Clinical trial results:
A Randomized, Double-blind, Placebo Controlled, 2-arm, Parallel-group, 26-week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Metformin and Sitagliptin Therapy

Summary

EudraCT number	2013-004819-40
Trial protocol	DE
Global end of trial date	11 September 2015

Results information

Result version number	v1 (current)
This version publication date	25 August 2016
First version publication date	25 August 2016

Trial information

Trial identification

Sponsor protocol code	28431754DIA4004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02025907
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	Turnhoutseweg 30, BEERSE, Belgium, 2340
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)	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	11 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives were to assess the effect of canagliflozin relative to placebo on glycosylated hemoglobin (HbA1c) and to assess the safety and tolerability of canagliflozin.

Protection of trial subjects:

The safety assessments included the clinical laboratory tests (hematology, serum chemistry, FPG, and urinalysis), fasting lipid, electrocardiogram (ECG), vital signs, hypoglycemic episodes, fasting self-monitored blood glucose (SMBG) and physical examinations. Adverse events (AEs) were assessed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	United States: 94
Worldwide total number of subjects	213
EEA total number of subjects	45

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)	161
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 390 subjects screened, out of that 218 subjects were randomly assigned in 1:1 ratio to canagliflozin or placebo treatment. However, One subject was randomized twice (once to placebo and once to canagliflozin) was excluded from the safety analysis set, therefore 216 of the 218 randomized subjects were included in the analyses.

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 administered with placebo (inactive medication) once daily for 26 weeks.

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

Dosage and administration details:

Subjects administered with matching placebo to canagliflozin orally, once daily for 26 weeks.

Arm title	Canagliflozin

Arm description:

Subjects administered canagliflozin (JNJ-28431754) 100 milligram (mg) titratable to 300 mg once daily for 26 weeks.

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

Dosage and administration details:

Subjects administered with canagliflozin orally, once daily for 26 weeks.

Number of subjects in period 1	Placebo	Canagliflozin
Started	106	107
Completed	81	96
Not completed	25	11
Physician decision	2	-
Consent withdrawn by subject	15	8
Adverse event, non-fatal	3	1
Lost to follow-up	2	2
Protocol deviation	2	-
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects administered with placebo (inactive medication) once daily for 26 weeks.	
Reporting group title	Canagliflozin
Reporting group description:	
Subjects administered canagliflozin (JNJ-28431754) 100 milligram (mg) titratable to 300 mg once daily for 26 weeks.	

Reporting group values	Placebo	Canagliflozin	Total
Number of subjects	106	107	213
Title for AgeCategorical			
Units: subjects			
Adults (18-64 years)	76	85	161
From 65 to 84 years	30	22	52
85 years and over	0	0	0
Title for AgeContinuous			
Units: years			
arithmetic mean	57.5	57.4	
standard deviation	± 10.14	± 9.28	-
Title for Gender			
Units: subjects			
Female	51	41	92
Male	55	66	121

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects administered with placebo (inactive medication) once daily for 26 weeks.	
Reporting group title	Canagliflozin
Reporting group description:	
Subjects administered canagliflozin (JNJ-28431754) 100 milligram (mg) titratable to 300 mg once daily for 26 weeks.	

Primary: Change From Baseline in Glycosylated Haemoglobin (HbA1c) at Week 26

End point title	Change From Baseline in Glycosylated Haemoglobin (HbA1c) at Week 26
End point description:	
The change in the value of glycosylated hemoglobin (the concentration of glucose bound to hemoglobin as a percent of the absolute maximum that can be bound) from baseline at Week 26 was compared between the different treatment groups. mITT population included all randomized subjects who received at least 1 dose of double blind study drug. A total of 3 subjects were excluded from the mITT population due to potential misconduct and GCP compliance issues. Here, 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this outcome measure.	
End point type	Primary
End point timeframe:	
Baseline and Week 26	

End point values	Placebo	Canagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	99		
Units: percentage of glycosylated hemoglobin				
least squares mean (standard error)	-0.01 (± 0.119)	-0.91 (± 0.113)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Canagliflozin
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.193
upper limit	-0.592
Variability estimate	Standard error of the mean
Dispersion value	0.152

Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) at Week 26

End point title	Change From Baseline in Fasting Plasma Glucose (FPG) at Week 26

End point description:

The change in fasting plasma glucose from baseline at Week 26 was compared between the different treatment groups. mITT population included all randomized subjects who received at least 1 dose of double blind study drug. A total of 3 subjects were excluded from the mITT population due to potential misconduct and GCP compliance issues. Here, 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo	Canagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	103		
Units: millimole(s)/litre				
least squares mean (standard error)	-0.14 (± 0.281)	-1.65 (± 0.264)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Canagliflozin
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.235
upper limit	-0.772

Variability estimate	Standard error of the mean
Dispersion value	0.371

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 percentage change in body weight from baseline to Week 26 was compared between the different treatment groups. mITT population included all randomized subjects who received at least 1 dose of double blind study drug. A total of 3 subjects were excluded from the mITT population due to potential misconduct and GCP compliance issues. Here, 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Placebo	Canagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	103		
Units: percent change				
least squares mean (standard error)	-1.6 (± 0.337)	-3.35 (± 0.324)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Canagliflozin
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.659
upper limit	-0.851
Variability estimate	Standard error of the mean
Dispersion value	0.459

Secondary: Percentage of Subjects With HbA1c Less Than (<) 7.0 Percent at Week

26	
End point title	Percentage of Subjects With HbA1c Less Than (<) 7.0 Percent at Week 26

End point description:

The percentage of participants achieved HbA1c less than 7 percent at Week 26 was compared between the different treatment groups. mITT population included all randomized subjects who received at least 1 dose of double blind study drug. A total of 3 subjects were excluded from the mITT population due to potential misconduct and GCP compliance issues. Here, 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	Canagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	96		
Units: percentage of subjects				
number (not applicable)	12.2	32.3		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Canagliflozin
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Generalized linear MMRM
Parameter estimate	Odds ratio (OR)
Point estimate	4.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.89
upper limit	10.86

Secondary: Change From Baseline in Systolic Blood Pressure (SBP) at Week 26	
End point title	Change From Baseline in Systolic Blood Pressure (SBP) at Week 26

End point description:

The change in systolic blood pressure from baseline at Week 26 was compared between the different treatment groups. mITT population included all randomized subjects who received at least 1 dose of double blind study drug. A total of 3 subjects were excluded from the mITT population due to potential misconduct and GCP compliance issues. Here, 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:
Baseline and Week 26

End point values	Placebo	Canagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	103		
Units: millimeter of mercury (mmHg)				
least squares mean (standard error)	0.09 (± 1.123)	-5.76 (± 1.078)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Canagliflozin
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-5.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.786
upper limit	-2.914
Variability estimate	Standard error of the mean
Dispersion value	1.489

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to follow up (Approximately 31 Weeks)

Adverse event reporting additional description:

Safety population included all randomized subjects who received at least 1 dose of double blind study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Canagliflozin

Reporting group description:

Subjects administered canagliflozin (JNJ28431754) 100 milligram (mg) titratable to 300 mg once daily for 26 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects administered with placebo (inactive medication) once daily for 26 Weeks.

Serious adverse events	Canagliflozin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 108 (1.85%)	2 / 108 (1.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Angina Unstable			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (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			
Cerebral Infarction			
subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			

subjects affected / exposed	0 / 108 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Canagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 108 (16.67%)	16 / 108 (14.81%)	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 108 (2.78%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	3 / 108 (2.78%)	3 / 108 (2.78%)	
occurrences (all)	3	3	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 108 (2.78%)	1 / 108 (0.93%)	
occurrences (all)	3	1	
Pain in Extremity			
subjects affected / exposed	3 / 108 (2.78%)	1 / 108 (0.93%)	
occurrences (all)	3	1	
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 108 (5.56%)	6 / 108 (5.56%)	
occurrences (all)	7	9	
Upper Respiratory Tract Infection			

subjects affected / exposed occurrences (all)	2 / 108 (1.85%) 2	3 / 108 (2.78%) 3	
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	 0 / 108 (0.00%) 0	 5 / 108 (4.63%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2014	The overall reason for the second amendment was to include PRO instruments to assess the subjects satisfaction with their health and their degree of diabetes-related distress.
18 September 2014	The overall reason for the third amendment was to lower the maximally or near-maximally effective dose of metformin to greater than or equal to (>=) 1,500 milligram per day (mg/day), to remove the prohibition of past use of SGLT2 inhibitors and to clarify the limitations of prior use of other SGLT2 inhibitors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported