**Janssen Research & Development**

**Clinical Study Report Synopsis**
**[Protocol 28431754DIA3009]**

**JNJ-28431754 (Canagliflozin)**

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## SYNOPSIS

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|---|---|
| Name of Sponsor/Company | Janssen Research & Development |
| Name of Finished Product | INVOKANA™ |
| Name of Active Ingredient(s) | Canagliflozin (JNJ-28431754) |

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**Status:** Final Approved

**Date:** 24 July 2013

**Prepared by:** Janssen Research & Development, LLC

**Protocol No.:** 28431754DIA3009

**Title of Study:** A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 100 mg and JNJ-28431754 300 mg Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin Monotherapy

**Study Name:** CANTATA-SU

**EudraCT Number:** 2009-009320-36

**NCT No.:** NCT00968812

**Clinical Registry No.:** CR016480

**Coordinating Investigator:** [redacted], MD, [redacted] USA

**Study Center(s):** 157 study centers in 19 countries, including 54 centers in North America, 39 centers in Europe[a], 9 centers in Central/South America, and 55 centers in the rest of world

**Publication (Reference):**

Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, Balis DA, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. The Lancet, Early Online Publication, 12 July 2013 doi:10.1016/S0140-6736(13)60683

**Study Period:** 28 August 2009 to 30 January 2013

**Phase of Development:** 3

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

**Objectives:**

The primary and secondary objectives related to assessments done at Week 52 are described in the Week 52 core double-blind period Clinical Study Report (CSR), referred to as the DIA3009 Week 52 core CSR.

Objectives related to assessments done through Week 104 of the study were to compare the durability of hemoglobin $A_{1C}$ ($HbA_{1C}$)-lowering efficacy in each canagliflozin group with the glimepiride group from Week 26 to Week 104, and to assess the overall safety and tolerability from baseline of canagliflozin compared with glimepiride in subjects with type 2 diabetes mellitus (T2DM).

Objectives related to assessments done after Week 104 of the study were to evaluate the effect of canagliflozin compared with glimepiride on the following:

- glycemic control ($HbA_{1C}$ and fasting plasma glucose [FPG])
- body weight, waist circumference, and body mass index (BMI)
- Incidence of hypoglycemia
- proportion of subjects with $HbA_{1C}$ <7.0% and <6.5%
- 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)
- systolic blood pressure (SBP) and diastolic blood pressure (DBP)
- time to receiving rescue therapy or discontinuing due to need for rescue therapy (unable to take protocol defined rescue therapy) through Week 104
- proportion of subjects receiving rescue therapy or discontinuing due to need for rescue therapy (and unable to take protocol defined rescue therapy) through Week 104
- β-cell function (proinsulin to insulin ratio and homeostasis model assessment [HOMA2-%B, calculated from measured FPG and C-peptide])
- urinary glucose excretion (UGE)

**Methodology:** This study was a randomized, double-blind, 3-arm, parallel-group, active-controlled, multicenter study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) compared with glimepiride in subjects with T2DM with inadequate glycemic control on a maximally effective dose of metformin. Metformin background therapy was required to be at maximally or near-maximally effective doses (protocol-specified: metformin ≥2,000 mg/day, or ≥1,500 mg/day, if unable to tolerate a higher dose).

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 evaluated blinded data for fracture, and hepatic, and renal events, (3) an Independent Data Monitoring Committee (IDMC) reviewed unblinded serious adverse events (all) 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 to enroll approximately 1,281 subjects into the study. A total of 1,452 subjects were randomized to glimepiride, canagliflozin 100 mg, and

canagliflozin 300 mg in a 1:1:1 manner. The numbers of subjects included in the various analysis sets by treatment group are summarized below.

**Summary of Analysis Sets and Disposition (All Randomized Subjects)**
(Study 28431754-DIA3009: All Randomized Subjects Analysis Set)

| | CANA 100 mg (N=483) n (%) | CANA 300 mg (N=485) n (%) | CANA Total (N=968) n (%) | Glimepiride (N=484) n (%) | Total (N=1452) n (%) |
|---|---|---|---|---|---|
| Subjects who were randomized | 483 (100) | 485 (100) | 968 (100) | 484 (100) | 1452 (100) |
| Subjects in the mITT analysis set | 483 (100) | 485 (100) | 968 (100) | 482 (99.6) | 1450 (99.9) |
| Subjects in the mITT analysis set who discontinued before the Week 104 visit | 140 (29.0) | 162 (33.4) | 302 (31.2) | 168 (34.7) | 470 (32.4) |
| Subjects in the mITT analysis set who received rescue therapy before the Week 104 visit | 96 (19.9) | 63 (13.0) | 159 (16.4) | 101 (20.9) | 260 (17.9) |
| Subjects in the extension mITT analysis set [a] | 363 (75.2) | 354 (73.0) | 717 (74.1) | 333 (68.8) | 1050 (72.3) |
| Subjects in the Week 104 completers' analysis set [b] | 265 (54.9) | 276 (56.9) | 541 (55.9) | 236 (48.8) | 777 (53.5) |
| Subjects in the PP analysis set | 264 (54.7) | 276 (56.9) | 540 (55.8) | 236 (48.8) | 776 (53.4) |
| Subjects in the safety analysis set | 483 (100) | 485 (100) | 968 (100) | 482 (99.6) | 1450 (99.9) |
| Subjects in the extension safety analysis set [c] | 393 (81.4) | 377 (77.7) | 770 (79.5) | 381 (78.7) | 1151 (79.3) |

[a] Includes mITT subjects who entered the extension period, took at least 1 dose of double-blind study medication, and didn't receive rescue medication in the core double-blind period. This analysis set is used in the efficacy analysis.
[b] Includes mITT subjects who completed the Week 104 visit and had not initiated rescue medication.
[c] Includes mITT subjects who entered the extension period and took at least 1 dose of double-blind study medication. This analysis set is used in the Week 52 to Week 104 safety analysis.
Key: CANA=canagliflozin, mITT=modified intent-to-treat, PP=per protocol
Note: Percentages were calculated with the number of subjects in each group as the denominator.
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**Diagnosis and Main Criteria for Inclusion:** Man or woman ≥18 and ≤80 years of age with T2DM with inadequate glycemic control on a maximally effective dose of metformin in monotherapy, meeting the following $HbA_{1C}$ criteria:

- on metformin monotherapy at a stable protocol-specified dose* for at least 12 weeks before screening and had $HbA_{1C}$ of ≥7.0% and ≤9.5% at screening, or
- on metformin monotherapy at a dose <2,000 mg/day with an $HbA_{1C}$ of ≥7.5% and ≤10.0% at screening and had a Week -2 visit $HbA_{1C}$ of ≥7.0% and ≤9.5%, after at least 10 weeks on a stable protocol-specified dose* of metformin, or
- on metformin at a stable protocol-specified dose in combination with one other oral non-thiazolidinedione (TZD) antihyperglycemic agent (AHA) with an $HbA_{1C}$ of ≥6.5% and ≤9.0% at screening and had a Week -2 visit $HbA_{1C}$ of ≥7.0% and ≤9.5%, after discontinuing the AHA and on a stable protocol-specified dose* of metformin for at least 10 weeks, or
- on metformin at a dose <2,000 mg/day in combination with one other oral non-TZD AHA with an $HbA_{1C}$ of ≥6.5% and ≤9.0% at screening and had a Week -2 visit $HbA_{1C}$ of ≥7.0% and ≤9.5%, after discontinuing the AHA and on a stable protocol-specified dose* of metformin for at least 10 weeks

(*Protocol-specified dose of metformin: ≥2,000 mg/day [or ≥1,500 mg/day, if unable to tolerate a higher dose].)

**Test Product, Dose and Mode of Administration, Batch No.:** Canagliflozin capsules containing active 100 mg (batch/lot numbers: PD3093, 09K06/G002, PD3390, 32783.11, 30845.5, 11A10/G002, 30845.12, 33977.6, 33977.4, and 11A11/G002) and 300 mg (batch/lot numbers: PD3154, PD3158, PD3302, PD3303, PD3393, PD3400, 30845.3, 32783.14, 30845.9, 32783.7, and 33977.8) for oral administration.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Glimepiride 1 mg (batch/lot numbers: PD2999, 09I25/G012, 30380.1, 30775.2, 30775.4, 33977.1, 32580.1, and 12A17/G012), Glimepiride 2 mg (batch/lot numbers: PD3000, 09I28/G013, 30380.2, 30775.1, 30775.6, 33977.2, 32580.3, and 12A18/G013), Glimepiride 4 mg (batch/lot numbers: PD3001, 09J01/G014, 30380.3, 30775.3, 30775.7, 33977.3, 32580.2, and 12A19/G014), and Placebo to match canagliflozin (batch/lot numbers: PD2776, PD2998, PD3091, PD3220, PD3221, 10B22/G001, 10I08/G001, 11C30/G001, 32580.4, 30845.13, 30845.8, 09J28/G001, and 11D26/G001).

**Duration of Treatment:** The total duration of the study, including the optional prescreening visit, the 2-week single-blind placebo run-in period, the 104-week double-blind treatment phase, and the 4-week follow-up period was approximately 111 weeks (for subjects on protocol-specified doses of metformin at the screening visit) to 124 weeks (for subjects on metformin below protocol-specified doses who had their AHA regimen adjusted to protocol-specified doses).

A separate report summarized the results of the 52-week core double-blind treatment period. This report summarizes the results of the entire 104-week double-blind treatment phase, including the 52-week core double-blind period and the 52-week extension double-blind period.

**Evaluations:** Efficacy laboratory assessments included $HbA_{1C}$, FPG, C-peptide, HOMA2-%B, calculated from measured FPG and C-peptide, fasting insulin and proinsulin (for the calculation of the proinsulin/insulin ratio), urine glucose and creatinine, for the calculation of UGE (the urine glucose to urine creatinine ratio), durability of glycemic control (as measured by a longitudinal profile of $HbA_{1C}$), fasting plasma lipids (LDL-C, HDL-C, non-HDL-C, total cholesterol and triglycerides). Additional efficacy measurements included body weight, waist circumference and BMI; SBP and DBP; hypoglycemia events; and use of and time to rescue therapy.

Safety assessment was based on reported adverse events, safety laboratory tests (including hematology, chemistry, routine urinalysis), 12-lead electrocardiograms, vital signs' measurements (blood pressure and pulse rate), body weight, waist circumference and BMI (calculated), physical examinations, self-monitored blood glucose (SMBG) and collection of hypoglycemia episodes (eg, from the diary provided to the subjects), regardless of whether considered to be adverse events by the reporting investigator.

**Statistical Methods:**

Sample Size Determination: Sample size determination was based on the primary endpoint (change in $HbA_{1C}$ from baseline) at Week 52, as discussed in the DIA3009 Week 52 core CSR. No study hypotheses were tested for evaluation at the Week 104 timepoint.

Efficacy: The primary efficacy analysis of change from baseline in $HbA_{1C}$ at Week 52 and key secondary endpoints at Week 52 are described in the DIA3009 Week 52 core CSR. The last post-baseline observation carried forward (LOCF) method was applied when the Week 104 values were missing. Only the data prior to the initiation of rescue medication were used for the Week 104 analysis.

An analysis of covariance (ANCOVA) model with treatment (canagliflozin 100 mg and canagliflozin 300 mg) and stratification factors (whether or not a subject underwent the metformin dose stabilization/AHA washout period prior to run-in, and country) as fixed effects and baseline value as covariate, based on the modified intent-to-treat (mITT) analysis set and extension MITT analysis set, was used to evaluate changes or percent changes from baseline at Week 104 in the following continuous efficacy variables: $HbA_{1C}$; FPG; body weight; SBP; DBP; fasting plasma lipids, including LDL-C, HDL-C, non-HDL-C, total cholesterol, ratio of LDL-C to HDL-C, and triglycerides; HOMA2-%B, insulin/proinsulin (and ratio), and waist circumference and BMI. The categorical efficacy endpoints (proportion of subjects with $HbA_{1C}$ <6.5% and <7.0%, subjects with at least 5% body weight reduction and the proportion of subjects with documented hypoglycemia) were summarized by treatment group at Week 104. The treatment comparisons (each canagliflozin group versus glimepiride) of the percentage of

subjects experiencing at least 1 documented hypoglycemia episode were assessed using a logistic regression model, with terms for treatment, stratification factors, and baseline $HbA_{1C}$ value. The 2-sided 95% CI for the odds ratio between each canagliflozin group and glimepiride and the corresponding p-value for the associated hypothesis test of treatment difference were derived from the model. The risk difference between each canagliflozin group and glimepiride was also estimated.

Durability: Several durability (of treatment effect) analyses were conducted. For subjects with an initial decrease from baseline in $HbA_{1C,}$ (≥0.4%) the time to develop an increase (≥0.3%) was analyzed using a Cox proportional hazard model. The coefficient of durability, defined as the rate of the rise of $HbA_{1C}$ from Week 26 to Week 104, was analyzed using a mixed effect model based on subjects who had Week 26 $HbA_{1C}$ measurements and at least 1 measurement after Week 26 (mITT). The number of subjects who achieved $HbA_{1C}$ <7% through Week 26 and who also maintained $HbA_{1C}$ <7% at Week 104 was analyzed using a Cochran-Mantel-Haenszel (CMH) test with control of randomization stratification factors.

Pharmacodynamics: Changes in urine glucose and creatinine and the ratio of urine glucose and creatinine concentrations were analyzed as described for continuous efficacy variables (see above).

Safety: The incidence (ie, number and percent of subjects with 1 or more adverse events 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. 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. The primary safety analyses for overall and specific adverse events excluded data after the initiation of rescue medication (refer to the DIA3009 Week 52 core CSR). Secondary safety analyses for overall and specific adverse events were performed including all data, regardless of the initiation of rescue medication. Predefined limits of change (PDLC) and descriptive statistics were provided for other safety parameters.

**RESULTS:**

STUDY POPULATION:

**Subject and Treatment Information and Baseline Characteristics**

A total of 3,316 subjects were screened and a total of 1,452 subjects were randomized to study treatment. Overall, 67.7% of subjects completed the entire 104-week double-blind phase. The most common reasons for discontinuation across all treatment groups (mITT analysis set) included adverse event (7.5% of subjects), “other” (7.0% of subjects), and withdrawal of consent (4.5% of subjects). The category of “Other” included a variety of reasons (personal reasons, moving, family- or job-related, lack of efficacy, disallowed therapy, treatment unblinded) and also included subjects who withdrew from the study due to updated information on preclinical safety findings (specifically, updated information on rat carcinogenicity study results), but agreed to continued follow-up (and hence were not classified as withdrawal of consent).”

The mITT analysis set and the safety analysis set were identical.

**Reasons for Discontinuation**
(Study 28431754-DIA3009: Modified Intent-to-Treat Analysis Set)

| | CANA 100 mg (N=483) n (%) | CANA 300 mg (N=485) n (%) | CANA Total (N=968) n (%) | Glimepiride (N=482) n (%) | Total (N=1450) n (%) |
|---|---|---|---|---|---|
| Total number of subjects discontinued | 140 (29.0) | 162 (33.4) | 302 (31.2) | 168 (34.9) | 470 (32.4) |
| Primary reason for discontinuation [a] | | | | | |
| Adverse event | 30 ( 6.2) | 46 ( 9.5) | 76 ( 7.9) | 33 ( 6.8) | 109 ( 7.5) |
| Creatinine or eGFR withdrawal criteria | 9 ( 1.9) | 13 ( 2.7) | 22 ( 2.3) | 7 ( 1.5) | 29 ( 2.0) |
| Death | 2 ( 0.4) | 2 ( 0.4) | 4 ( 0.4) | 1 ( 0.2) | 5 ( 0.3) |
| Lack of efficacy on rescue therapy | 9 ( 1.9) | 7 ( 1.4) | 16 ( 1.7) | 16 ( 3.3) | 32 ( 2.2) |
| Lost to follow-up | 17 ( 3.5) | 12 ( 2.5) | 29 ( 3.0) | 11 ( 2.3) | 40 ( 2.8) |
| Noncompliance with study drug | 4 ( 0.8) | 1 ( 0.2) | 5 ( 0.5) | 6 ( 1.2) | 11 ( 0.8) |
| Physician decision | 8 ( 1.7) | 5 ( 1.0) | 13 ( 1.3) | 9 ( 1.9) | 22 ( 1.5) |
| Protocol violation | 7 ( 1.4) | 4 ( 0.8) | 11 ( 1.1) | 3 ( 0.6) | 14 ( 1.0) |
| Withdrawal of consent | 17 ( 3.5) | 23 ( 4.7) | 40 ( 4.1) | 25 ( 5.2) | 65 ( 4.5) |
| Unable to take protocol defined rescue Therapy | 12 ( 2.5) | 12 ( 2.5) | 24 ( 2.5) | 17 ( 3.5) | 41 ( 2.8) |
| Other | 25 ( 5.2) | 37 ( 7.6) | 62 ( 6.4) | 40 ( 8.3) | 102 ( 7.0) |

[a] As indicated by the investigator on the eCRF for mITT subjects who discontinued before the Week 104 visit.
Key: CANA=canagliflozin; eGFR=estimated glomerular filtration rate
Note: Percentages were calculated with the number of subjects in each group as the denominator.
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The overall mean duration of subject exposure (prior to rescue medication) for the 104-week double-blind treatment phase was similar across canagliflozin treatment groups and slightly lower in the glimepiride group, with 55.7% of subjects in the combined canagliflozin group having at least 102 weeks of exposure, compared with 48.5% of subjects in the glimepiride group.

**Baseline Characteristics**

Baseline characteristics for the mITT analysis set were generally similar across treatment groups. The median age of subjects in the study was 57 years, and a slightly lower proportion of women than men were randomized. Consistent with the regions of the world in which subjects were recruited, 67% of the subjects were white, 4% were black or African American, and 20% were Asian; 17% of subjects were of Hispanic or Latino ethnicity.

For the mITT analysis set, baseline mean body weight was 86.6 kg and baseline mean BMI was 31.0 kg/m$^2$; these were generally similar across treatment groups, with approximately 54% of the subjects being obese (BMI ≥30 kg/m$^2$), based upon National Institutes of Health (NIH) criteria (NIH 1998).

EFFICACY RESULTS:

The least-squares (LS) mean changes from baseline in $HbA_{1C}$ at Week 104 in the mITT analysis were -0.74%, and -0.65% for the canagliflozin 300 mg and 100 mg groups, respectively, and -0.55% for the glimepiride group, with the 95% confidence interval (CI) around the difference from glimepiride excluding “0” for the canagliflozin 300 mg group. (Refer to the table below) The difference in $HbA_{1C}$ between each canagliflozin dose and glimepiride increased further from Week 52 to Week 104 (LS mean reductions from baseline in $HbA_{1C}$ at Week 52 in the mITT analysis of -0.93% and -0.82% for the canagliflozin 300 mg and 100 mg groups, respectively, and -0.81% for the glimepiride group, with the between group difference for canagliflozin 300 mg relative to glimepiride of -0.12% [95% CI: -0.218% to -0.024%] and the between-group difference of canagliflozin 100 mg relative to glimepiride of -0.01% [95% CI: -0.111% to 0.083%]). Substantial and sustained glycemic improvements were seen in FPG and percent change from baseline in body weight, with greater reductions seen with canagliflozin 300 mg relative to canagliflozin 100 mg. Reductions from baseline through Week 104 in SBP and DBP were observed in the canagliflozin groups compared with the glimepiride group that were dose related. In

addition, relative to the glimepiride group, percent increases from baseline in HDL-C at Week 104 were observed for both canagliflozin groups. Decreases in triglycerides, relative to glimepiride, were seen in both canagliflozin groups (increases were seen in all 3 groups). The risk of documented hypoglycemia was substantially decreased in both canagliflozin groups relative to glimepiride. (Refer to the table below) In the mITT analysis set, among subjects who had a decrease from baseline in $HbA_{1C}$ of ≥0.4% through Week 26, the median time to develop an increase in $HbA_{1C}$ of ≥0.3% from Week 26 through Week 104 was 183 days in the canagliflozin 300 mg group, 126 days in the canagliflozin 100 mg group, 126 days in the glimepiride group. The hazard ratio (95% CI) for canagliflozin 300 mg vs glimepiride was 0.70 (0.60; 0.82), and for the canagliflozin 100 mg vs glimepiride it was 0.88 (0.76; 1.02). A high proportion (>80%) of subjects in all groups had a decrease from baseline in $HbA_{1C}$ at Week 104. The coefficient of durability (COD [using the slope of $HbA_{1C}$ change from Week 26 to Week 104]) in subjects in the mITT analysis set for canagliflozin 300 mg, canagliflozin 100 mg, and glimepiride was 0.16%, 0.16%, and 0.37%, respectively. The 95% CI around the difference from glimepiride excluded "0" for both canagliflozin dose groups. The proportion of subjects who achieved an $HbA_{1C}$ <7% by Week 26 and maintained this value at Week 104 was 35.7% in the canagliflozin 300 mg group, 31.1% in the canagliflozin 100 mg group and 29.2% in the glimepiride group.

**Change From Baseline to Week 104 LOCF for Efficacy Endpoints**
(Study 28431754-DIA3009: Modified Intent-to-Treat Analysis Set)

| Endpoints | --------- CANA 100 mg --------- --- (Glimepiride-subtracted) -- Mean (95% CI) | --------- CANA 300 mg --------- --- (Glimepiride-subtracted) -- Mean (95% CI) |
|---|---|---|
| $HbA_{1C}$ change (%) | -0.09 ( -0.200; 0.010) | -0.18 ( -0.289; -0.078) |
| Proportion achieving 7% $HbA_{1C}$ target (%) | -1.4 ( -7.9; 5.1) | 6.3 ( -0.2; 12.9) |
| FPG change (mmol/L) | -0.49 ( -0.721; -0.253) | -0.66 ( -0.897; -0.430) |
| Body weight %change (%) | -5.1 ( -5.6; -4.5) | -5.2 ( -5.7; -4.6) |
| Risk of documented hypoglycemia | -34.0 ( -39.2; -28.9) | -32.6 (-37.9; -27.4) |
| Total cholesterol %Change (%) | 2.7 ( 0.4; 5.1) | 5.9 ( 3.5; 8.3) |
| HDL-C %change (%) | 8.7 ( 6.5; 10.8) | 9.3 ( 7.1; 11.4) |
| LDL-C %change (%) | 4.9 ( -0.4; 10.1) | 8.0 ( 2.7; 13.3) |
| LDL-C/HDL-C %change (%) | -3.4 ( -9.1; 2.3) | -2.4 ( -8.1; 3.4) |
| Non-HDL-C %Change (%) | 0.3 ( -3.0; 3.6) | 4.3 ( 1.0; 7.6) |
| Triglycerides %change (%) | -9.4 ( -15.9; -2.8) | -5.9 ( -12.5; 0.6) |
| SBP change (mmHg) | -3.74 ( -5.187; -2.302) | -4.81 ( -6.248; -3.363) |
| DBP change (mmHg) | -1.25 ( -2.177; -0.317) | -2.20 ( -3.135; -1.275) |

Key: ANCOVA=analysis of covariance, CI=confidence interval, $HbA_{1C}$=hemoglobin $A_{1C}$, DBP=diastolic blood pressure, CANA=canagliflozin, HDL-C=high-density lipoprotein-cholesterol, FPG=fasting plasma glucose, LDL-C=low-density lipoprotein-cholesterol, LOCF=last observation carried forward, mITT=modified intent-to-treat. SBP=systolic blood pressure
Note: For continuous endpoints, the LS mean is presented with associated p-values and CIs based on ANCOVA models with terms for treatment and stratification factors and adjusting for the baseline value as a covariate.
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## SAFETY RESULTS:

### Adverse Events

The overall incidence of adverse events over the 104-week double-blind treatment phase was slightly higher in the canagliflozin 300 mg group (77.9%) compared with the canagliflozin 100 mg group (73.3%) and similar to the incidence in the glimepiride group (78.4%). A higher incidence of drug-related adverse events, as assessed by investigators, compared to glimepiride was observed in both canagliflozin groups, with a trend toward dose-relationship. The overall higher incidence of drug-related adverse events was mainly driven by numerically higher incidences in specific adverse events consistent with male and female genital mycotic infections, and osmotic diuresis adverse events. The overall incidence of adverse events leading to discontinuation was low in all groups and highest in the canagliflozin 300 mg group. The overall incidence of serious adverse events was low and higher in the glimepiride group than in the canagliflozin groups. There were 8 deaths reported during the entire 104-week double-blind treatment phase (3 subjects in each of the canagliflozin groups and 2 subjects in the glimepiride group).

**Summary of Adverse Events During Entire Double-blind Treatment Phase - Regardless of Rescue Medication**
(Study 28431754-DIA3009: Safety Analysis Set)

| Number (%) of Subjects With At Least 1 TEAE of the Following Types | CANA 100 mg (N=483) n (%) | CANA 300 mg (N=485) n (%) | CANA Total (N=968) n (%) | Glimepiride (N=482) n (%) |
|---|---|---|---|---|
| Any adverse events | 354 (73.3) | 378 (77.9) | 732 (75.6) | 378 (78.4) |
| Adverse events leading to discontinuation | 30 ( 6.2) | 46 ( 9.5) | 76 ( 7.9) | 35 ( 7.3) |
| Adverse events related to study drug [a] | 138 (28.6) | 159 (32.8) | 297 (30.7) | 134 (27.8) |
| Adverse events related to study drug [a] and leading to discontinuation | 19 ( 3.9) | 27 ( 5.6) | 46 ( 4.8) | 13 ( 2.7) |
| Serious adverse events | 47 ( 9.7) | 47 ( 9.7) | 94 ( 9.7) | 69 (14.3) |
| Serious adverse events leading to discontinuation | 8 ( 1.7) | 8 ( 1.6) | 16 ( 1.7) | 13 ( 2.7) |
| Serious adverse events related to study drug [a] | 3 ( 0.6) | 3 ( 0.6) | 6 ( 0.6) | 2 ( 0.4) |
| Serious adverse events related to study drug [a] and leading to Discontinuation | 2 ( 0.4) | 1 ( 0.2) | 3 ( 0.3) | 0 |
| Deaths | 3 ( 0.6) | 3 ( 0.6) | 6 ( 0.6) | 2 ( 0.4) |

[a] Related to study drug includes relationship determined by investigators: possibly related, probably related, and very likely related.
Key: CANA=canagliflozin, TEAE=treatment-emergent adverse event.
Note: Percentages were calculated with the number of subjects in each group as the denominator.
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The overall incidence of adverse events that occurred in the 52-week extension double-blind period (ie, Week 52 to Week 104) was slightly higher in the glimepiride group (63.8%) relative to the combined canagliflozin groups (57.4%). A lower incidence of drug-related adverse events was seen in the canagliflozin groups relative to the glimepiride group. The incidence of adverse events leading to discontinuation was low and similar across groups. The overall incidence of serious adverse events was low across all groups and lower in the canagliflozin groups relative to the glimepiride group. Four subjects died, all of whom were in the canagliflozin groups. In the canagliflozin 100 mg group, [redacted] subjects died, 1 subject due to [redacted], 1 subject due to [redacted], and 1 subject due to massive [redacted] (the only death during the 104-week study assessed by the investigator as related [possibly] to study drug). In the canagliflozin 300 mg group, 1 subject died due to a [redacted].

**Summary of Adverse Events During the Extension Period - Regardless of Rescue Medication**
(Study 28431754-DIA3009: Extension Safety Analysis Set)

| Number (%) of Subjects With At Least 1 TEAE of the Following Types | CANA 100 mg (N=393) n (%) | CANA 300 mg (N=377) n (%) | CANA Total (N=770) n (%) | Glimepiride (N=381) n (%) |
|---|---|---|---|---|
| Any adverse event | 218 (55.5) | 224 (59.4) | 442 (57.4) | 243 (63.8) |
| Adverse events leading to discontinuation | 5 ( 1.3) | 14 ( 3.7) | 19 ( 2.5) | 8 ( 2.1) |
| Adverse events related to study drug [a] | 35 ( 8.9) | 42 (11.1) | 77 (10.0) | 51 (13.4) |
| Adverse events related to study drug [a] and leading to discontinuation | 2 ( 0.5) | 7 ( 1.9) | 9 ( 1.2) | 3 ( 0.8) |
| Serious adverse events | 24 ( 6.1) | 22 ( 5.8) | 46 ( 6.0) | 31 ( 8.1) |
| Serious adverse events leading to discontinuation | 2 ( 0.5) | 3 ( 0.8) | 5 ( 0.6) | 3 ( 0.8) |
| Serious adverse events related to study drug [a] | 1 ( 0.3) | 3 ( 0.8) | 4 ( 0.5) | 2 ( 0.5) |
| Serious adverse events related to study drug [a] and leading to Discontinuation | 0 | 1 ( 0.3) | 1 ( 0.1) | 0 |
| Deaths | 3 ( 0.8) | 1 ( 0.3) | 4 ( 0.5) | 0 |

[a] Related to study drug includes relationship determined by investigators: possibly related, probably related, and very likely related.
Key: CANA=canagliflozin, TEAE=treatment-emergent adverse event.
Note: Percentages were calculated with the number of subjects in each group as the denominator.
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Higher incidences in 1 or both canagliflozin treatment groups or the pooled canagliflozin treatment groups relative to the glimepiride group were seen, with the 95% CIs around the between-group differences excluding "0" for several specific adverse event terms reflecting osmotic diuresis adverse events (including thirst, pollakiuria, and urine output increased), specific adverse event terms reflecting female superficial genital infection (including vulvovaginal candidiasis, vaginal infection, vulvovaginal mycotic infection, vulvovaginitis, and vulvovaginal pruritus); specific adverse event terms reflecting male superficial genital infection (balanitis, balanoposthitis); and adverse events of influenza, hepatic enzyme increased, and weight decreased. The instances of these specific adverse events were generally low and few subjects discontinued due to these adverse events. A high incidence of drug-related adverse events compared to glimepiride were observed in both canagliflozin groups with a trend toward dose-relationship, mainly driven by numerically higher incidences of specific adverse events consistent with male and female genital mycotic infections and osmotic diuresis adverse events.

**Laboratory Results**

A few changes from baseline in laboratory safety analytes were observed at Week 104 with canagliflozin 100 mg and 300 mg, including an increase (3.0% to 3.5%, respectively) in hemoglobin, relative to a decrease (1.8%) in the glimepiride group. Increases in mean change from baseline in serum creatinine (2.2% to 4.3%) were observed in the canagliflozin groups, with a larger increase (6.7%) observed in the glimepiride group. Consistent with these findings, mean decreases in estimated glomerular filtration rate (eGFR) of 0.9% to 2.9% were seen in the canagliflozin groups compared with a 6.0% decrease in the glimepiride group at Week 104. A mean increase (17.0% to 20.2%) in blood urea nitrogen was observed in the canagliflozin groups, relative to a smaller increase (6.1%) in the glimepiride group at Week 104. Mean decreases from baseline through Week 104 in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (9.2% to 1.0%, respectively) were observed in the canagliflozin 300 mg group compared to increases (9.4% to 10.7%, respectively) in the glimepiride group. Smaller mean increases (0.9% to 1.7%, respectively) in ALT and AST were observed in the canagliflozin 100 mg group. These changes occurred concomitantly with increases in mean change from baseline (6.4% to 13.1%) in bilirubin in the canagliflozin groups, relative to a smaller increase (1.5%) in the glimepiride group. Four subjects in each canagliflozin group had elevations in their last ALT >3 times the upper limit of normal (ULN) compared with 2 subjects in the glimepiride group. No subjects in any treatment group had elevations in ALT >3 times ULN accompanied by elevation in total bilirubin >2 times ULN. A mean decrease (8.9% to 9.6%) in serum urate was seen in the canagliflozin treatment groups at Week 104, relative to an increase in the glimepiride group (8.3%). A mean increase (5.9% to 7.7%) in serum magnesium was observed in the canagliflozin groups, relative to no notable change (0.4%) in the glimepiride group at Week 104.

**Other Safety Assessments**

Treatment with canagliflozin 100 mg and 300 mg led to reductions in blood pressure (systolic reduction greater than diastolic). No meaningful change in pulse rate or electrocardiograms was seen with canagliflozin 100 mg and 300 mg.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- As previously reported, this study met the key Week 52 primary and secondary efficacy hypotheses. The extension study data from DIA3009 suggest more durable $HbA_{1C}$-lowering with canagliflozin, relative to glimepiride.
- Canagliflozin provided weight loss relative to weight gain with glimepiride.

- Canagliflozin provided improvements in other non-glycemic endpoints including SBP, DBP, HDL-C, and triglycerides; LDL-C levels increased with canagliflozin treatment
- Canagliflozin was overall well tolerated during 104 weeks of double-blind treatment; canagliflozin treatment was associated with an increased incidence of adverse events of male and female genital mycotic infections, urinary tract infections, osmotic diuresis (eg, polyuria, pollakiuria, and thirst) and volume depletion-related adverse events, but these events were generally considered mild and not leading to discontinuation of treatment.
- Both doses of canagliflozin have a substantially lower incidence of episodes of hypoglycemia relative to glimepiride.

Overall, the study hypotheses were met, suggesting a favorable efficacy profile (with the canagliflozin 300 mg dose providing additional benefit), and a safety and tolerability profile consistent with expectations.