 100 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of canagliflozin 100 mg once daily till Week 52.

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received orally 1 placebo tablet matching to canagliflozin 100/300 milligrams (mg) once-daily from Day 1 till Week 52. At Week 13, subjects who met re-randomisation criteria (glycated hemoglobin [HbA1c] of >=7.0%, estimated glomerular filtration rate [eGFR] >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised to receive orally 1 tablet of placebo matching canagliflozin 100 mg and 1 tablet of placebo matching canagliflozin 300 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of placebo matching to canagliflozin 100 mg once daily till Week 52.

Subject analysis set title	Canagliflozin
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received orally canagliflozin 100 mg tablet once daily from Day 1 till Week 12. At Week 13, subjects who met re-randomisation criteria (HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised (1:1 ratio) to receive orally 1 tablet of canagliflozin 100 mg tablet and 1 tablet of placebo matching canagliflozin 300 mg or canagliflozin 300 mg tablet and 1 tablet of placebo matching canagliflozin 100 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of canagliflozin 100 mg once daily till Week 52.

Primary: Change From Baseline in Glycated Hemoglobin (HbA1c) at Week 26

End point title	Change From Baseline in Glycated Hemoglobin (HbA1c) at Week 26

End point description:

Change from baseline in HbA1c at Week 26 was analysed using a pattern mixture model with multiple imputation. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. Full analysis set (FAS) included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c measurement. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline (Day 1), Week 26

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	84		
Units: Percent (%) of HbA1c				
least squares mean (standard error)	0.39 (± 0.191)	-0.37 (± 0.194)		

Statistical analyses

Statistical analysis title	Canagliflozin Vs Placebo
Comparison groups	Placebo v Canagliflozin
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	-0.27

Notes:

[1] - Imputed datasets were analyzed using analysis of covariance (ANCOVA) with terms for treatment, stratification factors (AHA background and age group), and baseline HbA1c.

Primary: Percentage of Subjects with Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects with Treatment-emergent Adverse Events (TEAEs)[2]

End point description:

AE was any untoward medical occurrence in a clinical study subject administered a pharmaceutical (investigational or non investigational) product. An AE did not necessarily have a causal relationship with the pharmaceutical/biological agent under study. TEAE was defined as the AEs occurring after first administration of study intervention (or worsened since then) up to 30 days post last dose of study intervention. Safety analysis set included all randomised subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to 30 days post last dose (up to Week 56)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87	67	17	
Units: Percentage of subjects				
number (not applicable)	74.7	76.1	82.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) at Weeks 26 and 52

End point title	Change From Baseline in Fasting Plasma Glucose (FPG) at Weeks 26 and 52

End point description:

Change from baseline in FPG at Weeks 26 and Week 52 was reported. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. FAS included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c measurement. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint and 'n' (number analysed) signifies number of subjects analysed at each specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 26 and 52

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	79		
Units: milligrams per deciliter (mg/dL)				
least squares mean (standard error)				
Week 26 (n=82, 76)	15.3 (± 6.68)	-11.5 (± 6.86)		
Week 52 (n=83, 79)	19.2 (± 6.90)	-16.4 (± 6.98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HbA1c Less Than (<)7.5 Percent (%), <7%, and <6.5% at Weeks 26 and 52

End point title	Percentage of Subjects With HbA1c Less Than (<)7.5 Percent (%), <7%, and <6.5% at Weeks 26 and 52

End point description:

The percentage of subjects achieving HbA1c <7.5%, <7.0%, and <6.0% at Weeks 26 and 52 was reported. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. FAS included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c

measurement.

End point type	Secondary

End point timeframe:

Weeks 26 and 52

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	84		
Units: Percentage of subjects				
number (not applicable)				
Week 26: HbA1c <7.5%	40.0	64.9		
Week 52: HbA1c <7.5%	29.3	69.0		
Week 26: HbA1c <7%	27.5	51.9		
Week 52: HbA1c <7%	22.7	54.9		
Week 26: HbA1c <6.5%	11.3	41.6		
Week 52: HbA1c <6.5%	12.0	36.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Received Rescue Therapy

End point title	Percentage of Subjects Who Received Rescue Therapy

End point description:

Percentage of subjects who received rescue therapy were reported. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. FAS included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c measurement.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 52

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	84		
Units: Percentage of subjects				
number (not applicable)	46.0	11.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Body Weight at Weeks 26 and 52

End point title	Percent Change From Baseline in Body Weight at Weeks 26 and 52

End point description:

The percent change in body weight from baseline to Weeks 26 and 52 were reported. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. FAS included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c measurement. N (number of subjects analysed) were defined subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 26 and 52

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	84		
Units: Percent change				
least squares mean (standard error)				
Week 26	-0.0 (± 0.51)	-1.6 (± 0.51)		
Week 52	0.4 (± 0.69)	-0.5 (± 0.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Fasting Plasma Lipids Levels at Weeks 26 and 52

End point title	Percent Change From Baseline in Fasting Plasma Lipids Levels at Weeks 26 and 52

End point description:

The percentage change from baseline in fasting plasma lipids (low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], total cholesterol, non-HDL-C, and triglycerides) at Weeks 26 and 52 were reported. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. FAS included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c measurement. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint and 'n' (number analysed) signifies number of subjects analysed at each specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 26, and 52

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78	76		
Units: Percent change				
least squares mean (standard error)				
Week 26: Total cholesterol (n-76,72)	1.2 (± 2.22)	8.2 (± 2.22)		
Week 52: Total cholesterol (n-78,76)	5.6 (± 2.16)	5.1 (± 2.13)		
Week 26: LDL-C (n=67,67)	3.3 (± 3.73)	12.4 (± 3.58)		
Week 52: LDL-C (n=72,74)	7.5 (± 3.57)	8.3 (± 3.44)		
Week 26: HDL-C (n=68,68)	1.5 (± 2.40)	6.4 (± 2.33)		
Week 52: HDL-C (n=73,74)	1.0 (± 2.58)	7.9 (± 2.52)		
Week 26: non-HDL-C (n=66,66)	1.7 (± 2.69)	6.8 (± 2.62)		
Week 52: non-HDL-C (n=71,74)	7.7 (± 3.02)	5.0 (± 2.95)		
Week 26: Triglyceride (n=76,72)	8.6 (± 6.32)	4.6 (± 6.28)		
Week 52: Triglyceride (n=78,76)	18.2 (± 7.17)	3.4 (± 7.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Mass Index (BMI) at Weeks 26 and 52

End point title	Change From Baseline in Body Mass Index (BMI) at Weeks 26 and 52

End point description:

Change from baseline in BMI at Weeks 26 and 52 were reported. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. FAS included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c measurement. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 26, and 52

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	84		
Units: kilograms per meter square (kg/m^2)				
least squares mean (standard error)				
Week 26	-0.4 (± 0.15)	-0.8 (± 0.15)		
Week 52	-0.5 (± 0.19)	-0.7 (± 0.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in LDL-C to HDL-C Ratio and Non-HDL-C to LDL-C Ratio at Weeks 26 and 52

End point title	Percent Change From Baseline in LDL-C to HDL-C Ratio and Non-HDL-C to LDL-C Ratio at Weeks 26 and 52

End point description:

The percentage change from baseline of LDL-C to HDL-C ratio and non-HDL-C to LDL-C ratio at Weeks 26 and 52 were reported. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. FAS included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c measurement. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint and 'n' (number analysed) signifies number of subjects analysed at each specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 26, and 52

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	74		
Units: Percent change				
least squares mean (standard error)				
Week 26: LDL-C/HDL-C (n=66,66)	0.5 (± 4.05)	2.5 (± 4.03)		
Week 52: LDL-C/HDL-C (n=71,74)	-1.5 (± 3.20)	4.0 (± 3.13)		
Week 26: non HDL-C/LDL-C (n=63,60)	1.1 (± 3.42)	3.3 (± 3.47)		
Week 52: non HDL-C/LDL-C (n=68,69)	-1.5 (± 3.20)	4.0 (± 3.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Diastolic Blood Pressure at Weeks 26 and 52

End point title	Change From Baseline in Diastolic Blood Pressure at Weeks 26 and 52

End point description:

Change from baseline in diastolic blood pressure at Weeks 26 and 52 were reported. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. FAS included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c measurement. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint and 'n' (number analysed) signifies number of subjects analysed at each specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 26, and 52

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	80		
Units: mmHg				
least squares mean (standard error)				
Week 26 (n=81,80)	-0.1 (± 0.78)	-0.1 (± 0.78)		
Week 52 (n=75,74)	0.7 (± 0.83)	-0.2 (± 0.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Systolic Blood Pressure at Weeks 26 and 52

End point title	Change From Baseline in Systolic Blood Pressure at Weeks 26 and 52

End point description:

Change from baseline in systolic blood pressure at Weeks 26 and 52 was reported. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. FAS included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c measurement. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint and 'n' (number analysed) signifies number of subjects analysed at each specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 26 and 52

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	80		
Units: millimetre of mercury (mmHg)				
least squares mean (standard error)				
Week 26 (n=81,80)	1.4 (± 1.04)	0.7 (± 1.04)		
Week 52 (n=75,74)	1.5 (± 1.06)	0.0 (± 1.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HbA1c at Weeks 12 and 52

End point title	Change From Baseline in HbA1c at Weeks 12 and 52

End point description:

Change from baseline in HbA1c at Weeks 12 and 52 were reported. Data for this endpoint was planned to be collected and analysed for the combined population of arm Canagliflozin 100 mg and Canagliflozin 300 mg. FAS included all subjects who were randomly assigned to a treatment group, received at least one dose of study agent and had a baseline HbA1c measurement. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint and 'n' (number analysed) signifies number of

subjects analysed at each specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 12, and 52

End point values	Placebo	Canagliflozin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	84		
Units: Percent (%) of HbA1c				
least squares mean (standard error)				
Week 12 (n=83,84)	0.10 (± 0.138)	-0.59 (± 0.137)		
Week 52 (n=75,71)	0.70 (± 0.182)	-0.32 (± 0.184)		

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Velocity at Weeks 26 and 52

End point title	Growth Velocity at Weeks 26 and 52

End point description:

Growth velocity (increase in height per year) at Weeks 26 and 52 were reported. Safety analysis set included all the subjects who were randomised and took at least 1 dose of study agent. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint and 'n' (number analysed) signifies number of subjects analysed at each specified timepoints.

End point type	Secondary

End point timeframe:

Weeks 26 and 52

End point values	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	64	16	
Units: centimetre per year (cm/year)				
arithmetic mean (standard deviation)				
Week 26 (n=81,64,16)	2.08 (± 3.148)	1.94 (± 2.791)	1.00 (± 4.294)	
Week 52 (n=75,59,15)	1.63 (± 2.624)	1.46 (± 1.824)	1.76 (± 3.004)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Changes in Tanner Staging (Females) From Baseline at Weeks 26 and 52

End point title	Number of Subjects with Changes in Tanner Staging (Females) From Baseline at Weeks 26 and 52

End point description:

Tanner Pubertal Staging were assessed in female (F) for pubic hair growth and for breast development in stages (S) 1 to 5. If a subject had reached Tanner S 5, no further Tanner pubertal S assessments were to be completed and reported as 'not done (ND)'. Pubic hair growth: Tanner S: Pubic hair (1: No hair, 2: Downy hair, 3: More coarse and curly hair, 4: Adult-like hair quality; 5: Hair extends to medial surface of the thighs); Breast development: (1: The nipple is raised a little in this stage. The rest of the breast is still flat, 2: Breast bud forms,3: More elevated, outside areola, 4: Increased breast size, 5: Final adult-size breasts). Categories with at least 1 non-zero data values are reported. Safety analysis: subjects who were randomised and took at least 1 dose of study drug. Baseline=B, Week=W. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint and 'n' (number analysed) signifies number of subjects analysed at each specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 26, and 52

End point values	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	47	7	
Units: Subjects				
Breast S: F: S2 (at B) to S3 (at W26) (n=56,47,7)	1	2	1	
Breast S: F: S 2 (at B) to ND (at W26) (n=56,47,7)	1	0	0	
Breast S: F: S3 (at B) to S3 (at W26) (n=56,47,7)	8	7	0	
Breast S: F: S3 (at B) to S4 (at W26) (n=56,47,7)	2	5	0	
Breast S: F: S4 (at B) to S4 (at W26) (n=56,47,7)	15	7	2	
Breast S: F: S4 (at B) to S5 (at W26) (n=56,47,7)	0	0	0	
Breast S: F: S5 (at B) to S5 (at W26) (n=56,47,7)	7	2	1	
Breast S: F: S5 (at B) to ND (at W26) (n=56,47,7)	19	13	2	
Breast S: F: S2 (at B) to S2 (at W26) (n=56,47,7)	0	3	0	
Breast S: F: S2 (at B) to S5 (at W26) (n=56,47,7)	0	1	0	
Breast S: F: S2 (at B) to S3 (at W52) (n=53,42,6)	1	3	1	
Breast S: F: S3 (at B) to S3 (at W52) (n=53,42,6)	3	2	0	
Breast S: F: S3 (at B) to S4 (at W52) (n=53,42,6)	6	8	0	
Breast S: F: S3 (at B) to S5 (at W52) (n=53,42,6)	1	0	0	
Breast S: F: S4 (at B) to S4 (at W52) (n=53,42,6)	11	5	1	
Breast S: F: S4 (at B) to S5 (at W52) (n=53,42,6)	5	3	1	

Breast S: F: S4 (at B) to ND (at W52) (n=53,42,6)	1	4	0	
Breast S: F: S5 (at B) to S5 (at W52) (n=53,42,6)	6	0	1	
Breast S: F: S5 (at B) to ND (at W52) (n=53,42,6)	19	14	2	
Breast S: F: S2 (at B) to S2 (at W52) (n=53,42,6)	0	1	0	
Breast S: F: S3 (at B) to S2 (at W 52) (n=53,42,6)	0	1	0	
Pubic Hair:F: S2 (at B) to S3 (at W26) (n=56,47,7)	1	0	0	
Pubic Hair:F: S3 (at B) to S3 (at W26) (n=56,47,7)	6	9	0	
Pubic Hair:F: S3 (at B) to S4 (at W26) (n=56,47,7)	2	5	0	
Pubic Hair:F: S3 (at B) to ND (at W26) (n=56,47,7)	1	0	0	
Pubic Hair:F: S4 (at B) to S4 (at W26) (n=56,47,7)	18	7	3	
Pubic Hair:F: S3 (at B) to S5 (at W26) (n=56,47,7)	4	6	1	
Pubic Hair:F: S5 (at B) to S5 (at W26) (n=56,47,7)	5	2	0	
Pubic Hair:F: S5 (at B) to ND (at W26) (n=56,47,7)	19	14	2	
Pubic Hair:F: S1 (at B) to S1 (at W26) (n=56,47,7)	0	1	1	
Pubic Hair:F: S2 (at B) to S2 (at W26) (n=56,47,7)	0	2	0	
Pubic Hair:F: S2 (at B) to S2 (at W52) (n=53,42,6)	0	1	0	
Pubic Hair:F: S2 (at B) to S3 (at W52) (n=53,42,6)	1	0	0	
Pubic Hair:F: S3 (at B) to S2 (at W52) (n=53,42,6)	0	0	1	
Pubic Hair:F: S3 (at B) to S3 (at W52) (n=53,42,6)	4	4	0	
Pubic Hair:F: S3 (at B) to S4 (at W52) (n=53,42,6)	3	8	0	
Pubic Hair:F: S3 (at B) to S5 (at W52) (n=53,42,6)	1	0	0	
Pubic Hair:F: S4 (at B) to S4 (at W52) (n=53,42,6)	12	4	2	
Pubic Hair:F: S4 (at B) to S5 (at W52) (n=53,42,6)	6	8	2	
Pubic Hair:F: S4 (at B) to ND (at W52) (n=53,42,6)	4	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Changes in Tanner Staging (Males) From Baseline at Weeks 26 and 52

End point title	Number of Subjects with Changes in Tanner Staging (Males) From Baseline at Weeks 26 and 52

End point description:

Tanner Pubertal Staging were assessed in male (M) for pubic hair growth and for genitalia development in S 1 to 5. If a subject had reached Tanner S5, no further Tanner pubertal S assessments were to be completed and reported as ND. Pubic hair growth: Tanner S: Pubic hair (1: No hair, 2: little soft, long, lightly curled hair at penis 3: More coarse and curly hair covered larger area, 4: Adult-like hair quality; 5: Hair extends to medial surface of the thighs); Genitalia development: (1: Testes, scrotum, and penis about same size, 2: Enlargement of scrotum, testes, and penis, 3: Enlargement of penis, 4: The penis and glans became larger, 5: Genitalia size and shape same an adult male). Categories with at least 1 non-zero data values are reported. Safety analysis: subjects who were randomised and took at least 1 dose of study drug. Here, 'N' (number of subjects analysed): subjects evaluable for this endpoint and 'n' (number analysed): subjects analysed at each specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 26, and 52

End point values	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	18	9	
Units: Subjects				
GD: M: S1 (at B) to S2 (at W26) (n=23,18,9)	0	0	1	
GD: M: S1 (at B) to S3 (at W26) (n=23,18,9)	0	1	0	
GD: M: S2 (at B) to S2 (at W26) (n=23,18,9)	1	0	0	
GD: M: S2 (at B) to S3 (at W26) (n=23,18,9)	1	1	0	
GD: M: S3 (at B) to S3 (at W26) (n=23,18,9)	8	2	3	
GD: M: S3 (at B) to S4 (at W26) (n=23,18,9)	1	3	0	
GD: M: S3 (at B) to S5 (at W26) (n=23,18,9)	1	0	0	
GD: M: S4 (at B) to S3 (at W26) (n=23,18,9)	1	0	0	
GD: M: S4 (at B) to S4 (at W26) (n=23,18,9)	5	7	2	
GD: M: S4 (at B) to S5 (at W26) (n=23,18,9)	1	0	0	
GD: M: S5 (at B) to S5 (at W26) (n=23,18,9)	0	1	1	
GD: M: S5 (at B) to ND (at W26) (n=23,18,9)	4	3	2	
GD: M: S1 (at B) to S4 (at W52) (n=23,18,9)	0	1	1	
GD: M: S2 (at B) to S2 (at W52) (n=23,18,9)	1	0	0	
GD: M: S2 (at B) to S3 (at W52) (n=23,18,9)	1	0	0	
GD: M: S3 (at B) to S3 (at W52) (n=23,18,9)	5	0	2	
GD: M: S3 (at B) to S4 (at W52) (n=23,18,9)	2	5	1	
GD: M: S3 (at B) to S5 (at W52) (n=23,18,9)	3	0	0	
GD: M: S4 (at B) to S4 (at W52) (n=23,18,9)	2	6	2	

GD: M: S4 (at B) to S5 (at W52) (n=23,18,9)	5	0	0	
GD: M: S5 (at B) to ND (at W52) (n=23,18,9)	2	4	2	
Pubic Hair:M: S1 (at B) to S2 (at W26) (n=23,18,9)	1	1	1	
Pubic Hair:M: S2 (at B) to S2 (at W26) (n=23,18,9)	1	0	0	
Pubic Hair:M: S2 (at B) to S3 (at W26) (n=23,18,9)	0	1	1	
Pubic Hair:M: S3 (at B) to S2 (at W26) (n=23,18,9)	1	0	0	
Pubic Hair:M: S3 (at B) to S3 (at W26) (n=23,18,9)	7	1	2	
Pubic Hair:M: S3 (at B) to S4 (at W26) (n=23,18,9)	2	3	0	
Pubic Hair:M: S3 (at B) to S5 (at W26) (n=23,18,9)	1	0	0	
Pubic Hair:M: S4 (at B) to S4 (at W26) (n=23,18,9)	5	8	2	
Pubic Hair:M: S4 (at B) to S5 (at W26) (n=23,18,9)	1	1	0	
Pubic Hair:M: S5 (at B) to S5 (at W26) (n=23,18,9)	0	0	1	
Pubic Hair:M: S5 (at B) to ND (at W26) (n=23,18,9)	4	3	2	
Pubic Hair:M: S1 (at B) to S2 (at W52) (n=23,18,9)	4	3	2	
Pubic Hair:M: S2 (at B) to S2 (at W52) (n=23,18,9)	1	0	0	
Pubic Hair:M: S3 (at B) to S3 (at W52) (n=23,18,9)	4	0	0	
Pubic Hair:M: S3 (at B) to S4 (at W52) (n=23,18,9)	4	4	0	
Pubic Hair:M: S3 (at B) to S5 (at W52) (n=23,18,9)	3	0	0	
Pubic Hair:M: S4 (at B) to S4 (at W52) (n=23,18,9)	2	7	2	
Pubic Hair:M: S4 (at B) to S5 (at W52) (n=23,18,9)	4	0	0	
Pubic Hair:M: S5 (at B) to ND (at W52) (n=23,18,9)	2	3	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Turnover Marker: Serum Osteocalcin and Serum Collagen Type 1 Carboxy-Telopeptide (CTx) at Weeks 26 and 52

End point title	Change From Baseline in Bone Turnover Marker: Serum Osteocalcin and Serum Collagen Type 1 Carboxy-Telopeptide (CTx) at Weeks 26 and 52

End point description:

Change from baseline in bone turnover marker: serum osteocalcin and CTx at Weeks 26 and 52 were reported. Safety analysis set included all the subjects who were randomised and took at least 1 dose of study agent. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint and 'n' (number analysed) signifies number of subjects analysed at each specified timepoints. Here, 99999 implies standard deviation was not estimable because only one subject was available for the analysis.

Here, 9999 implies standard deviation was not estimable as no subject was available for the analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 26 and 52

End point values	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	59	13	
Units: micrograms/liter (mcg/L)				
arithmetic mean (standard deviation)				
Week 26: Serum Osteocalcin (n=78,59,13)	-3.594 (± 17.0801)	-3.328 (± 15.1110)	-0.904 (± 10.3083)	
Week 52: Serum Osteocalcin (n=71,56,14)	-8.732 (± 19.3027)	-5.964 (± 16.8299)	-3.475 (± 9.2422)	
Week 26: CTx (n=3,2,1)	-0.1530 (± 0.26595)	0.3575 (± 0.34295)	0.3000 (± 99999)	
Week 52: CTx (n=1,1,0)	-0.0240 (± 99999)	-0.3710 (± 99999)	9999 (± 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary Albumin/Creatinine Ratio (ACR) at Weeks 26 and 52

End point title	Urinary Albumin/Creatinine Ratio (ACR) at Weeks 26 and 52

End point description:

Urinary ACR were reported at Weeks 26 and 52. Safety analysis set included all the subjects who were randomised and took at least 1 dose of study agent. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint and 'n' (number analysed) signifies number of subjects analysed at each specified timepoints.

End point type	Secondary

End point timeframe:

Weeks 26 and 52

End point values	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	48	12	
Units: milligrams/gram (mg/gm)				
geometric mean (confidence interval 95%)				
Week 26 (n=64,48,12)	15.62 (11.24 to 21.71)	14.41 (9.85 to 21.07)	24.84 (11.81 to 52.26)	
Week 52 (n=65,47,11)	14.98 (10.97 to 20.46)	15.45 (10.75 to 22.22)	21.27 (10.42 to 43.45)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) up to 30 days post last dose (up to Week 56)

Adverse event reporting additional description:

Safety was based on the safety analysis set that included all randomised subjects who received at least 1 dose of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received orally 1 placebo tablet matching to canagliflozin 100/300 milligrams (mg) once-daily from Day 1 till Week 52. At Week 13, subjects who met re-randomisation criteria (glycated hemoglobin [HbA1c] of >=7.0%, estimated glomerular filtration rate [eGFR] >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised to receive orally 1 tablet of placebo matching canagliflozin 100 mg and 1 tablet of placebo matching canagliflozin 300 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of placebo matching to canagliflozin 100 mg once daily till Week 52.

Reporting group title	Canagliflozin 300 mg

Reporting group description:

Subjects received orally canagliflozin 100 mg tablet once daily from Day 1 till Week 12. At Week 13, subjects who met re-randomisation criteria (HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised at 1:1 ratio to receive orally 1 tablet of canagliflozin 300 mg tablet and 1 tablet of placebo matching canagliflozin 100 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of canagliflozin 100 mg once daily till Week 52.

Reporting group title	Canagliflozin 100 mg

Reporting group description:

Subjects received orally canagliflozin 100 mg tablet once daily from Day 1 till Week 12. At Week 13, subjects who met re-randomisation criteria (HbA1c of >=7.0%, estimated eGFR >=60 mL/min/1.73 m^2) at Week 12 were alone re-randomised at 1:1 ratio to receive orally 1 tablet of canagliflozin 100 mg tablet and 1 tablet of placebo matching canagliflozin 300 mg once daily till Week 52. Subjects who did not meet the re-randomisation criteria continued to receive orally 1 tablet of canagliflozin 100 mg once daily till Week 52.

Serious adverse events	Placebo	Canagliflozin 300 mg	Canagliflozin 100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 87 (5.75%)	1 / 17 (5.88%)	7 / 67 (10.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Ankle Fracture			

subjects affected / exposed	1 / 87 (1.15%)	0 / 17 (0.00%)	0 / 67 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	1 / 87 (1.15%)	0 / 17 (0.00%)	0 / 67 (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
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 87 (0.00%)	0 / 17 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis Acute			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 17 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Tonsillar Hypertrophy			
subjects affected / exposed	1 / 87 (1.15%)	0 / 17 (0.00%)	0 / 67 (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
Psychiatric disorders			
Suicide Attempt			
subjects affected / exposed	0 / 87 (0.00%)	0 / 17 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Pneumonia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 17 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 87 (0.00%)	0 / 17 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 17 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 17 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	1 / 87 (1.15%)	0 / 17 (0.00%)	0 / 67 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	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	Placebo	Canagliflozin 300 mg	Canagliflozin 100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 87 (51.72%)	14 / 17 (82.35%)	37 / 67 (55.22%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 87 (3.45%)	0 / 17 (0.00%)	4 / 67 (5.97%)
occurrences (all)	4	0	6
Fatigue			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0

Thirst			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 87 (2.30%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	2	2	0
Psychiatric disorders			
Autism Spectrum Disorder			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood Glucose Increased			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Blood Ketone Body Increased			
subjects affected / exposed	2 / 87 (2.30%)	1 / 17 (5.88%)	1 / 67 (1.49%)
occurrences (all)	2	1	1
High Density Lipoprotein Decreased			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Skin Abrasion			
subjects affected / exposed	1 / 87 (1.15%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	3	1	0
Skin Laceration			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	2	0

Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 87 (1.15%)	1 / 17 (5.88%)	2 / 67 (2.99%)
occurrences (all)	1	1	4
Headache			
subjects affected / exposed	3 / 87 (3.45%)	1 / 17 (5.88%)	8 / 67 (11.94%)
occurrences (all)	3	2	11
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 87 (1.15%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 87 (1.15%)	2 / 17 (11.76%)	2 / 67 (2.99%)
occurrences (all)	1	2	2
Vomiting			
subjects affected / exposed	2 / 87 (2.30%)	2 / 17 (11.76%)	3 / 67 (4.48%)
occurrences (all)	2	3	4
Diarrhoea			
subjects affected / exposed	5 / 87 (5.75%)	1 / 17 (5.88%)	3 / 67 (4.48%)
occurrences (all)	7	1	3
Abdominal Pain			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	2 / 67 (2.99%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
Skin Lesion			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Ketonuria			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Musculoskeletal Pain			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 17 (5.88%)	1 / 67 (1.49%)
occurrences (all)	1	1	1
Infections and infestations			
Covid-19			
subjects affected / exposed	2 / 87 (2.30%)	1 / 17 (5.88%)	1 / 67 (1.49%)
occurrences (all)	2	1	1
Gastroenteritis Viral			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Genital Herpes			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	2	0
Genital Herpes Simplex			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Genital Infection Fungal			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
External Ear Cellulitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Bacterial Vaginosis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Balanitis Candida			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	1 / 67 (1.49%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	2 / 87 (2.30%)	1 / 17 (5.88%)	3 / 67 (4.48%)
occurrences (all)	2	1	3
Influenza			

subjects affected / exposed	4 / 87 (4.60%)	1 / 17 (5.88%)	2 / 67 (2.99%)
occurrences (all)	6	1	2
Urinary Tract Infection			
subjects affected / exposed	4 / 87 (4.60%)	5 / 17 (29.41%)	1 / 67 (1.49%)
occurrences (all)	4	6	1
Urinary Tract Infection Bacterial			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Viral Infection			
subjects affected / exposed	2 / 87 (2.30%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	2	1	0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 87 (1.15%)	1 / 17 (5.88%)	2 / 67 (2.99%)
occurrences (all)	1	1	2
Vulvovaginal Candidiasis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	1 / 67 (1.49%)
occurrences (all)	0	1	1
Upper Respiratory Tract Infection			
subjects affected / exposed	11 / 87 (12.64%)	1 / 17 (5.88%)	3 / 67 (4.48%)
occurrences (all)	17	2	4
Nasopharyngitis			
subjects affected / exposed	5 / 87 (5.75%)	0 / 17 (0.00%)	8 / 67 (11.94%)
occurrences (all)	6	0	10
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Pharyngotonsillitis			
subjects affected / exposed	1 / 87 (1.15%)	1 / 17 (5.88%)	1 / 67 (1.49%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 87 (1.15%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	1	1	0
Diabetes Mellitus Inadequate Control			

subjects affected / exposed	0 / 87 (0.00%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	5 / 87 (5.75%)	1 / 17 (5.88%)	1 / 67 (1.49%)
occurrences (all)	7	1	1
Vitamin D Deficiency			
subjects affected / exposed	6 / 87 (6.90%)	1 / 17 (5.88%)	3 / 67 (4.48%)
occurrences (all)	6	1	3
Hypoglycaemia			
subjects affected / exposed	8 / 87 (9.20%)	0 / 17 (0.00%)	3 / 67 (4.48%)
occurrences (all)	17	0	3
Hypertriglyceridaemia			
subjects affected / exposed	2 / 87 (2.30%)	1 / 17 (5.88%)	0 / 67 (0.00%)
occurrences (all)	2	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2017	The purpose of the amendment was to modify the study design to allow the assessment of canagliflozin when used with and without titration which is more reflective of how canagliflozin may be used in this pediatric population, and to add ketone monitoring procedures, and some minor editorial changes.
25 August 2017	The purpose of the amendment was to include changes in the statistical analysis, and minor editorial changes.
25 June 2018	The purpose of the amendment was to have an independently powered subset of subjects on a background of diet and exercise only where superiority of canagliflozin vs placebo could be assessed.
14 August 2020	The purpose of the amendment was to include the following changes: Due to slower than expected recruitment in the study and a high rate of screen failures, the power calculation was modified resulting in a reduced sample size. In addition, minor modifications to the inclusion and exclusion criteria had been made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Time to rescue therapy was plotted using the Kaplan Meier method and only graphical representation is available, hence not included in endpoint section based on the requirements.

Notes: