Research Paper

Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with type 2 diabetes mellitus

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HIGHLIGHTS

- Canagliflozin BID was evaluated in patients with type 2 diabetes on metformin.
- Canagliflozin 50 and 150 mg BID significantly reduced HbA1c vs placebo.
- Both doses also lowered fasting plasma glucose, body weight, and blood pressure.
- Efficacy findings were consistent with studies of canagliflozin 100 and 300 mg QD.
- Canagliflozin BID was generally well tolerated, similar to canagliflozin QD.

ABSTRACT

Aim: To evaluate the efficacy/safety of canagliflozin twice daily (BID) compared with placebo in patients with type 2 diabetes mellitus (T2DM) on metformin.

Methods: In this 18-week, randomized, double-blind, placebo-controlled study, patients (N = 279) at 60 centers in 7 countries received canagliflozin 50 or 150 mg or placebo BID. The pre-specified primary endpoint was change from baseline in HbA1c at Week 18. Pre-specified secondary endpoints included proportion of patients reaching HbA1c <7.0%, change in fasting plasma glucose (FPG), and percent change in body weight; changes in systolic blood pressure (BP) and fasting plasma lipids were also evaluated. Adverse events (AEs) were recorded throughout the study.

Results: From a mean baseline HbA1c of 7.6% (60 mmol/mol), canagliflozin 50 and 150 mg BID significantly reduced HbA1c compared with placebo at Week 18 (−0.45%, −0.61%, −0.01% [−5, −7, −0.1 mmol/mol], respectively; P < 0.001). More patients achieved HbA1c <7.0% with canagliflozin than placebo (P < 0.05). Relative to placebo, both canagliflozin doses significantly lowered FPG and body weight (P < 0.001), and reduced systolic BP. Overall AE incidence was 35.5%, 40.9%, and 36.6% with canagliflozin 50 and 150 mg BID and placebo, respectively. Canagliflozin was associated with increased incidences of urinary tract infections, female genital mycotic infections, and osmotic diuresis-related AEs; these led to few discontinuations. The incidence of documented hypoglycemia was low across groups.

Conclusions: Canagliflozin 50 and 150 mg BID provided significant glycemic efficacy and body weight reduction, and were generally well tolerated in patients with T2DM on background metformin.

ClinicalTrials.gov Identifier: NCT01340664

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease that often requires combination therapy with antihyperglycemic agents (AHAs) as the disease progresses [1–3]. Metformin is the standard first-line pharmacologic therapy for patients who do not achieve and maintain adequate glycemic control with diet and exercise alone [2]. Metformin is a biguanide that reduces hepatic glucose production and improves peripheral insulin sensitivity; immediate-release (IR) formulations of metformin are typically administered twice daily (BID) [4]. For patients on metformin monotherapy who require better glycemic control, several classes of AHAs may be added as dual therapy; however, some of these agents are associated with adverse effects such as weight gain or
hypoglycemia [2]. Of note, the HbA1c-lowering efficacy of oral AHAs has been shown to be impacted by patients’ baseline HbA1c values, with greater HbA1c lowering observed in patients with higher baseline HbA1c [5].

Canaglifl ozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed for the treatment of adult patients with T2DM [6–15]. Canaglifl ozin reduces plasma glucose in individuals with hyperglycemia by inhibiting renal glucose reabsorption and increasing urinary glucose excretion, and is associated with a mild osmotic diuresis. In Phase 3 studies in patients with T2DM, once-daily (QD) doses of canaglifl ozin 100 and 300 mg provided glyce-

mic improvements and reductions in body weight and systolic blood pressure (BP), and were generally well tolerated as mono-

therapy and in combination with a variety of other AHAs [7–13,15]. This 18-week, Phase 2 study evaluated the efficacy and safety of canaglifl ozin BID dosing, compared with placebo, as add-on therapy in patients with T2DM inadequately controlled with metformin monotherapy, to support the development of a fixed-dose combination of canaglifl ozin and metformin IR.

Patients, materials, and methods

Patients and study design

This was a randomized, double-blind, placebo-controlled, Phase 2 study conducted at 60 centers in 7 countries (ClinicalTrials. gov Identifier: NCT01340664). The study consisted of a 2-week, single-blind, placebo run-in period; an 18-week, double-blind, treatment period; and a 30-day, post-treatment follow-up period. Eligible patients were men and women with T2DM aged 18–80 years who had inadequate glycemic control (HbA1c ≥7.0% [53 mmol/mol] and ≤10.5% [91 mmol/mol]) on metformin monotherapy at protocol-specified doses (≥2000 mg/day, or ≥1500 mg/day if unable to tolerate a higher dose) for ≥8 weeks prior to screening. Patients also had fasting plasma glucose (FPG) <15 mmol/L at Week −2, and fasting fingerstick glucose ≥6.1 and <7.0 mmol/L on Day 1. Patients were excluded from the study if they had repeated FPG and/or fasting self-monitored blood glucose ≥15.0 mmol/L during the pretreatment phase; history of type 1 diabetes or diabetic ketoacidosis; history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident) within 3 months before screening; uncontrolled hypertension; treatment with a peroxisome proliferator-activated receptor γ agonist, insulin, another SGLT2 inhibitor, or any other AHA (except metformin monotherapy) within 12 weeks before screening; or estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m² (or <60 mL/min/1.73 m² if based upon restriction in local metformin label) or serum creatinine ≥124 μmol/L (men) or ≥115 μmol/L (women).

Eligible patients first entered the single-blind, placebo run-in period, during which they received placebo capsules matching the double-blind study drug. Patients were instructed to take placebo BID, with 1 capsule given with the morning meal and 1 given with the evening meal, along with metformin at each meal. Patients took the last dose of single-blind placebo the day before the baseline (Day 1) visit. Patients who met all enrollment criteria were then randomized to receive canaglifl ozin 50 or 150 mg or placebo BID in a 1:1:1 ratio. Randomization was balanced using permuted blocks and was stratified according to whether the patient’s HbA1c value at Week −2 was <8.0% or ≥8.0%. During the double-blind period, patients took their first dose of canaglifl ozin 50 or 150 mg or placebo on Day 1 at the study center. The last dose of the double-blind period was taken with the evening meal on the day prior to the Week 18 visit. After randomization, HbA1c and FPG values were masked to study centers; FPG values were unmasked if they met specific glycemic withdrawal criteria (≥15.0 mmol/L after Day 1 through Week 6, >13.3 mmol/L after Week 6 through Week 12, and >11.1 mmol/L after Week 12 through Week 18).

This study was conducted in accordance with ethical principles that comply with the Declaration of Helsinki, and are consistent with Good Clinical Practices and applicable regulatory requirements. The study protocol and amendments were approved by institutional review boards at participating institutions. All participants provided written informed consent prior to participation.

Endpoints and assessments

The pre-specified primary endpoint was change from baseline in HbA1c at Week 18. Pre-specified secondary endpoints at Week 18 included change in FPG, percent change in body weight, and the proportion of patients achieving HbA1c <7.0% (53 mmol/mol). It was noted that ~20% of patients who were eligible for the trial

Figure 1. Study flow diagram. PBO, placebo; CANA, canaglifl ozin; BID, twice daily; AE, adverse event; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat.
(based on HbA1c ≥7.0% at Week −2) had a baseline HbA1c <7.0%; therefore, a pre-specified sensitivity analysis was performed to assess change in HbA1c in patients with baseline HbA1c ≥7.0% (53 mmol/mol). Changes in systolic and diastolic BP and percent changes in 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) were also assessed.

Safety was evaluated based on adverse event (AE) reports, safety laboratory tests, vital sign measurements, 12-lead electrocardiograms, and physical examinations. AEs pre-specified for additional data collection included urinary tract infections (UTIs) and genital mycotic infections. Assessment of documented hypoglycemia episodes included biochemically documented episodes (concurrent fingerstick or plasma glucose <3.9 mmol/L with or without symptoms) and severe episodes (i.e., those requiring the assistance of another individual or resulting in seizure or loss of consciousness).

Statistical analyses

Sample size determination was based on the primary objective of demonstrating the superiority of canagliflozin 150 mg BID vs placebo in lowering HbA1c at Week 18. Using a 2-sample, 2-sided t-test with a type I error rate of 0.05, and assuming a group difference of 0.5% and a common standard deviation (SD) of 1.0%, 85 patients per group were estimated to be required to achieve 90% power. Sample size was expanded to 90 patients per group to account for potential patients with missing HbA1c values at study endpoint.

Efficacy analyses were performed using the modified intent-to-treat (mITT) population, consisting of all randomized patients who received ≥1 dose of study drug. The last observation carried forward (LOCF) approach was used to impute missing efficacy data. Safety analyses were performed on the same population analyzed according to the predominant treatment received; in this study, the safety analysis set was identical to the mITT analysis set.

Primary and continuous secondary efficacy endpoints were assessed using an analysis of covariance (ANCOVA) model with treatment and stratification factors (i.e., whether or not HbA1c at screening was ≥8.0%) as fixed effects and the corresponding baseline value as a covariate. Least squares (LS) mean differences between treatment groups and the associated 2-sided 95% confidence intervals (CIs) were estimated based on this model. A mixed model for repeated measures (MMRM), based on restricted maximum likelihood, was also pre-specified as a sensitivity analysis for the primary efficacy analysis, in order to assess the data longitudinally. The categorical secondary efficacy endpoint (i.e., proportion of patients reaching HbA1c <7.0% [53 mmol/mol]) was analyzed using a logistic regression model including terms for treatment and stratification factor, and adjusting for baseline HbA1c as a covariate. A pre-specified, hierarchical testing sequence was implemented to strongly control overall type I error due to multiplicity. All statistical tests were interpreted at a 2-sided significance level of 0.05, and P values are reported for pre-specified comparisons only.

Results

Patient disposition and baseline characteristics

A total of 279 patients were randomized, all of whom received ≥1 dose of study drug and were included in the mITT analysis set; of these, 251 (90%) completed 18 weeks of treatment (Figure 1). The rate of study discontinuation before Week 18 was 8.6%, 14.0%, and 7.5% with canagliflozin 50 and 150 mg BID and placebo, respectively. The 3 most common reasons for discontinuation were AEs (2.9%), withdrawal of consent (2.2%), and other (1.8%). Baseline demographic and disease characteristics were generally similar across groups (Table 1). Notably, 22.2% of patients had HbA1c <7.0% (53 mmol/mol) at baseline, despite the inclusion criteria of HbA1c ≥7.0% (53 mmol/mol) and ≤10.5% (91 mmol/mol).

| Characteristic                        | PRO (n = 93) | CANA 50 mg BID (n = 93) | CANA 150 mg BID (n = 93) | Total (N = 279) |
|---------------------------------------|-------------|-------------------------|-------------------------|----------------|
| **Sex, n (%)**                        |             |                         |                         |                |
| Male                                  | 46 (49.5)   | 40 (43.0)               | 44 (47.3)               | 130 (46.6)     |
| Female                                | 47 (50.5)   | 53 (57.0)               | 49 (52.7)               | 149 (53.4)     |
| **Age, y**                            | 57.0 (9.3)  | 58.6 (8.9)              | 56.7 (10.3)             | 57.4 (9.5)     |
| **Race, n (%)**                       |             |                         |                         |                |
| White                                 | 73 (78.5)   | 75 (80.6)               | 83 (89.2)               | 231 (82.8)     |
| Black or African American             | 4 (4.3)     | 5 (5.4)                 | 1 (1.1)                 | 10 (3.6)       |
| Asian                                 | 9 (9.7)     | 3 (3.2)                 | 6 (6.5)                 | 18 (6.5)       |
| Other                                 | 7 (7.5)     | 10 (10.8)               | 3 (3.2)                 | 20 (7.2)       |
| **HbA1c, % (mmol/mol)**               |             |                         |                         |                |
| <7.0%                                 | 20 (21.5)   | 21 (22.6)               | 21 (22.6)               | 62 (22.2)      |
| ≥7.0%                                 | 73 (78.5)   | 72 (77.4)               | 72 (77.4)               | 217 (77.8)     |
| **FPG, mmol/L**                       | 9.0 ± 1.9   | 9.0 ± 2.0               | 9.1 ± 1.9               | 9.0 ± 1.9      |
| BMI, kg/m²                             | 32.3 ± 5.7  | 33.0 ± 7.0              | 32.3 ± 6.8              | 32.5 ± 6.5     |
| **Duration of diabetes, y**           | 7.0 ± 6.4   | 6.7 ± 4.9               | 7.3 ± 6.0               | 7.0 ± 5.8      |
| **eGFR, ml/min/1.73 m²**              | 84.8 ± 16.5 | 86.9 ± 18.0             | 85.9 ± 15.3             | 85.9 ± 16.6    |
| **Metformin treatment at baseline**   |             |                         |                         |                |
| Category, n (%)                       |             |                         |                         |                |
| Extended release                      | 24 (26)     | 20 (22)                 | 15 (16)                 | 59 (21)        |
| Immediate release                     | 69 (74)     | 73 (78)                 | 78 (84)                 | 220 (79)       |
| Mean daily dose, mg/d                 | 2131 ± 343.1| 2137 ± 304.1            | 2128 ± 341.6            | 2132 ± 328.9   |

PRO, placebo; CANA, canagliflozin; BID, twice daily; FPG, fasting plasma glucose; BMI, body mass index; eGFR, estimated glomerular filtration rate; 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, Native Hawaiian or other Pacific Islander, multiple, and other.

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Efficacy

Glycemic parameters

From a mean baseline HbA1c of 7.6% (60 mmol/mol), canagliflozin 50 and 150 mg BID significantly reduced HbA1c from baseline compared with placebo at Week 18, with differences in LS mean changes of −0.44% (−5 mmol/mol) and −0.60% (−7 mmol/mol), respectively (P < 0.001 for both; Figure 2A and B). The pre-specified MMRM analysis showed similar changes in HbA1c. Significantly higher proportions of patients achieved HbA1c <7.0% (53 mmol/mol) at Week 18 with canagliflozin 50 and 150 mg BID compared with placebo (47.8%, 57.1%, and 31.5%, respectively; P < 0.05 and P < 0.001 vs placebo, respectively). In the pre-specified sensitivity analysis in patients with baseline HbA1c ≥7.0%, canagliflozin 50 and 150 mg BID reduced HbA1c compared with placebo (differences in LS mean changes of −0.5% [−6 mmol/mol] and −0.7% [−8 mmol/mol]; Figure 2C).

Both canagliflozin doses significantly reduced FPG compared with placebo (differences in LS mean changes of −1.3 mmol/L for both; P < 0.001; Figure 2D). The median reductions in FPG were −0.7 and −1.2 mmol/L with canagliflozin 50 and 150 mg BID, while a median increase in FPG was seen with placebo (0.3 mmol/L).

Body weight, BP, and lipids

Relative to placebo, canagliflozin 50 and 150 mg BID significantly reduced body weight at Week 18 (differences in LS mean changes of −2.2% and −2.6%, respectively; P < 0.001; Figure 2E). Changes from baseline in BP and fasting plasma lipids at Week 18 are presented in Table 2. Canagliflozin 50 and 150 mg BID lowered systolic BP compared with placebo at Week 18 (differences in LS mean changes of −5.4 and −5.7 mmHg, respectively). Diastolic BP was also reduced with both canagliflozin doses vs placebo, with minimal changes in pulse rate observed across groups (mean changes of 0.9, 1.4, and 0.0 beats per minute with canagliflozin 50 and 150 mg BID and placebo, respectively). Canagliflozin 150 mg BID was associated with an LS mean percent increase in triglycerides compared with canagliflozin 50 mg BID and placebo. A median percent decrease in triglycerides was seen with canagliflozin 150 mg BID, suggesting that the change in LS means may be

Figure 2. Changes in efficacy parameters (LOCF). (A) Change in HbA1c over time, (B) mean HbA1c over time, (C) change in HbA1c at Week 18 in patients with baseline HbA1c ≥7.0%, (D) change in FPG over time, and (E) percent change in body weight over time. LOCF, last observation carried forward; FPG, fasting plasma glucose; PBO, placebo; CANA, canagliflozin; BID, twice daily; LS, least squares; SE, standard error; CI, confidence interval. (To convert values for HbA1c in % into mmol/mol, subtract 2.15 and multiply by 10.929, or use the conversion calculator at www.HbA1c.nu/eng/)
The incidence of serious AEs was low across groups. The incidence of AEs leading to discontinuation was (0%, 3.2%, and 1.1% with canagliozin 50 mg BID and placebo, respectively). The incidence of AEs associated with genital mycotic infections in females was 11.3%, 2.0%, and 4.3%, respectively; most events with canagliozin were mild or moderate in intensity and none led to discontinuation. Two males reported genital mycotic infections: 1 (2.5%) in the canagliozin 50 mg BID group and 1 (2.2%) in the placebo group. The incidence of AEs related to osmotic diuresis (e.g., pollakiuria [increased urine frequency]) was 7.5% with canagliozin 150 mg BID, with none reported in the other groups; all events were mild and none led to discontinuation. No AEs related to volume depletion (e.g., postural dizziness, orthostatic hypotension) were reported.

In conclusion, canagliozin at a dose of either 50 or 150 mg BID, was well tolerated in patients with hyperlipidemia, and was associated with improvements in lipid parameters and blood pressure, compared with placebo. Canagliozin at 50 mg BID was associated with a higher incidence of genital mycotic infections in females than canagliozin 150 mg BID and placebo (11.3%, 2.0%, and 4.3%, respectively); most events with canagliozin were mild or moderate in intensity and none led to discontinuation. Two males reported genital mycotic infections: 1 (2.5%) in the canagliozin 50 mg BID group and 1 (2.2%) in the placebo group. The incidence of AEs related to osmotic diuresis (e.g., pollakiuria [increased urine frequency]) was 7.5% with canagliozin 150 mg BID, with none reported in the other groups; all events were mild and none led to discontinuation. No AEs related to volume depletion (e.g., postural dizziness, orthostatic hypotension) were reported.

The incidence of documented hypoglycemia was low and similar across groups (4.3%, 3.2%, and 3.2% with canagliozin 50 and 150 mg BID and placebo, respectively). No severe hypoglycemia events were reported.

Generally, only small differences were observed with canagliozin relative to placebo in mean percent changes from baseline in laboratory parameters over 18 weeks (Supplementary Table 1). Reductions in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed with canagliozin 150 mg BID, whereas increases were seen with canagliozin 50 mg BID and placebo. Mean percent increases in serum bilirubin and blood urea nitrogen were observed across groups, with relatively higher increases in canagliozin-treated patients compared with those receiving placebo. Small decreases in eGFR were observed across
groups, with commensurate changes seen in serum creatinine. Decreases in serum urate were observed with both canagliflorin doses, whereas minimal change was seen with placebo. Increases in hemoglobin were observed with both canagliflorin doses vs placebo. Median percent changes generally showed similar trends (Supplementary Table 1); differences between mean and median changes in some parameters (i.e., ALT, AST, and bilirubin) may be related to outliers.

**Discussion**

This Phase 2 study evaluated the efficacy and safety of canagliflorin BID dosing in patients with T2DM inadequately controlled on maximally effective doses of metformin monotherapy, in support of the development of a fixed-dose combination of canagliflorin and metformin IR. Canagliflorin doses of 50 and 150 mg BID were selected to provide the same total daily doses (i.e., 100 and 300 mg QD) as those approved for the treatment of patients with T2DM [6].

Canagliflorin 50 and 150 mg BID provided significant improvements in glycemic control and reductions in body weight compared with placebo. In the overall patient population with a lower than expected HbA1c at baseline (mean HbA1c of 7.6% [60 mmol/mol]) resulting from the high proportion of patients with HbA1c <7.0%, both canagliflorin doses significantly reduced HbA1c and a higher proportion of canagliflorin-treated patients achieved HbA1c <7.0% (53 mmol/mol) compared with placebo at Week 18. Reductions in HbA1c from baseline were also seen with canagliflorin vs placebo in a pre-specified sensitivity analysis in patients with baseline HbA1c values ≥7.0% (53 mmol/mol). Both canagliflorin doses were associated with reductions in FPG, body weight, and systolic and diastolic BP. Canagliflorin 150 mg BID was associated with a mean increase in triglycerides; however, a median percent decrease in triglycerides was seen with canagliflorin 150 mg BID, suggesting that the change in LS means may be influenced by outliers. Canagliflorin 150 mg BID was also associated with an increase in HDL-C, compared with canagliflorin 50 mg BID and placebo. No notable differences were observed across treatment groups in LDL-C, whereas dose-related increases in LDL-C have been observed in other Phase 3 studies of canagliflorin [7,9–13,15]. Differences in lipid outcomes relative to other canagliflorin studies may be derived from the small population in the present study.

Overall, efficacy findings with canagliflorin 50 and 150 mg BID in the present study were generally consistent with those observed in Phase 3 studies of canagliflorin 100 and 300 mg QD [7–13,15], with the canagliflorin 150 mg BID dose providing an incremental benefit in HbA1c and body weight reduction relative to the canagliflorin 50 mg BID dose. The lack of a dose-response in FPG changes may reflect an impact of outlying data, as the median reduction in FPG was greater with canagliflorin 150 mg BID than with canagliflorin 50 mg BID (−1.2 vs −0.7 mmol/L). The absence of substantive differences between BID and QD dosing of canagliflorin, at the same total daily doses, was expected based on previous Phase 1 studies that included both BID and QD dosing [16,17].

Of note, the HbA1c reduction reported for the overall population in the present study was lower than that reported in prior Phase 3 studies [7–13,15]. In a meta-analysis of the relationship between baseline glycemia and HbA1c reduction in published studies of oral AHAAs, baseline HbA1c was found to impact HbA1c reductions following AHA treatment, with a greater apparent treatment effect observed with higher baseline HbA1c [5]. Thus, the lesser HbA1c reduction observed in the present 18-week study relative to prior 26-week Phase 3 studies is likely related, in part, to the lower baseline HbA1c in the overall study population. Consistent with this, numerically greater HbA1c reductions were observed with both canagliflorin doses vs placebo when assessed in a subset of patients with baseline HbA1c ≥7.0% (53 mmol/mol). The difference in glycemic efficacy may also be related to the shorter duration of this study (18 weeks) compared with previous Phase 3 studies (26–52 weeks). Notably, in the overall study population, significantly higher proportions of canagliflorin-treated patients achieved HbA1c <7.0% (53 mmol/mol) compared with patients treated with placebo, demonstrating meaningful glycemic efficacy with canagliflorin treatment in this population.

Canagliflorin 50 and 150 mg BID were generally well tolerated, with 1 or both doses associated with increased incidences of UTIs, female genital mycotic infections, and AEs related to osmotic diuresis. These AEs were generally mild to moderate in severity, and infrequently led to study discontinuation. Canagliflorin treatment

### Table 3

**Summary of overall safety and selected AEs over 18 weeks**

| Patients, n (%) | PBO (n = 93) | CANA 50 mg BID (n = 93) | CANA 150 mg BID (n = 93) |
|----------------|-------------|------------------------|------------------------|
| Any AE         | 34 (36.6)   | 33 (35.5)              | 38 (40.9)              |
| AEs leading to discontinuation | 0          | 1 (1.1)*               | 7 (7.5)**              |
| AEs related to study drug†    | 2 (2.2)     | 11 (11.8)              | 15 (16.1)              |
| Serious AEs     | 1 (1.1)     | 0                      | 3 (3.2)                |
| Deaths          | 0           | 0                      | 1 (1.1)                |
| Selected AEs    |             |                        |                        |
| UTI            | 2 (2.2)     | 4 (4.3)                | 4 (4.3)                |
| Genital mycotic infection |             |                        |                        |
| Male†          | 1 (2.2)     | 1 (2.5)                | 0                      |
| Female†        | 2 (4.3)     | 6 (11.3)               | 1 (2.0)                |
| Osmotic diuresis–related AEs‡ | 0         | 0                      | 7 (7.5)                |
| Volume depletion AEs | 0          | 0                      | 0                      |

**AE, adverse event; PBO, placebo; CANA, canagliflorin; BID, twice daily; UTI, urinary tract infection.**

*Specific term of headache.
†Specific terms included colon cancer (n = 1), dermatitis allergic (n = 1), glomerular filtration rate decreased (n = 1), nephrolithiasis (n = 1), palpitations (n = 1), pyelonephritis (n = 1), and vulvovaginal pruritus (n = 2). One patient experienced 2 AEs (pyelonephritis and nephrolithiasis) that were reported to lead to discontinuation.
‡Possibly, probably, or very likely related to study drug, as assessed by investigators.
§PBO, n = 46; CANA 50 mg BID, n = 40; CANA 150 mg BID, n = 44.
¶Including balanitis candida and genital infection fungal.
∥PBO, n = 47; CANA 50 mg BID, n = 53; CANA 150 mg BID, n = 49.
∥Including vaginal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.
∥Including dry mouth, micturition urgency, pollakuria, and thirst.
was not associated with an increased incidence of hypoglycemia compared with placebo. The safety profile observed for canagliflozin BID dosing in the current study is generally similar to that seen with prior Phase 3 canagliflozin studies [7–13,15].

Despite several potential limitations of the current study, including the relatively small number of patients enrolled in the study, a generally lower baseline HbA1c in this patient population compared with those in Phase 3 studies, and a low representation of some races/ethnicities in the patient population (as a function of study centers), findings were generally consistent with Phase 3 studies of canagliflozin. Longer-term studies of canagliflozin 50 and 150 mg BID in larger and broader patient populations may be helpful for further elucidation of the efficacy and safety of canagliflozin BID dosing regimens. Furthermore, it would be beneficial to include canagliflozin 100 and 300 mg QD arms in future studies to allow for direct comparisons of BID and QD dosing.

In conclusion, canagliflozin BID dosing, at total daily doses of 100 and 300 mg, provided significant glycemic efficacy. Reductions in HbA1c were modest, consistent with the lower baseline HbA1c in the present study compared with previous Phase 3 studies of canagliflozin. Reductions in body weight and systolic BP were also observed, and canagliflozin BID was generally well tolerated as add-on to metformin monotherapy. Overall, findings from this study indicate a favorable efficacy and safety/tolerability profile of canagliflozin in combination with metformin.

Acknowledgments

This study was supported by Janssen Research & Development, LLC. The authors thank all investigators, study teams, and patients for participating in this study. Editorial support was provided by Janetrick Chebukati, PhD, of MedErgy, and was funded by Janssen Global Services, LLC. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation.

Conflict of interest: RQ, GC, and GM are full-time employees of Janssen Research & Development, LLC.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcte.2014.04.001.

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