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Original article

Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study

Kaj Stenlöf
Clinical Trial Center, Sahlgrenska University Hospital, Gothenburg, Sweden

William T. Cefalu
Pennington Biomedical Research Center, Baton Rouge, LA, USA
LSUHSC School of Medicine, New Orleans, LA, USA

Kyoung-Ah Kim
Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University School of Medicine, Goyang, Korea

Esteban Jodar
Department of Endocrinology, Hospital Quiron, Madrid, Spain

Maria Alba
Robert Edwards
Cindy Tong
William Canovatchel
Gary Meininger
Janssen Research & Development, LLC, Raritan, NJ, USA

Address for correspondence:
Kaj Stenlöf MD PhD, Clinical Trial Center, Sahlgrenska University Hospital, SE-413 45, Gothenburg, Sweden.
Tel: +46 31 342 70 96; Fax: +46 31 41 16 35;
kaj.stenlof@gu.se

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Abstract

Objective:
Canagliflozin is a sodium glucose co-transporter 2 inhibitor developed for treatment of type 2 diabetes mellitus (T2DM). The long-term efficacy and safety of canagliflozin monotherapy were evaluated over 52 weeks in patients with T2DM inadequately controlled with diet and exercise.

Research design and methods:
This randomized, double-blind, Phase 3 study included a placebo-controlled, 26-week core period (canagliflozin 100 or 300 mg vs placebo) and an active-controlled, 26-week extension (blinded switch of placebo-treated patients to sitagliptin 100 mg [placebo/sitagliptin]).

Clinical trial registration:
ClinicalTrials.gov, NCT01081834.

Main outcome measures:
Efficacy endpoints assessed at 52 weeks included changes in hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), and systolic blood pressure (BP); and percentage changes in body weight and fasting plasma lipids. Adverse events (AEs) were recorded throughout the study. Efficacy data are reported for canagliflozin 100 and 300 mg (placebo/sitagliptin group was used to maintain the double-blind and to serve as a control group for safety purposes; not as an efficacy comparator); safety data are reported for canagliflozin 100 and 300 mg and placebo/sitagliptin.

Results:
Efficacy analyses included 451 patients who were randomized and dosed, entered the extension, and did not receive rescue therapy during the core period. Safety analyses included 584 patients who were randomized and dosed. At Week 52, canagliflozin 100 and 300 mg provided dose-related decreases from baseline in HbA_{1c} of −0.81% and −1.11%. Canagliflozin 100 and 300 mg decreased FPG (−1.5 and −2.2 mmol/L [−27.4 and −39.1 mg/dL]), body weight (−3.3% and −4.4%), and systolic BP (−1.4 and −3.9 mmHg); decreased triglycerides and increased HDL-C and LDL-C were also seen. Over 52 weeks, overall AE rates were 67.2%, 66.0%, and 64.1% with canagliflozin 100 and 300 mg and placebo/sitagliptin; rates of serious AEs and AE-related discontinuations were low across groups. Compared with placebo/sitagliptin, canagliflozin was associated with higher rates of genital mycotic infections and AEs related to osmotic diuresis; these led to few discontinuations. Rates of volume depletion AEs and documented hypoglycemia were low across groups.

Conclusions:
Canagliflozin monotherapy provided sustained improvement in glycemic control and body weight reduction, and was generally well tolerated in patients with T2DM over 52 weeks.

Introduction

Management of individuals with type 2 diabetes mellitus (T2DM) is one of the most significant challenges facing the health care community. Efforts to treat patients with T2DM typically begin with a focus on diet and exercise[1], but lifestyle changes are often not sufficient to provide adequate or prolonged glycemic control[1,2]. Metformin has been established as the recommended first-line pharmacologic therapy for patients with T2DM; however, because of gastrointestinal concerns, it is not tolerated in some patients. In addition, in individuals with impaired renal function, it cannot be used[1]. In order to provide more viable options that allow for individualized treatment of patients with T2DM, new antihyperglycemic agents (AHAs) are needed that can provide not only glycemic control, but also additional benefits that address clinical needs such as body weight reduction and a low risk of hypoglycemia[1,3]. Due to the progressive nature of type 2 diabetes and the diminished efficacy of some available AHAs over time, agents that provide persistent effects on glycemic control with evidence of long-term safety and tolerability are of particular interest.

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed for the treatment of T2DM[4–11]. Canagliflozin inhibits renal glucose reabsorption by lowering the renal threshold for glucose (RT_G), thereby inducing urinary glucose excretion (UGE) and reducing plasma glucose, as well as leading to a mild osmotic diuresis and caloric loss[6,12–14]. In Phase 3 studies in patients with T2DM, canagliflozin has been shown to improve glycemic control and reduce body weight and systolic blood pressure (BP) in patients with T2DM on a variety of background AHAs[4,5,7,9].

In the Phase 3, CANagliflozin Treatment And Trial Analysis – Monotherapy (CANTATA-M) study in patients with T2DM inadequately controlled with diet and exercise, canagliflozin 100 and 300 mg monotherapy significantly reduced hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), body weight, and systolic BP compared with placebo, and was generally well tolerated over a 26-week core treatment period[8]. To evaluate the longer-term efficacy and safety of canagliflozin monotherapy, this study was extended for an additional 26 weeks. The present analysis focuses on the efficacy and safety findings from the entire 52-week treatment period, including the 26-week, double-blind extension period, in which patients who had received canagliflozin 100 or 300 mg during the core period continued on these treatments, while placebo-treated patients switched to sitagliptin 100 mg in a blinded fashion (placebo/sitagliptin group). Since therapy with canagliflozin and sitagliptin were not concurrently initiated, direct comparisons for efficacy parameters at Week 52 cannot be made, as the placebo/sitagliptin group served as a control group for safety purposes only. Therefore, efficacy findings are reported for the canagliflozin 100 and 300 mg groups, while safety findings are reported for both canagliflozin groups and the placebo/sitagliptin group.

Patients and methods

Patients and study design

This Phase 3, randomized, double-blind, placebo-controlled study (CANTATA-M) included both patients with inadequate glycemic control on diet and exercise, and patients on an AHA who had to undergo an 8-week AHA washout period with diet and exercise. All patients entered into a 2-week, single-blind placebo run-in period (Week –2 to Day 1) prior to randomization into a 26-week, double-blind, placebo-controlled core treatment period (findings previously reported[8]). Patients were randomly assigned in a 1:1:1 ratio to once-daily oral doses of canagliflozin 100 or 300 mg, or matching placebo, at entry into the core period[8]. Patients who completed the core study period then entered a 26-week, double-blind, active-controlled extension period (findings reported here). Those taking canagliflozin 100 or 300 mg continued treatment, while patients who had been assigned to placebo during the core period switched in a blinded fashion to double-blind, active treatment with sitagliptin 100 mg upon entering the extension period. Sitagliptin was used to maintain the double-blind while avoiding prolonged treatment with placebo in patients randomized to the placebo group.

Study patients were men and women ≥18 and ≤80 years of age with T2DM who met one of the following two criteria: (1) not on an AHA at screening (off for at least 12 weeks) with HbA_{1c} ≥7.0 and ≤10.0%; or (2) on oral AHA monotherapy (except a peroxisome proliferator-activated receptor gamma [PPARγ] agonist) or on low-dose combination therapy with metformin (≤1000 mg) and sulfonylurea (≤50% of maximally or near-maximally effective doses) with HbA_{1c} ≥6.5 and ≤9.5% at the screening (or pre-screening) visit and HbA_{1c} ≥7.0 and ≤10.0% and FPG <15 mmol/L (270 mg/dL) at Week –2 after the 8-week AHA washout period (patients that required AHA washout). Key exclusion criteria included FPG >15.0 mmol/L during the pre-treatment phase; a history of type 1 diabetes; history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident) within 3 months before screening; treatment with another SGLT2 inhibitor or any other AHA not specified in the inclusion criteria within 12 weeks before screening; and estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 at screening.

During the 52-week treatment period, patients experiencing deterioration of glycemic control were to receive rescue therapy with metformin based on pre-specified, progressively more stringent glycemic criteria: FPG >15 mmol/L (270 mg/dL) after Day 1 to Week 6, >13.3 mmol/L (240 mg/dL) after Week 6 to Week 12, and >11.1 mmol/L (200 mg/dL) after Week 12 to Week 26, and HbA_{1c} >8.0% after Week 26.

This study was conducted under the guidelines of Good Clinical Practices and the Declaration of Helsinki. Institutional review boards at participating institutions approved the study protocol and amendments, and written informed consent was provided by all patients prior to participation.

Endpoints and assessments

The primary efficacy endpoint of the CANTATA-M study was the change from baseline in HbA_{1c} at Week 26 (reported previously[8]). The key efficacy endpoint at Week 52 was the change from baseline in HbA_{1c}. Secondary endpoints assessed at Week 52 included change from baseline in FPG, systolic BP, and diastolic BP, and percentage change from baseline in body weight and fasting plasma lipids, including triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), LDL-C/HDL-C ratio, and non–HDL-C. No endpoints at Week 52 were pre-specified for statistical testing.

Assessments of safety and tolerability were based on reported adverse events (AEs), safety laboratory tests, vital sign measurements, physical examinations, and 12-lead electrocardiograms. Selected AEs including urinary tract infections (UTIs), genital mycotic infections, AEs related to osmotic diuresis, and volume depletion AEs were also evaluated. Adverse events were characterized by the investigator as not related, doubtfully, possibly, probably, or very likely related to study drug based on the availability of an alternative explanation (e.g., concomitant drug[s], concomitant disease[s]) and the relationship in time. Documented hypoglycemia episodes included biochemically documented episodes (≤3.9 mmol/L [70 mg/dL] with or without symptoms) and severe episodes (i.e., requiring the assistance of another individual or resulting in seizure or loss of consciousness). Laboratory measurements for this study were performed at a central clinical laboratory (Covance [Indianapolis, IN, USA; Geneva, Switzerland; Singapore]).

Statistical analyses

Sample size determination was based on the primary efficacy endpoint at Week 26 as described previously[8]. Efficacy endpoints at Week 52 were assessed in both the modified intent-to-treat (mITT) analysis set (all randomized patients who took ≥1 dose of study drug) and the extension mITT analysis set (all patients in the mITT population who entered the extension treatment period, took ≥1 dose of study drug during the extension period, and did not receive rescue therapy prior to entering the extension period). Efficacy data in the main body of this manuscript are for the extension mITT analysis set unless otherwise indicated; efficacy results from the mITT analysis set are reported in the Appendix. Missing data were imputed using the last observation carried forward (LOCF) approach; for patients who received glycemic rescue therapy, the last post-baseline value obtained prior to initiation of rescue therapy was used for analysis.

For continuous efficacy parameters, an analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and the corresponding baseline value as a covariate was used for analysis. Least squares (LS) mean changes from baseline and the associated 95% confidence intervals (CIs) were estimated. Categorical efficacy parameters were summarized by treatment group. No treatment differences were estimated for efficacy parameters.

Safety analyses included all reported AEs, regardless of rescue therapy, and laboratory results including data up to within 2 days after the last dose of study drug. The safety analysis set for the 52-week, double-blind treatment period was comprised of the same patients as those in the mITT analysis set; an analysis of safety during the 26-week extension period consisted of the extension safety analysis set (all patients who entered the extension period, regardless of rescue therapy, and received ≥1 dose of extension double-blind study drug).

There was no pre-specified hypothesis testing conducted for Week 52 assessments; therefore, no *P* values are reported. Descriptive statistics are provided for changes in efficacy parameters from baseline to Week 52.

Results

Patient disposition and baseline characteristics

A total of 584 patients were randomized into the study and received ≥1 dose of study drug, comprising the mITT analysis set and safety analysis set. Of the 507 patients who completed the 26-week core treatment period, 495 entered the 26-week extension period and 452 completed the entire 52-week study (Figure 1); 451 patients entered the extension period without receiving rescue in the core period and were included in the extension mITT analysis set. The proportions of patients who discontinued before Week 52 with canagliflozin 100 and 300 mg and placebo/sitagliptin were 22.1%, 16.2%, and 29.7%, respectively. Over 52 weeks, 13.8%, 7.1%, and 32.5% of patients received glycemic rescue therapy with

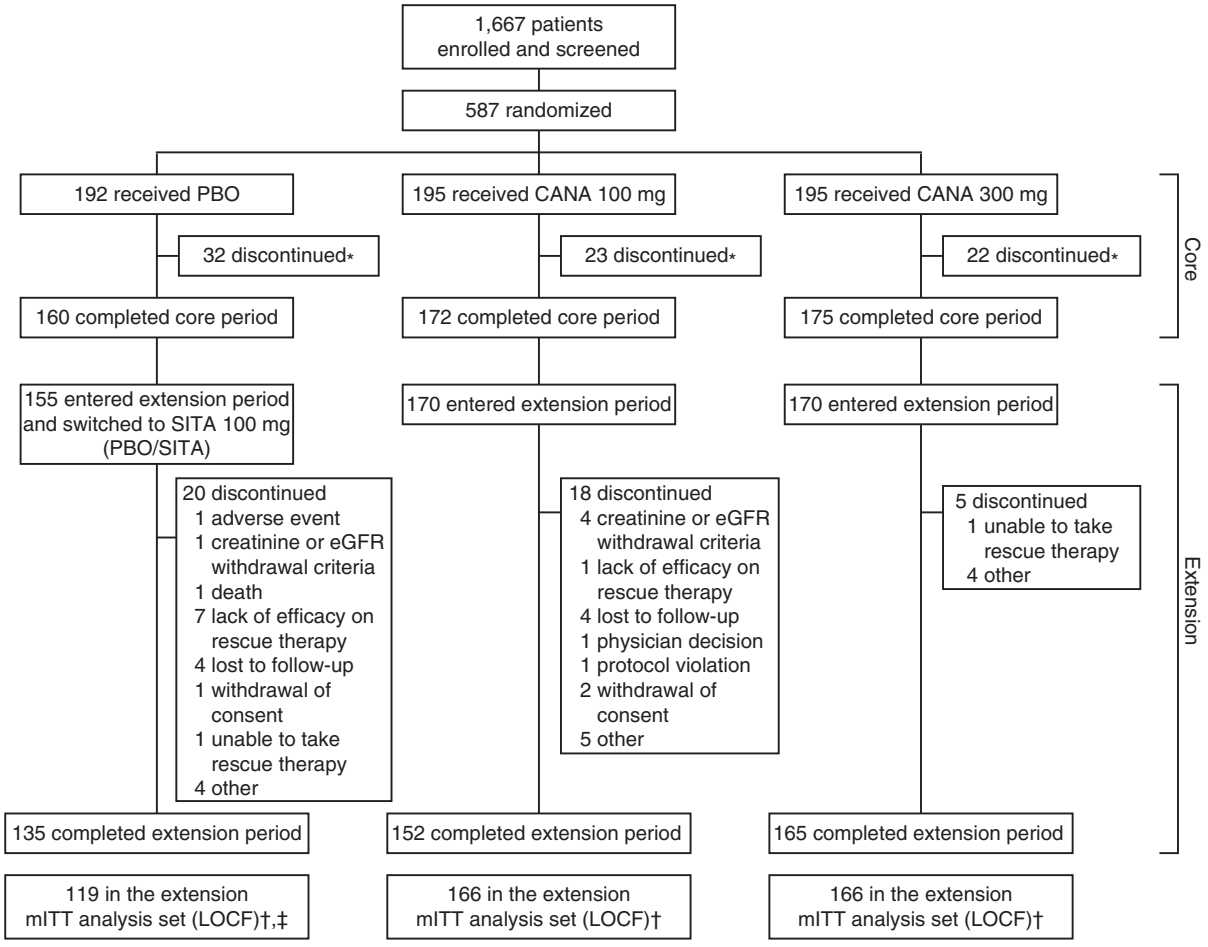

Figure 1. Study flow diagram.
PBO, placebo; CANA, canagliflozin; SITA, sitagliptin; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat; LOCF, last observation carried forward. *Reasons for discontinuation in core period are published.[8] †Randomized patients who entered the extension period, took ≥1 dose of double-blind study drug, and did not receive rescue therapy prior to entering the extension period. ‡Patients in the extension mITT analysis set for the PBO/SITA group were not evaluated for efficacy parameters.

canagliflozin 100 and 300 mg and placebo/sitagliptin, respectively; 11.2%, 5.1%, and 9.8%, respectively, received glycemic rescue therapy during the extension period. Demographic and baseline characteristics for the safety analysis set and the extension mITT analysis set are reported in Table 1 and Appendix Table 1, respectively.

Efficacy

Glycemic efficacy endpoints

Canagliflozin 100 and 300 mg provided stable, dose-related reductions from baseline in HbA_{1c} over 52 weeks (Figure 2A and 2B). At Week 52, LS mean changes (95% CI) from baseline in HbA_{1c} of −0.81% (−0.94, −0.68) and −1.11% (−1.24, −0.98) were observed with canagliflozin 100 and 300 mg, respectively, in the extension mITT analysis set. In the mITT analysis set, LS mean changes (95% CI) in HbA_{1c} were −0.75% (−0.89, −0.62) and −1.04% (−1.17, −0.90) with canagliflozin 100 and 300 mg, respectively (Appendix Figure 1); additional efficacy endpoints in the mITT analysis set are reported in Appendix Table 2.

At Week 52, the proportion of patients who achieved HbA_{1c} <7.0% with canagliflozin 100 and 300 mg was 52.4% and 64.5%, respectively; 22.9% and 30.1% of patients achieved HbA_{1c} <6.5% (Figure 2C). Dose-dependent reductions from baseline in FPG were observed with canagliflozin over 52 weeks, with reductions observed at the first scheduled visit (Week 6) that were maintained thereafter (Figure 2D). The LS mean changes (95% CI) in FPG from baseline to Week 52 were −1.5 mmol/L (−1.8, −1.3) and −2.2 mmol/L (−2.4, −1.9) (−27.4 mg/dL [−31.8, −23.0] and −39.1 mg/dL [−43.6, −34.7]) with canagliflozin 100 and 300 mg, respectively.

Body weight, blood pressure, and lipids

Canagliflozin 100 and 300 mg provided dose-proportionate percent reductions from baseline in body weight over

Table 1. Baseline demographic and disease characteristics (safety analysis set)*.

Characteristic	PBO/SITA ($n=192$)	CANA 100 mg ($n=195$)	CANA 300 mg ($n=197$)	Total ($N=584$)
Sex, *n* (%)				
Male	88 (45.8)	81 (41.5)	89 (45.2)	258 (44.2)
Female	104 (54.2)	114 (58.5)	108 (54.8)	326 (55.8)
Age, y	55.7 ± 10.9	55.1 ± 10.8	55.3 ± 10.2	55.4 ± 10.6
Race, *n* (%)†				
White	134 (69.8)	124 (63.6)	137 (69.5)	395 (67.6)
Black or African American	9 (4.7)	18 (9.2)	14 (7.1)	41 (7.0)
Asian	29 (15.1)	27 (13.8)	29 (14.7)	85 (14.6)
Other‡	20 (10.4)	26 (13.3)	17 (8.6)	63 (10.8)
HbA_{1c}, %	8.0 ± 1.0	8.1 ± 1.0	8.0 ± 1.0	8.0 ± 1.0
FPG, mmol/L (mg/dL)	9.3 ± 2.1 (167.6 ± 38.6)	9.6 ± 2.4 (173.0 ± 42.9)	9.6 ± 2.4 (173.0 ± 43.2)	9.5 ± 2.3 (171.2 ± 41.6)
Body weight, kg	87.6 ± 19.5	85.8 ± 21.4	86.9 ± 20.5	86.8 ± 20.4
BMI, kg/m^2	31.8 ± 6.2	31.3 ± 6.6	31.7 ± 6.0	31.6 ± 6.2
eGFR, mL/min/1.73 m^2	86.0 ± 21.5	88.5 ± 20.2	86.6 ± 19.1	87.1 ± 20.3
Duration of diabetes, y	4.2 ± 4.1	4.5 ± 4.4	4.3 ± 4.7	4.3 ± 4.4
Patients on AHA at screening, *n* (%)	92 (47.9)	94 (48.2)	95 (48.2)	281 (48.1)

PBO, placebo; SITA, sitagliptin; CANA, canagliflozin; HbA_{1c}, hemoglobin A_{1c}; FPG, fasting plasma glucose; BMI, body mass index; eGFR, estimated glomerular filtration rate; AHA, antihyperglycemic agent; SD, standard deviation.
*Data are mean ± SD unless otherwise indicated.
†Percentages may not total 100.0% due to rounding.
‡Includes American Indian or Alaska Native, other, unknown, and not reported.

52 weeks, with reductions observed by Week 26 that remained stable through Week 52 (Figure 3). LS mean percentage changes (95% CI) in body weight were −3.3% (−3.9, −2.6), and −4.4% (−5.1, −3.7) with canagliflozin 100 and 300 mg, respectively; absolute changes were −2.8 kg (−3.4, −2.1) and −3.9 kg (−4.6, −3.3), respectively. The proportions of patients who achieved body weight reductions of ≥5% were 29.5% and 40.4% with canagliflozin 100 and 300 mg, respectively.

At Week 52, canagliflozin 100 and 300 mg were associated with reductions from baseline in systolic BP (LS mean changes [95% CI] of −1.4 mmHg [−3.0, 0.2] and −3.9 mmHg [−5.5, −2.3], respectively; Figure 4). Systolic BP reductions were observed by Week 6 with both canagliflozin doses, and canagliflozin 300 mg provided greater reductions than canagliflozin 100 mg over 52 weeks. Canagliflozin 100 and 300 mg were also associated with reductions in diastolic BP at Week 52 (−0.4 and −0.7 mmHg, respectively); changes in pulse rate were −2.1 and 0.4 beats per minute, respectively.

Over 52 weeks, canagliflozin 100 and 300 mg were associated with dose-dependent increases in HDL-C (LS mean percentage changes of 11.1% and 14.7%, respectively) and LDL-C (6.3% and 11.2%, respectively; Table 2). From Week 26 to Week 52, greater increases in HDL-C and LDL-C were seen with canagliflozin 300 mg compared with canagliflozin 100 mg. Reductions in triglycerides were seen with canagliflozin 100 and 300 mg at Week 52 (−2.0% and −2.1%, respectively). Canagliflozin 100 and 300 mg were associated with decreases in the LDL-C/HDL-C ratio (−3.1% and −0.1%, respectively) and increases in non–HDL-C (1.8% and 5.6%, respectively) that were smaller than the observed increases in LDL-C over 52 weeks.

Safety and tolerability

The overall incidences of AEs over 52 weeks were 67.2%, 66.0%, and 64.1% with canagliflozin 100 and 300 mg and placebo/sitagliptin, respectively; rates of serious AEs were 5.6%, 2.5%, and 5.7% (Table 3). The incidence of AEs leading to discontinuation was low across groups, but higher with canagliflozin 100 and 300 mg compared with placebo/sitagliptin (3.1%, 2.0%, and 1.0%, respectively). The overall incidence of AEs during the extension period was higher with placebo/sitagliptin than with canagliflozin 100 and 300 mg (43.9%, 40.0%, and 36.5%, respectively; Appendix Table 3). There were three deaths during the 52-week study period (two with placebo/sitagliptin and one with canagliflozin 100 mg); none were considered to be drug-related by the investigator.

The incidences of documented hypoglycemia over 52 weeks were 5.1%, 3.6%, and 3.6% with canagliflozin 100 and 300 mg and placebo/sitagliptin, respectively, with no events leading to discontinuation. Over 52 weeks, the incidence of genital mycotic infections was higher with canagliflozin than with placebo/sitagliptin in females and males (Table 3); the majority of these AEs were mild or moderate in intensity, none were serious, and two led to study discontinuation (canagliflozin 100 mg, one female; canagliflozin 300 mg, one male). Of the 23 canagliflozin-treated females with genital mycotic infections, 22 received antifungal therapy; all female genital mycotic infections resolved or were resolving by Week 52. Of the

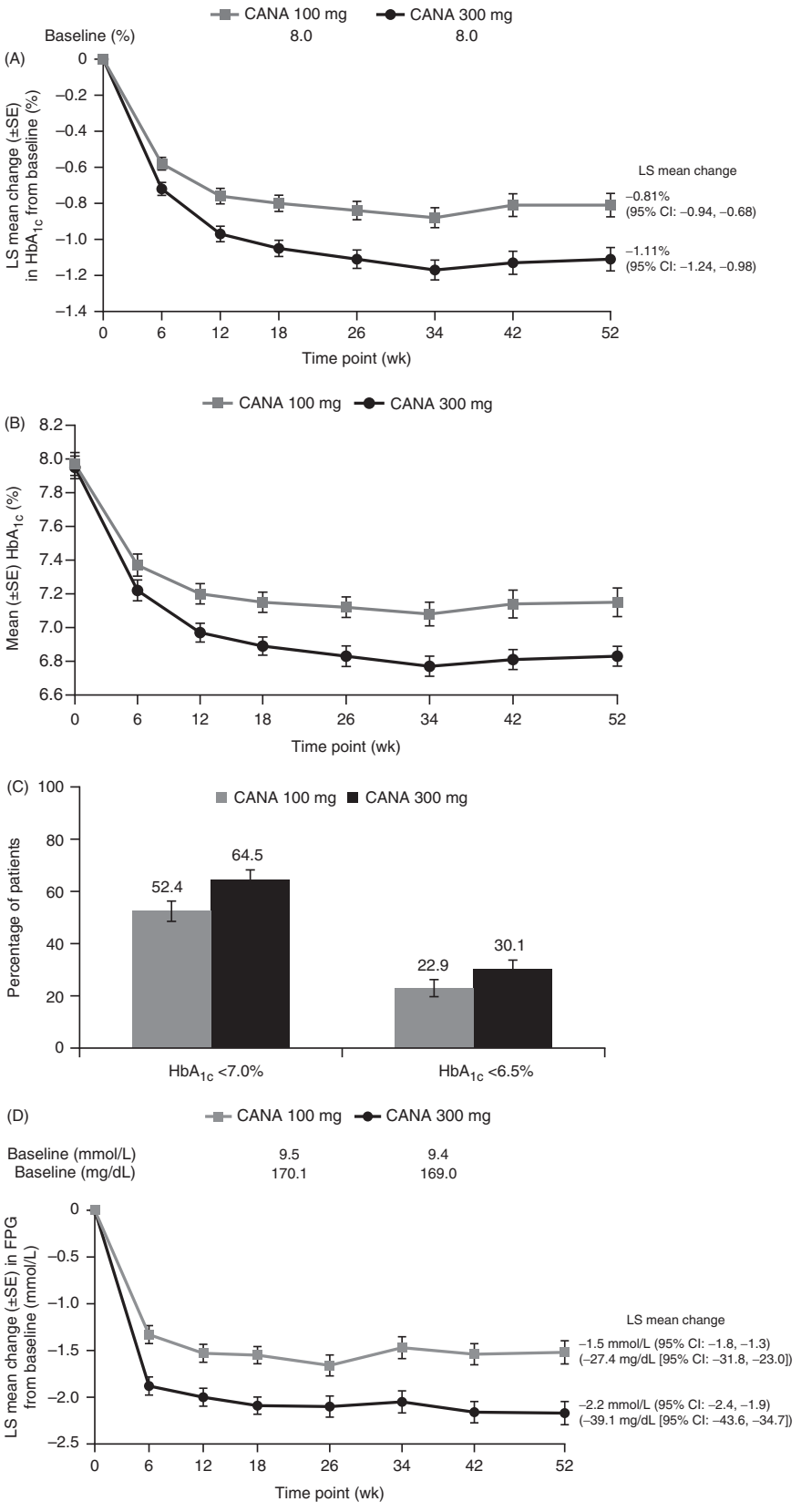

Figure 2. Changes in glycemic parameters (LOCF). (A) LS mean change in HbA_{1c} over time; (B) HbA_{1c} mean values over time; (C) proportion of patients reaching HbA_{1c} goals; and (D) LS mean change in FPG over time.
LOCF, last observation carried forward; LS, least squares; HbA_{1c}, hemoglobin A_{1c}; FPG, fasting plasma glucose; CANA, canagliflozin; SE, standard error; CI, confidence interval.

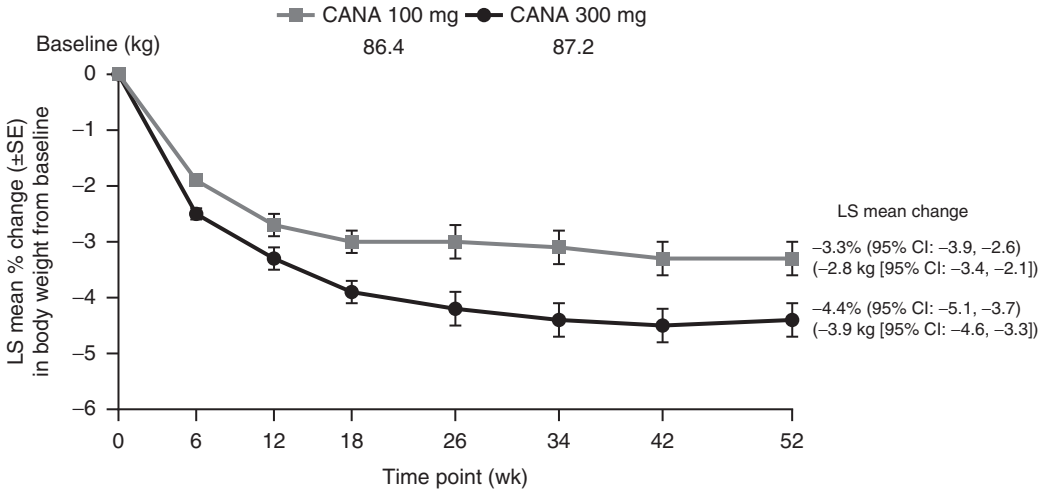

Figure 3. Percentage change in body weight over time (LOCF).
LOCF, last observation carried forward; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.

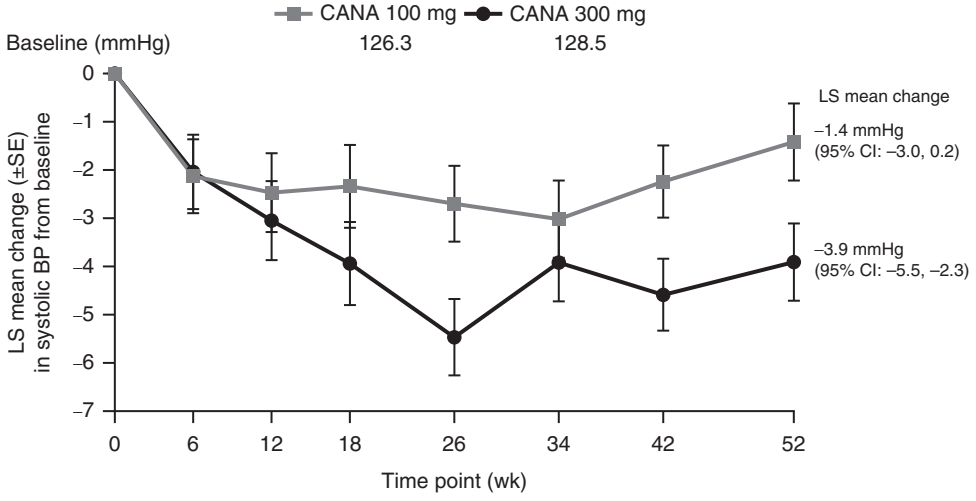

Figure 4. Change in systolic BP over time (LOCF).
BP, blood pressure; LOCF, last observation carried forward; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.

13 canagliflozin-treated male patients with genital mycotic infections, 12 (92.3%) were uncircumcised; overall, 68.8% of canagliflozin-treated males in the study were uncircumcised. Eleven of these 13 male patients received antifungal therapy. Two male patients (canagliflozin 300 mg group) and two female patients (one in each canagliflozin group) who had genital mycotic infections during the extension period had prior events reported in the core period. The incidences of UTIs were 8.2%, 7.1%, and 6.3% with canagliflozin 100 and 300 mg and placebo/sitagliptin, respectively; there were no serious events or incidences of upper UTIs (i.e., pyelonephritis), and no UTI AEs led to study discontinuation. Incidences of AEs related to osmotic diuresis (e.g., pollakiuria, polyuria, thirst) were higher with canagliflozin than with placebo/sitagliptin during the 52-week treatment period; one of these AEs led to study discontinuation in the canagliflozin 300 mg group but none were considered serious. All osmotic diuresis-related AEs with canagliflozin occurred during the core 26-week period. The incidence of volume depletion AEs (e.g., postural dizziness, orthostatic hypotension) was low across groups; none of these AEs were serious or led to study discontinuation.

Changes from baseline in safety laboratory parameters at 52 weeks with canagliflozin 100 and 300 mg and placebo for patients with data at baseline and Week 52 are reported in Table 4. Decreases in alanine aminotransferase and gamma glutamyl transferase, with concomitant increases in bilirubin, were seen with canagliflozin relative to placebo/sitagliptin. Canagliflozin was associated with increases in serum creatinine and commensurate decreases in eGFR compared with placebo/sitagliptin. Decreases in

Table 2. Summary of changes from baseline in fasting plasma lipids at Week 52 (LOCF).

	CANA 100 mg ($n = 165$)	CANA 300 mg ($n = 166$)
Triglycerides		
Mean ± SD baseline, mmol/L (mg/dL)	1.9 ± 1.2 (171.9 ± 109.1)	1.9 ± 1.1 (172.2 ± 99.5)
LS mean ± SE change	−0.22 ± 0.07 (−19.3 ± 6.6)	−0.09 ± 0.07 (−8.4 ± 6.6)
Median (IQR) percentage change	−8.1 (−29.5, 16.1)	−9.1 (−30.9, 21.2)
LS mean ± SE percentage change	−2.0 ± 3.0	−2.1 ± 3.0
LDL-C		
Mean ± SD baseline, mmol/L (mg/dL)	3.0 ± 0.9 (117.8 ± 36.8)	2.8 ± 0.9 (109.7 ± 36.1)
LS mean ± SE change	0.09 ± 0.06 (3.6 ± 2.2)	0.19 ± 0.06 (7.2 ± 2.1)
Median (IQR) percentage change	1.9 (−9.0, 16.1)	7.4 (−6.1, 25.9)
LS mean ± SE percentage change	6.3 ± 2.1	11.2 ± 2.1
HDL-C		
Mean ± SD baseline, mmol/L (mg/dL)	1.2 ± 0.3 (46.3 ± 12.1)	1.2 ± 0.3 (44.9 ± 11.2)
LS mean ± SE change	0.11 ± 0.02 (4.4 ± 0.7)	0.16 ± 0.02 (6.1 ± 0.7)
Median (IQR) percentage change	9.5 (0, 20.5)	11.8 (2.4, 24.8)
LS mean ± SE percentage change	11.1 ± 1.5	14.7 ± 1.5
LDL-C/HDL-C		
Mean ± SD baseline, mol/mol	2.7 ± 1.1	2.6 ± 0.9
LS mean ± SE change	−0.14 ± 0.05	−0.13 ± 0.05
Median (IQR) percentage change	−6.8 (−21.0, 6.8)	−3.7 (−18.8, 13.9)
LS mean ± SE percentage change	−3.1 ± 2.1	−0.1 ± 2.1
Non–HDL-C		
Mean ± SD baseline, mmol/L (mg/dL)	3.9 ± 1.1 (151.7 ± 41.2)	3.7 ± 1.0 (143.6 ± 38.0)
LS mean ± SE change	−0.01 ± 0.06 (−0.4 ± 2.4)	0.13 ± 0.06 (5.0 ± 2.4)
Median (IQR) percentage change	−0.7 (−13.0, 12.6)	2.8 (−8.2, 16.6)
LS mean ± SE percentage change	1.8 ± 1.7	5.6 ± 1.7

LOCF, last observation carried forward; CANA, canagliflozin; SD, standard deviation; LS, least squares; SE, standard error; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 3. Summary of overall safety and selected adverse events over 52 weeks*.

	Patients, *n* (%)		
	PBO/SITA ($n = 192$)	CANA 100 mg ($n = 195$)	CANA 300 mg ($n = 197$)
Any AE	123 (64.1)	131 (67.2)	130 (66.0)
AEs leading to discontinuation	2 (1.0)	6 (3.1)	4 (2.0)
AEs related to study drug†	23 (12.0)	44 (22.6)	53 (26.9)
Serious AEs	11 (5.7)	11 (5.6)	5 (2.5)
Deaths‡	2 (1.0)	1 (0.5)	0
Selected AEs			
UTI	12 (6.3)	16 (8.2)	14 (7.1)
Genital mycotic infection			
Male§,|	0	5 (6.2)	8 (9.0)
Female¶,#	5 (4.8)	13 (11.4)	10 (9.3)
Osmotic diuresis-related AEs**	4 (2.1)	9 (4.6)	15 (7.6)
Volume depletion AEs††	1 (0.5)	3 (1.5)	4 (2.0)

PBO, placebo; SITA, sitagliptin; CANA, canagliflozin; AE, adverse event; UTI, urinary tract infection.
*All AEs are reported regardless of rescue medication.
†Possibly, probably, or very likely related to study drug, as assessed by investigators.
‡One death in the PBO/SITA group due to intracranial hemorrhage and brain hernia; one death in the PBO/SITA group due to pulmonary tuberculosis; one death in the CANA 100 mg group due to pneumonia, septic shock, acute renal failure, and ischemic hepatitis that were reported as serious AEs; none was considered to be drug-related by the reporting investigator.
§PBO/SITA, $n = 88$; CANA 100 mg, $n = 81$; CANA 300 mg, $n = 89$.
|Including balanitis, balanitis candida, balanoposthitis, genital candidiasis, and genital infection fungal.
¶PBO/SITA, $n = 104$; CANA 100 mg, $n = 114$; CANA 300 mg, $n = 108$.
#Including genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.
**Including dry mouth, micturition disorder, micturition urgency, nocturia, pollakiuria, polydipsia, polyuria, and thirst.
††Including dizziness postural, hypotension, orthostatic hypotension, and presyncope.

Table 4. Mean percentage changes in clinical laboratory parameters from baseline to Week 52 (safety analysis set).

	PBO/SITA	CANA 100 mg	CANA 300 mg
ALT, *n*	132	149	158
Mean baseline, U/L	26.4	27.7	28.5
Mean ± SD percentage change	0.9 ± 33.5	−6.9 ± 40.9	−10.9 ± 33.8
Bilirubin, *n*	132	149	158
Mean baseline, μmol/L	9.3	9.1	9.6
Mean ± SD percentage change	0.1 ± 33.2	11.2 ± 37.5	10.3 ± 39.0
BUN, *n*	132	150	159
Mean baseline, mmol/L	5.4	4.9	5.2
Mean ± SD percentage change	6.9 ± 20.2	21.0 ± 38.2	22.5 ± 30.0
Creatinine, *n*	132	150	159
Mean baseline, μmol/L	75.0	71.3	73.1
Mean ± SD percentage change	5.2 ± 11.4	1.8 ± 10.6	4.4 ± 11.4
eGFR, *n*	132	150	159
Mean baseline, mL/min/1.73 m^2	85.0	90.1	86.9
Mean ± SD percentage change	−4.7 ± 12.1	−1.6 ± 11.7	−3.6 ± 12.2
GGT, *n*	132	150	159
Mean baseline, U/L	41.0	38.6	43.5
Mean ± SD percentage change	−0.3 ± 27.2	−3.1 ± 97.9	−11.4 ± 36.0
Urate, *n*	132	150	159
Mean baseline, μmol/L	329.4	316.9	323.3
Mean ± SD percentage change	6.9 ± 20.7	−14.3 ± 17.1	−12.5 ± 17.2
Hemoglobin, *n*	133	148	157
Mean baseline, g/L	144.9	144.3	144.9
Mean ± SD percentage change	−1.0 ± 6.7	4.8 ± 5.1	4.7 ± 5.2

PBO, placebo; SITA, sitagliptin; CANA, canagliflozin; ALT, alanine aminotransferase; SD, standard deviation; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyl transferase.

eGFR were seen within the first 12 weeks of treatment in all groups, but levels were generally stable after Week 26 with canagliflozin 100 and 300 mg, whereas a further decrease was observed with placebo/sitagliptin (Figure 5). Increases in blood urea nitrogen and hemoglobin, and decreases in serum urate were also observed with canagliflozin compared with placebo/sitagliptin.

Discussion

This Phase 3 study evaluating canagliflozin monotherapy enrolled patients with T2DM inadequately controlled with diet and exercise; the population represented a broad range of age and racial/ethnic backgrounds and 54.5% of patients were obese based on National Institutes of Health criterion (body mass index ≥30 kg/m^2)[15]. In this study population, canagliflozin 100 and 300 mg provided improvements in glycemic control, and reductions in body weight and systolic BP from baseline over 52 weeks. Reductions in HbA_{1c}, FPG, body weight, and systolic BP at Week 52 were generally similar to those observed at the conclusion of the 26-week core period[8], suggesting a sustained response with canagliflozin treatment. The improvements in glycemic control, body weight, and systolic BP observed with canagliflozin occurred in a dose-dependent fashion throughout the entire 52-week study period.

The body weight reductions observed with canagliflozin treatment (i.e., in the range of 3.3–4.4%) are felt to be clinically important for patients with T2DM, especially in the context that some oral AHA agents tend to increase body weight or are weight neutral[1]. The magnitude of body weight reduction with canagliflozin at Week 52 was similar to that observed at Week 26, suggesting a durable weight loss response. The body weight reductions seen with canagliflozin in this study were comparable to those reported with weight maintenance therapeutics (orlistat [3.9%][16] and lorcaserin [4.5–5.0%][17]) in patients with T2DM over 1 year.

Levels of HDL-C and LDL-C increased incrementally with canagliflozin treatment; HDL-C increased to a greater extent, leading to decreases in the LDL-C/HDL-C ratio with canagliflozin 100 and 300 mg. Reductions in triglycerides were seen with both canagliflozin doses. The mechanism of the increase in LDL-C with canagliflozin treatment is unknown. The clinical implications of changes in lipid parameters with canagliflozin are being assessed as part of ongoing analyses of impact on cardiovascular risk across the Phase 3 program. A meta-analysis of cardiovascular events in the CANagliflozin cardioVascular Assessment Study (CANVAS) has shown no increase in cardiovascular risk with canagliflozin treatment[18].

Canagliflozin 100 and 300 mg were generally well tolerated over 52 weeks. The overall incidence of AEs during the entire 52-week study period was similar

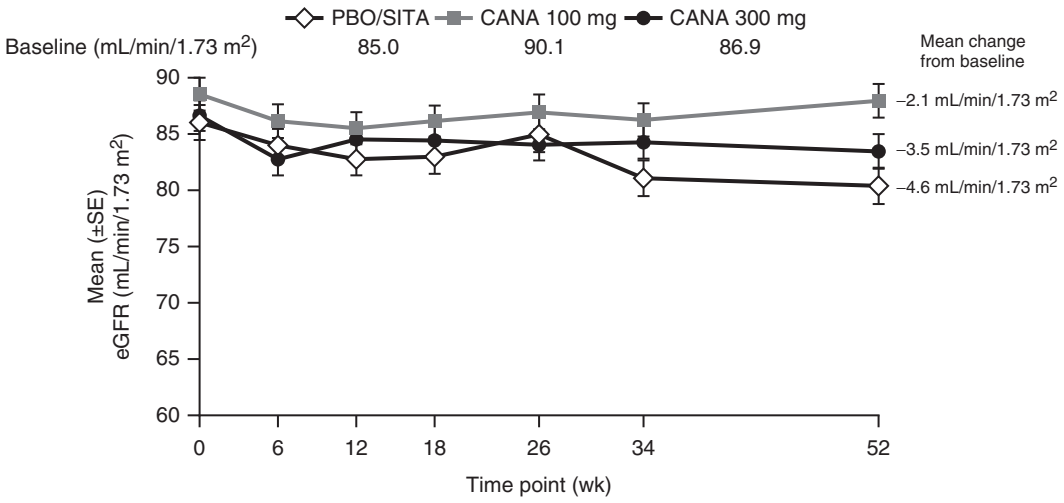

Figure 5. Mean eGFR over time.
PBO, placebo; SITA, sitagliptin; CANA, canagliflozin; eGFR, estimated glomerular filtration rate; SE, standard error.

across treatment groups; rates of AE-related discontinuations were slightly higher with canagliflozin relative to placebo/sitagliptin and rates of serious AEs were lower with canagliflozin 300 mg compared with canagliflozin 100 mg and placebo/sitagliptin. Compared with the entire 52-week study period, the proportion of patients reporting any AE was lower during the extension period in all treatment groups.

Higher rates of genital mycotic infections and AEs related to osmotic diuresis were observed with canagliflozin versus placebo/sitagliptin during the 52-week treatment period; these AEs led to few study discontinuations. UTI rates were generally similar across groups. The low incidence of hypoglycemia was anticipated because the observed RT_G with canagliflozin is above the usual threshold for hypoglycemia ($\leq$3.9 mmol/L)[6,12,13]. The pattern of decrease in eGFR with canagliflozin is consistent with a hemodynamic effect, and is not suggestive of renal injury.

The current study has several potential limitations. Since patients receiving placebo switched to sitagliptin 100 mg after 26 weeks, statistical comparisons at Week 52 cannot be made between treatment groups that had different exposure to antihyperglycemic therapy. However, comparisons to baseline with descriptive statistics are still useful to provide clinical evidence of the efficacy of canagliflozin as monotherapy over 52 weeks. Additional studies with active comparator arms will help to delineate the efficacy and safety of canagliflozin relative to other AHAs. Studies of even longer duration will be of interest to further evaluate the efficacy and safety of canagliflozin in different patient populations.

The efficacy and safety findings with canagliflozin in the current study are supported by previously reported Phase 3 studies of canagliflozin, including placebo-controlled studies in older patients[4] and patients with chronic kidney disease[9], as well as active-controlled studies in patients on background metformin[5,11] and metformin plus sulfonylurea[7]. Across these studies, canagliflozin treatment was associated with improvements in HbA_{1c}, FPG, body weight, and systolic BP and was generally well tolerated, with low incidences of serious AEs and a low risk of hypoglycemia; higher incidences of genital mycotic infections and AEs related to osmotic diuresis were observed across studies, which led to few study discontinuations. Treatment with other SGLT2 inhibitors as monotherapy[19,20] or combination therapy[21–24] has also been associated with improvements in glycemic control and similar safety and tolerability profiles.

Conclusions

Over 52 weeks, canagliflozin 100 and 300 mg monotherapy provided sustained improvements in glycemic control, body weight, and systolic BP. Both canagliflozin doses were generally well tolerated, with a safety and tolerability profile consistent with that previously reported for the 26-week core treatment period[8].

Transparency

Declaration of funding
Canagliflozin has been developed by Janssen Research & Development LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation. Janssen Research & Development LLC was involved in study design and conduct, and acquisition, analysis, and interpretation of the data. The manuscript was prepared by the authors, with editorial assistance funded by the sponsor. All authors had full access to the data, were responsible for the

integrity of the data and the accuracy of the data analysis, and reviewed, edited, and approved the manuscript for publication.

Declaration of financial/other relationships

K.S. and K.-A.K. have no proprietary interest in the tested product, do not have a significant equity interest in the sponsor of the covered study, and have not received significant payments of other sorts from the sponsor. W.T.C. has served as principal investigator on both basic research and clinical research grants received by his institutions from AstraZeneca, Johnson & Johnson, LLC, MannKind Corporation, GlaxoSmithKline, Sanofi, Proctor & Gamble, Nutrition 21, and Lexicon Pharmaceuticals; served as a consultant for Shire Development, LLC, Lexicon Pharmaceuticals, Halozyme Therapeutics, and Intarcia Therapeutics Inc.; and provided a lecture unrelated to product development to key opinion leaders as part of a Novo Nordisk symposium and an agreement made to his institution. E.J. has served on advisory panels for Novo Nordisk, Bristol-Myers Squibb, AstraZeneca, and Laboratorios FAES; served as a principal clinical investigator for Novo Nordisk, Eli Lilly and Company, Boehringer Ingelheim, Merck Sharpe & Dohme, and Janssen; and served on the speakers bureau of Eli Lilly and Company, Novo Nordisk, and Merck Sharpe & Dohme. M.A., R.E., C.T., W.C., and G.M. are full-time employees of Janssen Research & Development LLC, and M.A. owns stock in the company.

CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

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Appendix

Appendix Table 1. Baseline demographic and disease characteristics (extension mITT analysis set)*.

Characteristic	PBO/SITA ($n=119$)	CANA 100 mg ($n=166$)	CANA 300 mg ($n=166$)	Total ($N=451$)
Sex, *n* (%)				
Male	54 (45.4)	70 (42.2)	74 (44.6)	198 (43.9)
Female	65 (54.6)	96 (57.8)	92 (55.4)	253 (56.1)
Age, years	56.1 ± 10.6	55.2 ± 10.3	55.4 ± 10.5	55.5 ± 10.4
Race, *n* (%)				
White	83 (69.7)	103 (62.0)	115 (69.3)	301 (66.7)
Black or African American	5 (4.2)	17 (10.2)	9 (5.4)	31 (6.9)
Asian	19 (16.0)	23 (13.9)	26 (15.7)	68 (15.1)
Other†	12 (10.1)	23 (13.9)	16 (9.6)	51 (11.3)
HbA_{1c}, %	7.7 ± 0.8	8.0 ± 0.9	7.9 ± 0.9	7.9 ± 0.9
FPG, mmol/L (mg/dL)	8.5 ± 1.7 (153.2 ± 30.3)	9.4 ± 2.3 (169.4 ± 41.8)	9.4 ± 2.3 (169.4 ± 41.1)	9.2 ± 2.2 (165.8 ± 39.5)
Body weight, kg	88.1 ± 18.3	86.4 ± 21.3	87.2 ± 20.8	87.1 ± 20.3
BMI, kg/m^2	32.2 ± 6.1	31.4 ± 6.3	31.8 ± 6.1	31.8 ± 6.2
eGFR, $mL/min/1.73\,m^2$	87.1 ± 23.7	89.6 ± 20.2	87.0 ± 18.9	88.0 ± 20.7
Duration of diabetes, years	3.4 ± 3.9	4.3 ± 4.1	3.8 ± 4.1	3.9 ± 4.1
Patients on AHA at screening, *n* (%)	41 (34.5)	80 (48.2)	80 (48.2)	201 (44.6)

mITT, modified intent-to-treat; PBO, placebo; SITA, sitagliptin; CANA, canagliflozin; HbA_{1c}, hemoglobin A_{1c}; FPG, fasting plasma glucose; BMI, body mass index; AHA, antihyperglycemic agent; SD, standard deviation.
*Data are mean ± SD unless otherwise indicated.
†Includes American Indian or Alaska Native and other.

Appendix Table 2. Changes from baseline in efficacy endpoints at Week 52 (mITT*, LOCF).

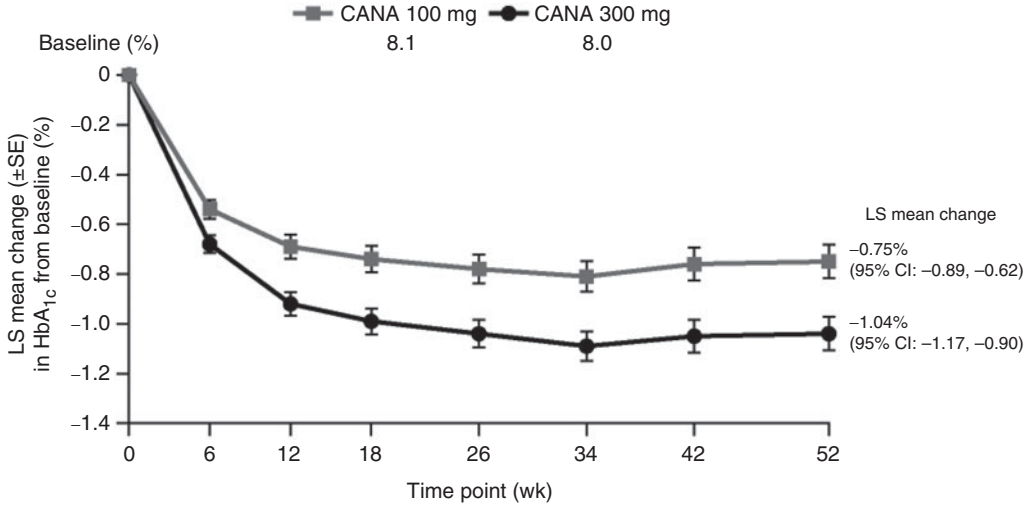
	CANA 100 mg ($n=195$)	CANA 300 mg ($n=197$)
HbA_{1c}, %		
LS mean ± SE change	−0.8 ± 0.1	−1.0 ± 0.1
Patients achieving HbA_{1c} <7.0%		
n (%)	93 (48.7)	117 (60.3)
FPG, mmol/L (mg/dL)		
LS mean ± SE change	−1.5 ± 0.1 (−26.3 ± 2.3)	−2.1 ± 0.1 (−37.0 ± 2.3)
Body weight, kg		
LS mean ± SE percentage change	−3.1 ± 0.3	−4.1 ± 0.3
Systolic BP, mmHg		
LS mean ± SE change	−2.4 ± 0.8	−3.8 ± 0.7
Diastolic BP, mmHg		
LS mean ± SE change	−0.6 ± 0.5	−0.9 ± 0.5
Triglycerides, mmol/L		
LS mean ± SE percentage change	0.3 ± 3.0	−3.0 ± 2.9
LDL-C, mmol/L		
LS mean ± SE percentage change	4.9 ± 1.9	10.9 ± 1.9
HDL-C, mmol/L		
LS mean ± SE percentage change	11.2 ± 1.4	13.8 ± 1.4
LDL-C/HDL-C, mol/mol		
LS mean ± SE percentage change	−4.4 ± 2.0	0.2 ± 2.0
Non–HDL-C, mmol/L		
LS mean ± SE percentage change	1.2 ± 1.6	5.4 ± 1.6

mITT, modified intent-to-treat; LOCF, last observation carried forward; CANA, canagliflozin; HbA_{1c}, hemoglobin A_{1c}; LS, least squares; SE, standard error; FPG, fasting plasma glucose; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
*mITT analysis set includes all randomized patients who took ≥1 dose of study medication.

Appendix Table 3. Summary of overall safety and selected adverse events (Weeks 26-52; extension period)*.

Patients, *n* (%)	PBO/SITA (*n* = 155)	CANA 100 mg (*n* = 170)	CANA 300 mg (*n* = 170)
Any AE	68 (43.9)	68 (40.0)	62 (36.5)
AEs leading to discontinuation	1 (0.6)	0	0
AEs related to study drug†	9 (5.8)	15 (8.8)	9 (5.3)
Serious AEs	7 (4.5)	3 (1.8)	3 (1.8)
Deaths	1 (0.6)	0	0
Selected AEs			
UTI	5 (3.2)	5 (2.9)	5 (2.9)
Genital mycotic infection			
Male‡,§	0	3 (4.2)	5 (6.5)
Female|,¶	1 (1.2)	3 (3.0)	3 (3.2)
Osmotic diuresis-related AEs#	3 (1.9)	0	0
Volume depletion AEs**	0	1 (0.6)	0

PBO, placebo; SITA, sitagliptin; CANA, canagliflozin; AE, adverse event; UTI, urinary tract infection.
*All AEs are reported regardless of rescue medication.
†Possibly, probably, or very likely related to study drug, as assessed by investigators.
‡PBO/SITA, *n* = 70; CANA 100 mg, *n* = 71; CANA 300 mg, *n* = 77.
§Including balanitis, balanitis candida, balanoposthitis, and genital candidiasis.
|PBO/SITA, *n* = 85; CANA 100 mg, *n* = 99; CANA 300 mg, *n* = 93.
¶Including genital infection fungal, vaginal infection, vulvovaginal candidiasis, and vulvovaginal mycotic infection.
#Including pollakiuria.
**Including dizziness postural.



Appendix Figure 1. Change in HbA_{1c} over time (mITT, LOCF). HbA_{1c}, hemoglobin A_{1c}; mITT, modified intent-to-treat; LOCF, last observation carried forward; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.