SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	INVOKANA
Name of Active Ingredient(s)	JNJ-28431754 (Canagliflozin) + JNJ-1158196 (Metformin)

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Status: Approved

Date: 16 April 2015

Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA3011

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

EudraCT Number: 2011-000400-17

NCT No.: NCT01809327

Clinical Registry No.: CR100034

Coordinating Investigator: Leonard Chuck, PhD, MD; PPD

Study Centers: 158 centers in 12 countries including 73 centers in Europe (5 in Czech Republic, 7 in Hungary, 6 in Romania, 23 in Russian Federation, 9 in Slovakia, 23 in Ukraine), 58 in North America (11 in Mexico, 47 in United States), 15 centers in South America (12 in Argentina, 3 in Brazil), and 12 in the rest of the word (7 in South Africa, 5 in South Korea).

Publication (Reference): None

Study Period: 16 May 2013 to 01 December 2014; Database Lock: 30 December 2014

Phase of Development: Phase 3

Objectives: The study was designed to assess the efficacy, safety, and tolerability of canagliflozin (Cana) in combination with metformin (Met) as initial combination therapy in the treatment of subjects with type 2 diabetes mellitus (T2DM) who had inadequate glycemic control with diet and exercise.

Primary Objectives

In subjects with T2DM with inadequate glycemic control with diet and exercise after 26 weeks:

- to assess the effect of the co-administration of canagliflozin and metformin extended-release (XR) compared with canagliflozin alone on hemoglobin A_{1c} (HbA_{1c})
- to assess the effect of the co-administration of canagliflozin and metformin XR compared with metformin XR alone on HbA_{1c}

- to assess the safety and tolerability of the co-administration of canagliflozin and metformin XR, canagliflozin alone, and metformin XR alone

Secondary objectives

In subjects with T2DM with inadequate glycemic control with diet and exercise after 26 weeks:

- to assess the effect of co-administration of canagliflozin and metformin XR on change from baseline in HbA_{1c}
- to assess the effect of co-administration of canagliflozin and metformin XR relative to baseline and to each agent alone on:
  - fasting plasma glucose (FPG)
  - proportion of subjects with HbA_{1c} <7.0% and <6.5%
  - body weight
  - systolic and diastolic blood pressure
  - fasting plasma lipids (ie, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], total cholesterol, non-HDL-C, LDL-C to HDL-C ratio, and triglycerides)
- to assess the effect of canagliflozin alone relative to metformin XR alone on:
  - HbA_{1c}
  - body weight
- to assess the effect of canagliflozin relative to baseline on:
  - glycemic control (HbA_{1c} and FPG)
  - proportion of subjects with HbA_{1c} <7.0% and <6.5%
  - body weight
  - systolic and diastolic blood pressure
  - fasting plasma lipids (ie, LDL-C, HDL-C, total cholesterol, non-HDL-C, LDL-C to HDL-C ratio, and triglycerides)

Methodology: This was a Phase 3 randomized, double-blind, active-controlled, parallel-group, 5-arm, multicenter study that evaluated the efficacy, safety, and tolerability of the co-administration of canagliflozin and metformin XR, as initial combination therapy, relative to canagliflozin alone or metformin XR alone after 26 weeks of treatment, in subjects with T2DM with inadequate glycemic control with diet and exercise. Subjects with T2DM ≥18 and <75 years of age with inadequate glycemic control (ie, HbA_{1c} of ≥7.5% to ≤12.0%, as determined by central laboratory) on diet and exercise at screening (and who were not on an antihyperglycemic agent (AHA) for at least 12 weeks before screening) were eligible to participate. Eligible subjects were randomly assigned to 1 of 5 treatment groups (in a 1:1:1:1:1 ratio) (metformin XR alone, canagliflozin 100 mg alone, canagliflozin 300 mg alone, co-administration of canagliflozin 100 mg and metformin XR, or co-administration of canagliflozin 300 mg and metformin XR) for 26 weeks of double-blind treatment. These treatment groups are referred to as Met XR alone, Cana 100 mg alone, Cana 300 mg alone, Cana 100 mg/Met XR, and Cana 300 mg/Met XR, respectively, in the results sections of this report.

An Independent Data Monitoring Committee (IDMC) reviewed unblinded serious adverse events and cardiovascular (CV) events and 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): Approximately 1,200 subjects were planned. A total of 1,186 subjects were randomly assigned to study treatment. The numbers of subjects included in the various analysis sets are summarized by treatment group in the table below.

Summary of Analysis Sets and Disposition
(Study 28431754-DIA3011: All Randomized Subjects Analysis Set)

	Met XR (N=237) n (%)	Cana 100 mg (N=237) n (%)	Cana 300 mg (N=238) n (%)	Cana 100 mg /Met XR (N=237) n (%)	Cana 300 mg /Met XR (N=237) n (%)	Total (N=1186) n (%)
Subjects who were randomized	237 (100)	237 (100)	238 (100)	237 (100)	237 (100)	1186 (100)
Subjects in the mITT analysis set	237 (100)	237 (100)	238 (100)	237 (100)	237 (100)	1186 (100)
Subjects in the mITT analysis set who discontinued before the Week 26 visit	32 (13.5)	26 (11.0)	22 (9.2)	12 (5.1)	25 (10.5)	117 (9.9)
Subjects in the completers analysis set	205 (86.5)	211 (89.0)	216 (90.8)	225 (94.9)	212 (89.5)	1069 (90.1)
Subjects in the PP analysis set	205 (86.5)	211 (89.0)	215 (90.3)	224 (94.5)	208 (87.8)	1063 (89.6)
Subjects in the safety analysis set	237 (100)	237 (100)	238 (100)	237 (100)	237 (100)	1186 (100)

Key: Cana=canagliflozin, mITT=modified intent-to-treat, Met=metformin, N=total number of subjects, n=total number of subjects in subgroup, PP=per-protocol, XR=extended release.
Note: Percentages calculated with the number of subjects in each group as denominator.
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Diagnosis and Main Criteria for Inclusion: Men or women ≥18 and <75 years of age with T2DM, who had inadequate glycemic control (ie, HbA_{1c} of ≥7.5% to ≤12.0%, as determined by the central laboratory) with diet and exercise at screening (and who had not been on an AHA for at least 12 weeks before screening) were eligible to participate.

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin overencapsulated tablets containing 100 mg (bulk lot numbers: 37236.5, HG-13F032) and 300 mg (bulk lot numbers: 37236.8, 37236.9, HG-13F027) for oral administration. Placebo to match canagliflozin (bulk lot numbers: 11D26/G001, 11H24/G001, 12I10/G001, HG-13E017, HG-13F025).

Reference Therapy, Dose and Mode of Administration, Batch No.: Metformin XR 500 mg tablets (bulk lot numbers: MTBT1104R, MTBT1105R, MTCT1294R) for oral administration. Placebo to match metformin XR (bulk lot numbers: MTBPL11030, MTCPL1295R).

Duration of Treatment: The total duration of the study, including the 2-week single-blind placebo run-in period, the 26-week double blind treatment phase, and the 4-week follow-up phase was approximately 33 weeks for each subject.

Evaluations: Efficacy evaluations included HbA_{1c}, FPG, body weight, fasting lipid profile, systolic blood pressure, and proportion of subjects with an HbA_{1c} <7.0% and <6.5%.

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

Statistical Methods:

Sample Size Determination: The primary hypothesis for this study was that each dose of canagliflozin in combination with metformin XR is superior to the respective doses of canagliflozin alone and metformin XR alone in glycemic control, as measured by the change from baseline to Week 26 in HbA_{1c}. Assuming a minimum group difference of 0.4% in change in HbA_{1c} from baseline to Week 26 between each dose of canagliflozin in combination with metformin XR versus the respective monotherapies and an associated common standard deviation of 1.15%, and using a 2-sample, 2 sided t-test with Type I error rate of 0.05,

it was is estimated that approximately 216 subjects per group were required to achieve 90% power for both comparisons.

Efficacy: The primary efficacy endpoint was the change in HbA_{1c} from baseline through Week 26. The change from baseline in HbA_{1c} was analyzed using a mixed model for repeated measures (MMRM) - a restricted maximum likelihood (REML) approach. The analysis was based on observed data and included the fixed categorical effects of treatment, stratification factor related to glycemic control before randomization (ie, whether or not the screening HbA_{1c} value for the subject is <9% or ≥9.0%), 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-subject errors. The between-treatment differences for each dose of canagliflozin in combination with metformin XR and the respective doses of canagliflozin alone and metformin XR alone in the least-squares means and their 2-sided 95% confidence intervals (CI) were estimated at Week 26 based on this model.

For supportive purposes and to facilitate comparison with historical results, an analysis of covariance (ANCOVA) model (using the modified intent-to-treat [mITT] dataset and the last observation carried forward [LOCF] approach) was performed with treatment and the stratification factor related to glycemic control before randomization as a fixed effect and the corresponding baseline HbA_{1c} value as a covariate. Only post-baseline measurements were eligible for LOCF imputation. Non-inferiority of each dose of canagliflozin alone (100 mg and 300 mg) versus metformin XR alone in terms of HbA_{1c} reduction was also determined (with a noninferiority margin of 0.35%) as a secondary efficacy endpoint.

Continuous secondary endpoints (ie, body weight, systolic blood pressure) were analyzed with an MMRM model similar to the primary efficacy endpoint from baseline to Week 26 in the mITT analysis set whereas the non-inferiority HbA_{1c} comparison was based on the primary efficacy model. The least square (LS) means and their 2-sided 95% CIs for the treatment differences were estimated based on these models. The binary secondary efficacy endpoint of maintaining HbA_{1c} <7% was analyzed longitudinally using a generalized linear mixed model including the fixed, categorical effects of treatment, stratification factor, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction.

A hierarchical testing procedure, which strongly controls the overall Type I error rate (two-sided alpha level of 0.05), was implemented.

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, and serious adverse events leading to discontinuation of study drug were summarized by treatment group. Predefined limits of change and descriptive statistics were provided for other safety parameters.

RESULTS:

STUDY POPULATION:

Subject and Treatment Information

A total of 2,000 subjects were screened and a total of 1,186 (59.3%) subjects were randomly assigned to study treatment. All of the 1,186 subjects randomized received at least 1 dose of study drug to comprise the mITT analysis set, of which 1,069 (90.1%) subjects completed the 26-week study. Subjects were stratified according to their screening HbA_{1c} values (<9% or ≥9.0%). A total of 566 subjects with screening HbA_{1c} <9.0% and 620 subjects with screening HbA_{1c} ≥9.0% were randomly assigned to study treatment. A summary of the analysis sets is provided above in the summary table under, “Number of Subjects (planned and analyzed)”. The reasons for discontinuation from the study are summarized in the table below.

Reasons for Discontinuation

(Study 28431754-DIA3011: Modified Intent-To-Treat Analysis Set)

	Met XR (N=237) n (%)	Cana 100 mg (N=237) n (%)	Cana 300 mg (N=238) n (%)	Cana 100 mg /Met XR (N=237) n (%)	Cana 300 mg /Met XR (N=237) n (%)	Total (N=1186) n (%)
Primary Reason for Discontinuation [a]	32 (13.5)	26 (11.0)	22 (9.2)	12 (5.1)	25 (10.5)	117 (9.9)
Adverse Event	4 (1.7)	3 (1.3)	7 (2.9)	4 (1.7)	8 (3.4)	26 (2.2)
Creatinine/eGFR Withdrawal Criteria	0	0	1 (0.4)	0	2 (0.8)	3 (0.3)
Death	1 (0.4)	0	0	0	0	1 (0.1)
Glycemic Withdrawal Criteria	12 (5.1)	7 (3.0)	3 (1.3)	3 (1.3)	2 (0.8)	27 (2.3)
Initiation and Planned Continued Use of Disallowed Therapy	0	1 (0.4)	0	0	0	1 (0.1)
Lost to Follow-Up	5 (2.1)	2 (0.8)	4 (1.7)	2 (0.8)	3 (1.3)	16 (1.3)
Physician Decision	1 (0.4)	1 (0.4)	0	0	0	2 (0.2)
Pregnancy	1 (0.4)	0	0	0	0	1 (0.1)
Protocol Violation	0	1 (0.4)	0	0	0	1 (0.1)
Subject Discontinued for Personal Reasons, Agrees to Follow up	3 (1.3)	4 (1.7)	2 (0.8)	2 (0.8)	4 (1.7)	15 (1.3)
Subject Is Persistently in Poor Compliance with Study Treatment or Procedures	1 (0.4)	3 (1.3)	1 (0.4)	0	2 (0.8)	7 (0.6)
Subject Is Unable to Tolerate the Minimum Dose Metformin XR (1,000 mg/day)	0	3 (1.3)	0	0	0	3 (0.3)
Treatment with A Corticosteroid for More Than 14 Consecutive Days	0	0	0	0	1 (0.4)	1 (0.1)
Withdraw of Consent, Not Agreeable to Follow up	3 (1.3)	0	2 (0.8)	0	1 (0.4)	6 (0.5)
Other	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	2 (0.8)	7 (0.6)

Key: Cana=canagliflozin, eCRF=electronic case report form, eGFR=estimated glomerular filtration rate, mITT=modified intent-to-treat, Met=metformin, N=total number of subjects, n=total number of subjects in subgroup, XR=extended release

[a] As indicated by the investigator on the eCRF for mITT subjects who discontinued before the Week 26 visit.

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

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The overall mean duration of subject exposure for the 26-week double-blind treatment period was approximately 25 weeks. Approximately 90% of subjects across all groups had at least 24 weeks of exposure.

Baseline Characteristics

There were no notable differences in the demographic and anthropometric characteristics among the treatment groups. The study subjects had a median age of 56.0 years (range, 20-75 years) and 52.0% of subjects were female. The majority of subjects were white (81.6%) and not Hispanic or Latino (70.0%).

The mean baseline body weight for the mITT analysis set was 91.0 kg and the mean baseline body mass index (BMI) was 32.5 kg/m^2. The mean baseline HbA_{1c} was 8.8%, with 40.7% of subjects who had baseline HbA_{1c} >9%; the median duration of T2DM was 1.6 years; and the mean baseline eGFR was 87.6 $mL/min/1.73m^2$. Approximately 14% of subjects were reported to have a history of a diabetic microvascular complication (one or more of retinopathy, nephropathy, or neuropathy). Three hundred thirty-two subjects (28%) had previous AHA treatment before entering the study (but were off drug for at least 12 weeks before screening), while the remainder of subjects (854 [72%]) were treatment naïve before entering the study.

EFFICACY RESULTS: Statistically significant reductions in HbA_{1c} at Week 26 were observed for both doses of Cana/Met XR relative to both doses of Cana alone and Met XR alone, confirming the study's primary hypothesis. The differences in LS mean changes from baseline for Cana 300 mg/Met XR group

relative to the Cana 300 mg alone group and the Met XR alone group were -0.36% and -0.48%, respectively (adjusted p=0.001 for both comparisons). The differences in LS mean changes from baseline for Cana 100 mg/Met XR group relative to Cana 100 mg alone and Met XR alone groups, were -0.40% and -0.46%, respectively (adjusted p=0.001 for both comparisons).

The study also met the key secondary endpoint of noninferiority of HbA_{1c} (using a prespecified 0.35% margin) for both doses of Cana alone (300 mg and 100 mg) as compared with Met XR alone (adjusted p=0.001 for both comparisons).

Based on the pre-specified hierarchical testing sequence, both doses of Cana/Met XR achieved statistical significance with respect to the superiority of the secondary endpoints of percent change from baseline in body weight versus Met XR alone and the proportion of subjects with HbA_{1c} <7% versus Met XR alone. Additionally, both doses of Cana alone achieved statistical significance compared to Met XR alone with respect to the percent change from baseline in body weight. Systolic blood pressure and percent change in lipids (ie, HDL-C and triglycerides) were also tested for both doses of Cana/Met XR compared to Met XR alone, however, these endpoints failed to achieve statistical significance, as summarized in the table below.

Change From Baseline to Week 26 for Primary and Secondary Efficacy Endpoints
(Study 28431754-DIA3011: Modified Intent-To-Treat Analysis Set)

	Comparisons with Cana 300 mg		Comparisons with Cana 100 mg	
	Difference (95% CI)	p-value [a]	Difference (95% CI)	p-value [a]
HbA_{1c} Change (%)				
Cana/Met XR vs Cana	-0.36(-0.557; -0.169)	0.001	-0.40(-0.594; -0.207)	0.001
Cana/Met XR vs Met XR	-0.48(-0.670; -0.280)	0.001	-0.46(-0.657; -0.269)	0.001
Body Weight % Change (%)				
Cana/Met XR vs Met XR	-2.1(-2.9; -1.4)	0.001	-1.4(-2.1; -0.6)	0.001
HbA_{1c} Change (%) [b]				
Cana vs Met XR	-0.11(-0.307; 0.082)	0.001	-0.06(-0.258; 0.133)	0.001
Body Weight % Change (%)				
Cana vs Met XR	-1.8(-2.6; -1.1)	0.002	-0.9(-1.6; -0.2)	0.016
Achieving 7% HbA_{1c} target				
Cana/Met XR vs Met XR	13.81(3.863; 23.762)	0.016	6.56(-3.306; 16.423)	0.027
Systolic BP Change (mmHg)				
Cana/Met XR vs Met XR	-1.31(-3.058; 0.431)	0.147	-1.91(-3.641; -0.182)	0.060
HDL-C % Change (%)				
Cana/Met XR vs Met XR	4.3(0.2; 8.5)	0.147	5.3(1.2; 9.5)	0.147
Triglycerides % Change (%)				
Cana/Met XR vs Met XR	1.3(-7.3; 10.0)	0.806	-3.7(-11.1; 3.4)	0.608

Key: BP=blood pressure, Cana=canagliflozin, CI=confidence interval, HDL-C= high-density lipoprotein cholesterol, LOCF=last observation carried forward, Met=metformin, n=total number of subjects in subgroup, XR=extended release.

[a] Adjusted p-value.

[b] For Family 3 in the hypothesis testing sequence, the p-value for HbA_{1c} change corresponds to a comparison that canagliflozin is non-inferior to Metformin XR within a margin of 0.35%.

Note: Observed data are used for HbA_{1c} change (%), body weight %change (%) and systolic BP change (mmHg) and achieving 7% HbA_{1c} target analysis; LOCF data are used for HDL-C % change (%) and triglycerides % change (%) analysis.

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SAFETY RESULTS:

Adverse events: The overall incidence of adverse events was higher in the Cana 100 mg/Met XR and Cana 300 mg/Met XR (41.8% and 44.3%, respectively) groups relative to the Cana alone and Met XR alone groups. The incidence of adverse events in the Cana 100 mg alone, Cana 300 mg alone, and

Met XR alone groups was comparable (37.1%, 39.9%, and 37.6%, respectively). The proportion of subjects who discontinued due to adverse events was low, and slightly higher in the Cana 300 mg/Met XR and Cana 300 mg alone groups (3.0% and 2.9%, respectively), relative to the Cana 100 mg/Met XR, Cana 100 mg alone, and Met XR alone groups (1.7%, 1.3%, and 1.7%, respectively). The incidence of serious adverse events was also low, ranging from 1.7% to 3.0%, with no clear trend by treatment group or by dose. There was 1 death reported during the study, which occurred in the Met XR alone group.

Across treatment groups, the incidence of specific adverse events was generally low. No specific adverse events with an incidence ≥5% were reported in any treatment group. The most commonly reported adverse event was diarrhea, with the highest incidence seen in the Cana 100 mg/Met XR and Cana 300 mg/Met XR groups, each with an incidence of 4.2%, relative to the incidence in the Cana 100 mg (1.3%), Cana 300 mg (1.7%), and Met XR (1.3%) groups. Higher incidences of specific drug-related adverse events, including adverse events of urinary tract infection, male and female genital infections or genital symptom-related adverse events, and adverse events consistent with osmotic diuresis (eg, polyuria and pollakiuria) were observed in the 4 treatment groups containing canagliflozin, relative to the Met XR alone group. The proportion of subjects who experienced biochemically documented hypoglycemia was low, with a slightly higher incidence in the Cana 300 mg/Met XR group (5.5%), relative to the Cana 100 mg/Met XR group (4.2%), Cana 100 mg alone group (3.0%), Cana 300 mg alone group (3.8%), and Met XR alone group (4.6%). The overall summary of adverse events is provided in the table below.

Summary of Treatment-Emergent Adverse Events
(Study 28431754-DIA3011: Safety Analysis Set)

Number (%) of Subjects with at least 1 Adverse Event of the following Types	Met XR (N=237) n (%)	Cana 100 mg (N=237) n (%)	Cana 300 mg (N=238) n (%)	Cana 100 mg /Met XR (N=237) n (%)	Cana 300 mg /Met XR (N=237) n (%)
Any Adverse Events	89 (37.6)	88 (37.1)	95 (39.9)	99 (41.8)	105 (44.3)
Adverse Events Leading to Discontinuation	4 (1.7)	3 (1.3)	7 (2.9)	4 (1.7)	7 (3.0)
Adverse Events Related to Study Drug [a]	17 (7.2)	24 (10.1)	22 (9.2)	15 (6.3)	35 (14.8)
Adverse Events Related to Study Drug [a] and Leading to Discontinuation	2 (0.8)	2 (0.8)	2 (0.8)	1 (0.4)	5 (2.1)
Serious Adverse Events	7 (3.0)	4 (1.7)	7 (2.9)	7 (3.0)	4 (1.7)
Serious Adverse Events Leading to Discontinuation	1 (0.4)	0	3 (1.3)	2 (0.8)	2 (0.8)
Serious Adverse Events Related to Study Drug [a]	0	0	2 (0.8)	0	0
Serious Adverse Events Related to Study Drug [a] and Leading to Discontinuation	0	0	1 (0.4)	0	0
Deaths	1 (0.4)	0	0	0	0

Key: Cana=canagliflozin, Met=metformin, N=total number of subjects, n=total number of subjects in subgroup, XR=extended release.

[a] Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.

Note: Percentages calculated with the number of subjects in each group as denominator.
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Safety Laboratory Assessment:

A few small changes in laboratory safety analytes were observed in the 4 treatment groups containing canagliflozin, including a small mean increase in hemoglobin, a modest mean increase in blood urea nitrogen, and a small decrease in serum alanine aminotransferase (ALT) levels. Initial decreases in estimated glomerular filtration rate (eGFR) and commensurate increases in serum creatinine were also seen in the 4 treatment groups containing canagliflozin; however, maximal at Week 6 and attenuated over time by Week 26. The mean percent changes from baseline for selected safety laboratory parameters are summarized below.

Mean Percent Changes from Baseline for Selected Safety Laboratory Parameters – Within 2 Days of the Last Dose of Study Drug[a]
(Study 28431754-DIA3011: Safety Analysis Set)

	Mean % Change from Baseline				
Parameter	Met XR	Cana 100 mg	Cana 300 mg	Cana 100 mg /Met XR	Cana 300 mg /Met XR
Hemoglobin	-1.5 (6.3)	4.4 (7.1)	4.2 (11.2)	1.6 (7.3)	2.9 (6.9)
ALT	-0.4 (57.8)	-16.1 (40.5)	-12.9 (49.0)	-16.9 (33.8)	-13.5 (52.7)
AST	0.8 (37.2)	-10.1 (29.0)	-4.5 (37.6)	-7.3 (32.1)	-3.5 (42.5)
ALP	-0.6 (32.2)	2.3 (18.2)	1.2 (30.3)	-1.5 (25.0)	-4.7 (18.8)
GGT	10.9 (87.9)	-7.1 (35.0)	4.2 (84.2)	-2.3 (67.7)	-9.8 (43.5)
Serum bilirubin	4.2 (45.3)	8.4 (48.9)	9.4 (45.1)	0.1 (36.4)	1.4 (35.8)
BUN	0.7 (26.3)	13.0 (30.9)	12.1 (35.8)	16.0 (42.5)	12.2 (30.3)
Serum creatinine	-1.2 (18.0)	1.0 (12.9)	1.5 (12.6)	0.4 (28.7)	-0.4 (12.5)
eGFR	4.6 (19.7)	0.5 (13.8)	0.0 (14.2)	4.0 (20.3)	2.4 (15.7)
Chloride	-0.1 (3.2)	0.2 (2.7)	0.4 (2.8)	0.4 (2.9)	0.5 (3.0)
Sodium	-0.2 (2.2)	-0.0 (2.0)	-0.0 (2.1)	0.1 (2.0)	0.2 (2.1)
Magnesium	-1.2 (7.9)	6.2 (8.5)	7.8 (12.8)	4.5 (9.2)	5.1 (9.0)
Potassium	1.6 (11.6)	0.7 (10.7)	1.1 (10.5)	2.4 (11.6)	0.6 (12.0)
Serum urate	12.0 (24.4)	-4.2 (27.7)	-6.7 (19.8)	-2.2 (22.9)	-3.1 (31.4)

Key: ALT=alanine aminotransferase, ALP=alkaline phosphatase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, Cana=canagliflozin, eGFR=estimated glomerular filtration rate, GGT=gamma-glutamyl transferase, Met=metformin, XR=extended release.

[a] This summary includes data collected up to a maximum of 2 days after a subject's last dose of study drug in the 26-week core-double blind period (data collected beyond 2 days after the subject's last dose of study drug are excluded from this summary).

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

CONCLUSION(S):

- Both doses of Cana/Met XR (ie, Cana 100 mg/Met XR and Cana 300 mg/Met XR) provided statistically significant greater HbA_{1c}-lowering, body weight reduction, and proportion of subjects with HbA_{1c} <7% at Week 26 compared with their respective Cana alone doses (ie, Cana 100 mg and Cana 300 mg) or Met XR alone.
- Both doses of canagliflozin alone also demonstrated noninferiority on HbA_{1c}-lowering and statistically significant greater reductions in body weight compared with Met XR alone.
- Both doses of Cana/Met XR were overall well tolerated, and no new safety signals were identified with the co-administration of canagliflozin and metformin. Canagliflozin was associated with a low incidence of adverse events of urinary tract infection, genital mycotic infections, osmotic diuresis, reduced intravascular volume, and a low rate of events of hypoglycemia.

Overall, the study met the primary and key secondary hypotheses, suggesting a favorable efficacy profile for Cana/Met XR for initial combination use, and a safety and tolerability profile consistent with expectations based upon the prior Phase 3 program for canagliflozin.