Janssen Research & Development

Clinical Study Report Synopsis
[Protocol 28431754DIA3015; Phase 3]

JNJ-28431754 (Canagliflozin)

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SYNOPSIS

Issue Date: 03 May 2012

Document No.: EDMS-ERI-42926327:1.0

Name of Sponsor/Company	Janssen Research & Development, LLC
Name of Finished Product	To be determined
Name of Active Ingredient(s)	Canagliflozin (JNJ-28431754)

Protocol No.: 28431754DIA3015

Title of Study: A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy

Study Name: The CANTATA-D2 Trial (CANagliflozin Treatment and Trial Analysis – DPP-4 Inhibitor Second Comparator Trial)

EudraCT Number: 2010-020053-14

NCT No.: NCT01137812

Clinical Registry No.: CR017185

Coordinating Investigator(s): [redacted] MD, [redacted]

Study Center(s): A total of 140 study centers in 17 countries participated, 70 of which were in North America (57 in the United States [US], 13 in Canada); 21 of which were in Europe[a] (8 in Poland, 3 in France, 3 in Germany, 2 in Netherlands, 2 in Denmark, 2 in Austria, 1 in Belgium)); 10 of which were in Central/South America (10 in Brazil), and 39 of which were in the rest of world (10 in Ukraine, 8 in South Korea, 6 in India, 5 in New Zealand, 4 in Israel, 4 in Malaysia, 2 in Singapore).

Publication (Reference): None

Study Period: 30 June 2010 to 09 March 2012; DBL: 14March12

Phase of Development: Phase 3

Objectives: The primary objectives included, in subjects with type 2 diabetes mellitus (T2DM) with inadequate glycemic control on combination therapy with metformin and a sulphonylurea (SU): (1) to assess the addition of treatment with canagliflozin 300 mg compared with sitagliptin 100 mg on glycosylated hemoglobin (HbA_{1c})-lowering efficacy after 52 weeks; and (2) to assess the safety and tolerability of canagliflozin. Secondary objectives included, after 52 weeks of treatment, to assess the effect of the addition of treatment with canagliflozin compared with the addition of treatment with sitagliptin on: body weight; fasting plasma glucose (FPG); the proportion of subjects with HbA_{1c} <7.0% or <6.5%; fasting plasma lipids (ie, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol, LDL-C to HDL-C ratio, and triglycerides); systolic blood pressure (SBP) and diastolic blood pressure (DBP); time to and proportion of subjects discontinued early for meeting glycemic withdrawal criteria; and fasting measures of beta-cell function (ie, HOMA-B, proinsulin to insulin ratio). An additional objective was to assess, after 52 weeks of treatment, the effect of the addition of treatment with canagliflozin compared with the addition of treatment with sitagliptin in

[a] Includes the European Union, European Economic Area, European Free Trade Association countries

subjects with poorer baseline glycemic control prior to randomization (ie, HbA_{1C} ≥9.0% at the Week 2 visit) on glycemic control (HbA_{1C} and FPG) and the proportion of subjects with HbA_{1c} <7.0% or <6.5%. Objectives in a subset of subjects (approximately 20% of total subjects) who underwent a frequently-sampled mixed-meal tolerance test (FS-MMTT) were to assess the addition of treatment with canagliflozin compared with sitagliptin on: (1) post-prandial plasma glucose concentrations (including 2-hour postprandial plasma glucose (PPG) and glucose area under the curve [AUC]); (2) measures of insulin sensitivity (S_I) using a minimal-model-based approach that accounts for urinary glucose excretion (UGE); (3) Measures of insulin secretion (including insulinogenic index, AUC C-peptide/AUC glucose, and parameters of beta-cell sensitivity derived from a model based assessment of insulin secretion rate relative to glucose concentrations); and (4) disposition index (model based overall measure of insulin secretion multiplied by model-based measure of insulin sensitivity).

Methodology: Randomized, double-blind, active-controlled, 2 arm, parallel-group, multicenter study of treatment with once daily canagliflozin 300 mg or sitagliptin 100 mg (1:1 randomization ratio) over 52 weeks in subjects with type 2 diabetes mellitus (T2DM) who were ≥18 years of age and had inadequate glycemic control (ie, HbA_{1c} of ≥7.0% to ≤10.5%) on the combination of metformin and a SU, with both agents at maximally or near-maximally effective doses. Unlike other studies in the canagliflozin program, this study did not provide glycemic rescue therapy; subjects meeting prespecified glycemic criteria (as applied in other studies for rescue therapy initiation) were discontinued.

Several data monitoring committees were commissioned for the canagliflozin development program, as follows: (1) an independent Endpoint Adjudication Committee (EAC) reviewed blinded data for selected adverse events, including major adverse cardiovascular (CV) events and events of hospitalized unstable angina (collectively referred to as MACE-plus); hospitalized congestive heart failure; venous thromboembolism/pulmonary embolism; and all deaths, (2) independent assessment committees reviewed blinded data for assessment of fracture, and hepatic, and renal events, (3) an Independent Data Monitoring Committee (IDMC) reviewed unblinded serious adverse events and CV events, and (4) a company internal Medical Safety Review Committee (MSRC) monitored the safety of subjects participating in the study by reviewing blinded data on a regular basis.

Number of Subjects (planned and analyzed): It was planned that approximately 360 subjects per treatment group (a total of 720 subjects) would be randomly assigned to once daily administration of canagliflozin 300 mg or sitagliptin 100 mg (1:1 randomization ratio) in order to meet the sample size required for the per protocol analysis, assuming a discontinuation rate of 35%.. The numbers of subjects included in the various analysis sets by treatment group are summarized below.

Summary of Analysis Sets and Disposition
(Study 28431754DIA3015: All Randomized Subjects Analysis Set)

	CANA 300 mg (N=378) n (%)	Sita 100 mg (N=378) n (%)	Total (N=756) n (%)
Subjects who were randomized	378 (100)	378 (100)	756 (100)
Subjects who were randomized, but not dosed	1 (0.3)	0	1 (0.1)
Subjects in the mITT analysis set	377 (99.7)	378 (100)	755 (99.9)
Subjects in the safety analysis set	377 (99.7)	378 (100)	755 (99.9)
mITT subjects who discontinued	123 (32.5)	168 (44.4)	291 (38.5)
Subjects in the completers' analysis set	254 (67.2)	210 (55.6)	464 (61.4)
mITT subjects in the PP analysis set	247 (65.3)	207 (54.8)	454 (60.1)

Key: CANA=canagliflozin, mITT=modified intent-to-treat, N=total number of subjects, n=total number of subjects in subgroup, PP=per protocol, Sita=sitagliptin
Note: Percentages were calculated with the number of subjects in each group as the denominator.

Diagnosis and Main Criteria for Inclusion: Man or woman ≥18 years of age with T2DM and currently treated with metformin and an SU, meeting the following HbA_{1c} eligibility criteria:

	HbA_{1c}	
Subjects	Screening Visit	Week -2 Visit
On metformin and an SU at protocol-specified doses[a] for at least 8 weeks prior to screening	≥7.0% and ≤10.5%	n/a [b]
On metformin and an SU, either or both at doses below protocol-specified [a]	≥7.5%	≥7.0% and ≤10.5%

[a] Metformin ≥2,000 mg/day (or ≥1,500 mg/day if intolerant of higher dose; protocol-specified SU doses outline in the body of the CSR

[b] If measured at screening more than 3 weeks prior to the Week -2 visit, obtain HbA_{1c} at the Week -2 visit to assess inclusion criterion.

Key: CANA=canagliflozin, SU=sulphonylurea

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin capsules containing active 300 mg tablets for oral administration (batch/lot nos.: PD3392, PD3394, PD3391, 30845.15, PD3402, 32783.3).

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo to match canagliflozin (batch/lot nos.: 09L16/G001, 09J28/G001, 30845.2) for oral administration. Commercially available sitagliptin containing 2 50 mg tablets (2x50 mg) identical in appearance to canagliflozin (batch/lot nos.: 10C31/G018, 30009.1, 30485.1, 30485.2) for oral administration.

Duration of Treatment: The total duration of the study, including the optional prescreening visit, the 52 week double-blind treatment phase, and the 4-week follow-up period was approximately 59 weeks (for subjects on protocol-specified doses of metformin and an SU at the screening visit) to 72 weeks (for subjects on metformin and an SU, with 1 or both agents below protocol-specified doses who had their antihyperglycemic agent (AHA) regimen adjusted to protocol-specified doses).

Criteria for Evaluation: Efficacy laboratory assessment included HbA_{1c}, FPG, HDL-C, and triglycerides. Additional efficacy measurements included body weight, SBP, and proportion of subjects with HbA_{1c} <7.0%. In the subset of subjects who underwent the FS-MMTT, frequently sampled measurements for glucose, C-peptide, and insulin were obtained to assess indices of insulin secretion and indices of insulin sensitivity. In addition, UGE was assessed during the FS-MMTT.

Safety assessment was based on reported adverse events, safety laboratory tests (including hematology, chemistry, routine urinalysis), 12-lead electrocardiograms (ECGs), vital sign measurements (blood pressures and pulse rates), body weight, physical examinations and self-monitored blood glucose (SMBG) and collection of hypoglycemic episodes (eg, from the diary provided to the subjects), regardless of whether considered to be adverse events by the reporting investigator.

A blood sample was collected on Day 1 from subjects who had consented to participate in the pharmacogenomics component of the study to allow for pharmacogenomic research, as necessary.

Statistical Methods: Sample Size Determination

The primary hypothesis for this study was to demonstrate that canagliflozin 300 mg was non inferior to sitagliptin in reducing HbA_{1c} from baseline at Week 52. A non-inferiority margin of 0.3% has been selected for non-inferiority testing purposes with reference to the typical values suggested in the Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention (FDA 2008), the CHMP Scientific Advice for Canagliflozin (Procedure No. EMEA/H/SA/1252/1/2008/III), and the historical data for sitagliptin (Januvia EPAR 2009). Assuming a difference between canagliflozin and sitagliptin of 0.0% and a common standard deviation (SD) of 1.0%

with respect to change in HbA_{1c}, and using a 2-sample, 1-sided t-test with a Type I error rate of 0.025, it was estimated that 234 subjects per group would provide approximately 90% power to demonstrate the noninferiority of canagliflozin compared with sitagliptin. Assuming a discontinuation rate of 35% in 52 weeks, based on information from the development of a similar compound, approximately 360 subjects per treatment group (a total of 720 subjects) would be randomly assigned in order to meet the sample size required for the per protocol analysis.

Efficacy

Primary Efficacy Analysis

The primary efficacy endpoint was the change in HbA_{1c} from baseline through Week 52, using the last observation carried forward (LOCF) method when the Week 52 values were missing. An analysis of covariance (ANCOVA) model with treatment and stratification factors (whether or not HbA_{1c} value at Week -2 or at the screening visit for subjects directly entering the AHA adjustment period ≥ 9.0%; and whether or not a subject participated in the FS-MMTT procedure) as fixed effects, and the baseline HbA_{1c} value as covariate was used for the primary efficacy analysis. The treatment difference (canagliflozin minus sitagliptin) in least-squares mean (LS mean) and its 2-sided 95% confidence interval (CI) were obtained based on this model. The upper bound of the 95% CI of the treatment difference in LS means was used in the non-inferiority testing of the comparison with the non-inferiority margin of 0.3%.

Supportive Efficacy Analyses for Non-inferiority:

The primary efficacy endpoint analysis comparing canagliflozin versus sitagliptin, described above, was also conducted based on the PP analysis set and the 52-week completers' analysis set as supporting analyses.

As an additional supportive analysis, change from baseline in HbA_{1c} was analyzed using a mixed model repeated measures (MMRM) ─ a restricted maximum likelihood (REML) repeated measures approach. The analysis was based on observed data and included the fixed, categorical effects of treatment, stratification factors, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance was used to model the within-patient errors. The treatment comparison was made between canagliflozin and sitagliptin at Week 52 and significance test was based on the difference of the least-squares (LS) means.

Superiority of Canagliflozin versus Sitagliptin

If non-inferiority on the primary efficacy endpoint of canagliflozin versus sitagliptin was concluded, and if the upper bound of the 2-sided 95% CI of the treatment difference in LS means (canagliflozin minus sitagliptin) from the ANCOVA model was less than 0, then it would be concluded that the canagliflozin 300 mg was superior to sitagliptin. However, the outcome of the superiority evaluation was not part of the hierarchical testing sequence.

Major Secondary Efficacy Analysis

The secondary efficacy endpoints involved in the hypothesis testing of canagliflozin group versus sitagliptin at Week 52 included percent change from baseline in body weight; change from baseline in FPG and SBP; percent change from baseline in fasting triglycerides, and in fasting HDL-C. These continuous secondary endpoints were analyzed with an ANCOVA model similar to the primary efficacy endpoint from baseline through Week 52 using the LOCF approach and the modified-intent-to-treat (mITT) analysis set. The treatment differences (canagliflozin minus sitagliptin) in the LS means and their 2-sided 95% CIs were estimated based on this model. If necessary, non-parametric analysis was considered for these continuous secondary endpoints. A sequential testing procedure was applied in

testing the treatment differences of the primary and the major secondary endpoints, such that the family-wise error rate was strongly-controlled at the 5% significance level.

Pharmacodynamics

Beta-cell function was assessed using 3 different methodologies. First, the homeostatic model analysis method (HOMA) was used to assess beta-cell function based on fasting glucose and C-peptide concentrations. For the subset of subjects that underwent the FS-MMTT, further assessment of beta-cell function was performed using the ratio of C-peptide to glucose and a model-based method. Insulin sensitivity was assessed from the plasma glucose and insulin measurements using a minimal-model based method that explicitly accounted for UGE. Mean and median changes from baseline in UGE measurements to Week 52 LOCF observed in subject participating in the FS-MMTT were provided. Renal threshold for glucose (RT_G) values were calculated when the measured UGE over the 0- to 3-hour interval was greater than or equal to 500 mg.

Safety

The incidence (ie, number and percent of subjects with 1 or more adverse event in each category) of adverse events, serious adverse events, deaths, adverse events leading to discontinuation, drug-related adverse events, serious drug-related adverse events, drug-related adverse events leading to discontinuation of study drug, serious adverse events leading to discontinuation of study drug, and serious drug-related adverse events were summarized by treatment group. Specific adverse events that were predefined in the protocol as requiring the collection of additional information, to support additional analysis (eg, time to first event), included urinary tract infection adverse events and male and female genital infections. Predefined limits of change and descriptive statistics were provided for other safety parameters.

RESULTS:

STUDY POPULATION:

Subject and Treatment Information and Baseline Characteristics

A total of 1,672 subjects were screened/prescreened and 756 subjects were randomized into the study, of whom 755 subjects comprised the mITT analysis set; 464 (61%) subjects completed 52 weeks of treatment. The mITT analysis set and the safety analysis set (ie, randomized subjects received at least 1 dose of study drug) were identical. (Refer to summary of analysis sets and subject disposition above). The majority of subjects (95%) went directly into the study and did not enter the AHA adjustment period, and approximately 33% consented to participate in the FS-MMTT (the target was to have approximately 20% of subjects participate in the FS-MMTT). The discontinuation rate was lower in canagliflozin 300 mg (33%) than in sitagliptin 100 mg group (44%). More subjects in the sitagliptin group discontinued from the study due to meeting the glycemic withdrawal criteria (23% versus 11%), which was the most common reason for discontinuation for both treatment groups (refer to the tabular summary below); this study did not include glycemic rescue criteria. The second most common reason for withdrawal from the study was in the category of "other" (6%). The "other" category included a variety of reasons, some reported in ≤2 subjects (transportation issues, moving, family- or job-related, lack of efficacy (0 subjects in the canagliflozin group and 1 subject in the sitagliptin group), disallowed therapy, site closure) and also included 35 subjects who withdrew from the study due to a decision not to continue dosing based upon updated informed consent form information related to the rat carcinogenicity study results, but who agreed to continued follow- up (and hence were not classified as withdrawal of consent). Among subjects who completed the 52-week double-blind treatment phase (ie, completers' analysis set), 10 subjects (7 in the canagliflozin 300 mg group and 3 in the sitagliptin group) were excluded from the PP analysis population due to having protocol deviations, which could potentially have affected the interpretation of the primary efficacy endpoint. The deviations were due to a change in background AHA medication

(9 subjects) and taking prohibited medication (1 subject). Because 98% of subjects in completers' analysis set were also in the PP analysis set, these analysis sets were very similar.

Reasons for Discontinuation

(Study 28431754DIA3015: Modified Intent-to-Treat Analysis Set)

Subject Disposition Category	CANA 300 mg (N=377) n (%)	Sita 100 mg (N=378) n (%)	Total (N=755) n (%)
Primary reason for discontinuation [a]	123 (32.6)	168 (44.4)	291 (38.5)
Adverse event	21 (5.6)	14 (3.7)	35 (4.6)
Creatinine or eGFR withdrawal criteria [b]	22 (5.8)	14 (3.7)	36 (4.8)
Death	2 (0.5)	0	2 (0.3)
Lost to follow-up	6 (1.6)	8 (2.1)	14 (1.9)
Noncompliance with study drug	4 (1.1)	4 (1.1)	8 (1.1)
Physician decision	2 (0.5)	3 (0.8)	5 (0.7)
Protocol violation	1 (0.3)	0	1 (0.1)
Study terminated by sponsor	1 (0.3)	0	1 (0.1)
Withdrawal of consent	5 (1.3)	13 (3.4)	18 (2.4)
Subject met glycemic withdrawal criteria	40 (10.6)	85 (22.5)	125 (16.6)
Other	19 (5.0)	27 (7.1)	46 (6.1)

[a] as indicated by the investigator on the eCRF for mITT subjects who discontinued.

[b] based upon metformin label at investigational site.

Key: CANA=canagliflozin; eCRF=electronic case report form, eGFR=estimated glomerular filtration rate, mITT=modified intent-to-treat, N=total number of subjects, n=total number of subjects in subgroup, Sita=sitagliptin

Note: Percentages were calculated with the number of subjects in each group as the denominator.

Baseline Characteristics

The majority of subjects were white (64%), 18% of the subjects were Asians, 12% of subjects black or African-American, and approximately 21% of subjects were of Hispanic or Latino ethnicity. There were slightly more male (56%) than female subjects in this study and the median age was 57 years. The mean baseline HbA_{1c} was 8.1%, the mean body mass index (BMI) was 31.6 kg/m^2, with more than half (53%) of subjects being obese (BMI ≥30 kg/m^2) based upon National Institutes of Health (NIH) criteria. The mean diabetes disease duration was approximately 10 (median of 8 years), reflective of a population already on dual combination AHA therapy. With this relatively long duration of disease, a moderate proportion (approximately 33%) had at least 1 microvascular complication of diabetes complication. Overall, the baseline characteristics were similar between the 2 treatment groups.

EFFICACY RESULTS:

Primary Endpoint: Clinically useful reductions in HbA_{1c} at Week 52 were observed with both agents; the reduction was larger with canagliflozin 300 mg than with sitagliptin 100 mg: a LS mean change from baseline of -1.03% with canagliflozin and -0.66% with sitagliptin. The upper limit of the 95% CI for the between-group difference in change from baseline in HbA_{1c} for canagliflozin relative to sitagliptin was less than the prespecified noninferiority (NI) margin of 0.30% (a difference in LS means for canagliflozin relative to sitagliptin of -0.37%, with the upper bound of the 95% CI around the between-group difference of -0.25%) confirming the study's non-inferiority hypothesis. Examination of the upper limit of the 95% CI for the between-group difference showed that this was less than 0, demonstrating the superiority of canagliflozin relative to sitagliptin in HbA_{1c}-lowering efficacy. The results for the PP analysis set showed that the between-treatment difference was -0.21% (95% CI: [-0.337; -0.078]). This point estimate was likely conservative because the analysis was performed based on the observed data (without using the LOCF approach) and twice as many subjects in the sitagliptin group who discontinued due to meeting the glycemic withdrawal criteria were not included. The results for the completers' analysis set and from a

mixed model repeated measures approach were consistent with the findings from the primary efficacy analysis.

*Secondary Endpoints Ba*sed on the prespecified hierarchical testing sequence, canagliflozin 300 mg achieved statistical significance at Week 52 compared with the sitagliptin 100 mg with respect to the following endpoints: (1) percent change in body weight, (2) change from baseline in FPG, and (3) change from baseline in SBP. In subsequent hierarchical testing, the canagliflozin group did not achieve statistical significance at Week 52 for the endpoints of percent change from baseline in triglycerides and the percent change from baseline in HDL-C. Note that the nominal p value for the between-treatment comparison in HDL-C endpoint was < 0.001.

Change From Baseline to Week 52 LOCF for Primary and Secondary Efficacy Endpoints in Order of Predefined Hierarchical Testing Sequence
(Study 28431754DIA3015: Modified Intent-to-Treat Analysis Set)

	---------- CANA 300 mg ---------- ---------- (Sita-subtracted) ----------	
Endpoints	Mean (95% CI)	p-value
HbA_{1c} change (%)	-0.37 (-0.500; -0.250)	
Body weight percent change (%)	-2.8 (-3.3; -2.2)	<0.001
FPG change (mmol/L)	-1.34 (-1.658; -1.012)	<0.001
Systolic blood pressure change (mmHg)	-5.91 (-7.642; -4.175)	<0.001
Triglycerides percent change (%)	-2.3 (-9.8; 5.3)	0.554
HDL-C percent change (%)	7.0 (4.6; 9.3)	<0.001 [a]

[a] Nominal p-value.

KEY: CANA=canagliflozin, CI=confidence interval, FPG=fasting plasma glucose, HbA_1c=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol,

Note: For continuous endpoints, the least-squares mean is presented with associated p-values and CI based on ANCOVA models with terms for treatment and stratification factors and adjusting for the baseline value as a covariate.

SAFETY RESULTS:

Adverse events: The overall incidence of subjects with adverse events was similar in the canagliflozin 300 mg group and sitagliptin 100 mg group (76.7% and 77.5%, respectively). A modestly higher incidence of drug-related adverse events was observed in the canagliflozin group relative to the sitagliptin group. The higher rate of drug-related adverse events in the canagliflozin group was largely due to a higher incidence of several specific adverse events (superficial genital infections, eg, vulvovaginitis and balanitis, and related terms). To identify other specific adverse events that occurred at a higher incidence in the canagliflozin group for additional assessment, the 95% CIs around between-group differences were determined. This analysis showed that only for the adverse events of abdominal pain upper, herpes zoster, balanoposthitis, and vulvovaginal pruritus did the CI exclude “0”. The incidence of osmotic-diuresis related AEs (eg, thirst, pollakiuria) was low in both treatment groups with a higher incidence in the canagliflozin group. The incidence of volume-related adverse events (eg, hypotension, changes in renal function) was low and similar between the 2 groups. The incidence of urinary tract infections was slightly lower in the canagliflozin group relative to the sitagliptin group. The overall incidence of adverse events leading to discontinuation was low, and was higher in the canagliflozin group relative to the sitagliptin group. The overall incidence of serious adverse events was low and similar in the canagliflozin group relative to the sitagliptin group. There were 2 deaths reported during the 52-week double-blind treatment phase, both in the canagliflozin group; neither of which was considered as related to study drug.

Adverse Events
(Study 28431754DIA3015: Safety Analysis Set)

Number (%) of Subjects with at least 1 adverse events of following types	CANA 300 mg (N=377) n (%)	Sita 100 mg (N=378) n (%)
Any adverse events	289 (76.7)	293 (77.5)
Adverse events leading to discontinuation	20 (5.3)	11 (2.9)
Adverse events related to study drug [a]	128 (34.0)	105 (27.8)
Adverse events related to study drug [a] and leading to discontinuation	12 (3.2)	6 (1.6)
Serious adverse events	24 (6.4)	21 (5.6)
Serious adverse events leading to discontinuation	5 (1.3)	2 (0.5)
Serious adverse events related to study drug [a]	1 (0.3)	0
Serious adverse events related to study drug [a] and leading to discontinuation	1 (0.3)	0
Deaths	2 (0.5)	0

[a] Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.
KEY: CANA=canagliflozin, N=total number of subjects, n=total number of subjects in subgroup, Sita=sitagliptin
Note: Percentages were calculated with the number of subjects in each group as the denominator.

Safety Laboratory Assessment: The following changes in laboratory safety analytes were observed with canagliflozin relative to the changes observed in the sitagliptin group. Consistent with the expected modest effect on plasma volume, small mean increases (<4%) in hemoglobin were observed; a small increase (approximately 5%) in serum creatinine was seen; a moderate (approximately 18%) increase in urea nitrogen was observed. Small to moderate mean decreases in serum uric acid (approximately 7%), alanine amino transferase (ALT) (approximately 4%), and gamma glutamyl transferase (GGT) levels (approximately 12%) were observed. All of these changes occurred early in the study and remained stable. Aspartate aminotransferase (AST) levels increased by approximately 1%.

Other safety assessments: Reductions from baseline in SBP (-6.08 mmHg) and a slightly lesser reduction from baseline in DBP (-3.25 mmHg) were observed at Week 52 relative to the sitagliptin 100 mg group (SBP and DBP change from baseline: 1.01 mmHg and -0.81 mmHg, respectively). There were no clinically important changes in ECGs observed.:

STUDY LIMITATIONS: No notable study limitations were identified by the sponsor.

CONCLUSION(S):

- Canagliflozin 300 mg provided clinically important glycemic improvements (in HbA_{1c} change from baseline, proportion of subjects achieving HbA_{1c} <7% goal, and FPG) relative to sitagliptin over the 52-week period.
- Canagliflozin 300 mg provided clinically important weight loss, and reductions in SBP relative to sitagliptin.
- Canagliflozin 300 mg improved fasting (HOMA2-%B) and dynamic (FS-MMTT model based endpoints) indices of beta-cell function.

- Canagliflozin 300 mg was overall well tolerated over the 52-week period, with a safety profile consistent with expectations (based upon the results of Phase 2b and other canagliflozin Phase 3 studies in subjects with T2DM), including an increase in adverse events of genital mycotic infections and adverse events related to osmotic diuresis (eg, polyuria, pollakiuria, thirst), but with these events generally considered mild and not generally leading to discontinuation of treatment.

Overall, this study met the key primary and many of the secondary hypotheses, suggesting a favorable efficacy profile, and a safety and tolerability profile consistent with expectations.