original article

Diabetes, Obesity and Metabolism 14: 539–545, 2012.

ORIGINAL ARTICLE

Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin

D. Devineni[1], L. Morrow[2], M. Hompesch[2], D. Skee[1], A. Vandebosch[3], J. Murphy[1], K. Ways[1] & S. Schwartz[4]

[1]*Janssen Research & Development, LLC, Raritan, NJ, USA*
[2]*Profil Institute for Clinical Research, Chula Vista, CA, USA*
[3]*Janssen Research & Development, Division of Janssen Pharmaceutica NV, Beerse, Belgium*
[4]*DGD Research, San Antonio, TX, USA*

Aim: Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that is being investigated for the treatment of type 2 diabetes mellitus (T2DM).

Methods: This was a randomized, double-blind, placebo-controlled, parallel-group, 28-day study conducted at two sites, in 29 subjects with T2DM not optimally controlled on insulin and up to one oral antihyperglycaemic agent. Subjects were treated with canagliflozin 100 mg QD or 300 mg twice daily (BID) or placebo. Safety, tolerability, pharmacokinetic characteristics and pharmacodynamic effects of canagliflozin were examined. Glucose malabsorption following a 75-g oral glucose challenge was also examined.

Results: Canagliflozin pharmacokinetics were dose-dependent, and the elimination half-life ranged from 12 to 15 h. After 28 days, the renal threshold for glucose excretion was reduced; urinary glucose excretion was increased; and A1C, fasting plasma glucose and body weight decreased in subjects administered canagliflozin (A1C reductions: 0.19% with placebo, 0.73% with 100 mg QD, 0.92% with 300 mg BID; body weight changes: 0.03 kg increase with placebo, 0.73 kg reduction with 100 mg QD, 1.19 kg reduction with 300 mg BID). Glucose malabsorption was not observed with canagliflozin treatment. There were no deaths, serious adverse events or severe hypoglycaemic episodes. The incidence of adverse events was similar across groups. There were no clinically meaningful changes in routine laboratory safety tests, vital signs or electrocardiograms.

Conclusion: In subjects receiving insulin and oral antihyperglycaemic therapy, canagliflozin was well tolerated without evidence for glucose malabsorption, had pharmacokinetic characteristics consistent with once-daily dosing, and improved glycaemic control.

Keywords: clinical trial, insulin, pharmacodynamics, pharmacokinetics, SGLT2 inhibitor, type 2 diabetes

Date submitted 26 July 2011; date of first decision 6 September 2011; date of final acceptance 23 December 2011

Introduction

Canagliflozin is a potent and selective inhibitor of the sodium-glucose co-transporter 2 (SGLT2) currently being investigated for the treatment of patients with type 2 diabetes mellitus (T2DM). In preclinical and phase 1 clinical trials, canagliflozin blocks renal glucose reabsorption, which causes a decrease in the renal threshold for glucose (RT_G), an increase in urinary glucose excretion (UGE) and a reduction in blood glucose levels [1–4]. This study was conducted to evaluate the safety, tolerability, pharmacokinetic properties and pharmacodynamic effects of canagliflozin over 28 days in subjects with T2DM with inadequate glycaemic control on insulin alone or in combination with an oral antihyperglycaemic agent (AHA).

Correspondence to: Damayanthi Devineni, PhD, Janssen Research & Development, LLC, 920 Route 202, Raritan, NJ 08869, USA.
E-mail: DDevinen@its.jnj.com

Materials and Methods

Design

This was a randomized, double-blind, placebo-controlled, two-cohort, parallel-group, 28-day phase 1b study conducted at two centres in the USA. The study was conducted in accordance with current International Conference on Harmonization guidelines on Good Clinical Practice, the Declaration of Helsinki, as well as applicable regulatory and legal requirements. Approval was obtained from two institutional review boards (Schulman Associates, Cincinnati, OH, USA; RCRC Independent Review Board, Austin, TX, USA). Subjects gave informed, written consent before any study-related procedure.

Subjects

Subjects were men and women ≥18 to ≤65 years of age, with T2DM of at least 6 months duration on stable doses of insulin for at least 2 weeks alone or in combination with metformin,

sitagliptin and/or a thiazolidinedione. Subjects also had to have stable body weight with a body mass index of ≥25 to ≤45 kg/m^2, a fasting plasma glucose (FPG) of 3.3 to 15.00 mmol/l, an A1C of ≥7 to ≤ 10.5% and a serum creatinine <132.6 umol/l for men or <123.8 umol/l for women on screening and day −3 before randomization.

Key exclusion criteria included significant illness such as cardiovascular, haematologic, respiratory, renal or gastrointestinal disease. Subjects were also excluded if they had a history of type 1 diabetes or had received continuous subcutaneous insulin infusion within the past 3 months, or a history of diabetic ketoacidosis. To be eligible, women had to be either postmenopausal, surgically sterile or practicing an effective method of birth control.

Treatment

Subjects underwent an overnight fast for at least 8 h beginning on day −4, after which they received a placebo for the 3 days before randomization (on day 1). In cohort 1, 15 subjects were randomized to receive canagliflozin 100 mg once daily (QD) (n = 10) or placebo (n = 5). In cohort 2, 14 subjects were randomized to receive canagliflozin 300 mg twice daily (BID) (n = 10) or placebo BID (n = 4). Study drug or placebo was to be administered just before the morning meal in cohort 1 and before morning and evening meals in cohort 2, both for 27 days. Subjects were domiciled at the investigational site until the morning of day 3, returned once weekly (days 7, 14 and 21) in the morning for blood sampling, and then returned to be domiciled at the investigational site from day 27 through day 29. Subjects continued on the same insulin therapy; fixed stable doses of oral antidiabetic agents were also allowed. Insulin rescue therapy was allowed if subjects had FPG determinations ≥15 mmol/l without a known self-limited aetiology.

Measurements

Pharmacokinetics. Venous blood samples for determination of canagliflozin plasma concentrations were collected at predose and at prespecified time points after dosing on day 27. Canagliflozin concentrations were determined at PRA International, Assen, The Netherlands using a validated method (liquid chromatography coupled to mass spectrometry/mass spectrometry). The following plasma canagliflozin pharmacokinetic parameters were estimated for each subject using the actual times of blood sampling: observed maximum plasma concentration (C_{max}), time to reach the maximum observed plasma concentration, AUC over the time interval 0–24 h ($AUC_{0-24\,h}$), and elimination half-life associated with the terminal slope of the semilogarithmic drug concentration-time curve.

Pharmacodynamics. Blood samples for FPG were collected on days −3, −2, −1, 1, 2, 7, 14, 21, 26, 27, 28 and 29. Blood samples for plasma glucose (PG) were collected predose on day −1 and at 0.5, 1, 1.5, 2, 3, 4.5 (before meal), 5, 5.5, 6, 7, 8, 9, 10.5 (before meal), 11, 12, 13, 14, 16, 19 and 22 h on days −1, 1 and 27. The mean 24-h PG concentration was calculated as $AUC_{0-24\,h}$ divided by 24 h. Blood samples were collected on days −3 and 27 for determination of A1C. Urine samples for determination of UGE were collected at 0–2 h, 2–4.5 h (before meal), 4.5–7 h, 7–10.5 h (before meal), 10.5–13 h and 13–24 h on days −1, 1 and 27. The UGE rate was calculated as the amount of glucose excreted over the specific collection time period, and as the cumulative amount over each 24-h period.

RT_G is defined as the glucose concentration below which minimal UGE occurs, and above which UGE rises in direct proportion to PG. The RT_G was calculated from PG profiles, UGE and glomerular filtration rate (GFR) (estimated from measured 24-h creatinine clearance) based on the threshold relationship described below, with minimal UGE when PG concentrations are below RT_G and increasing UGE proportional to PG, with PG above RT_G. The threshold relationship within a collection interval can be described mathematically by:

$$\text{rate of UGE} = \begin{cases} \text{GFR} \times (\text{PG} - \text{RT}_G) & \text{if PG} > \text{RT}_G \\ 0 & \text{if PG} \le \text{RT}_G \end{cases}$$

Over the intervals where UGE was collected, the above equation was integrated, the measured values of GFR and PG were substituted, and the unique value of RT_G that makes UGE calculated from the integral equal to the measured UGE over that interval was solved. The RT_G was determined based on PG and UGE collected on days −1, 1 and 27.

Safety

Safety evaluations were performed throughout the study by assessment of adverse events, including hypoglycaemic episodes, urine and blood clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, body weight and physical examination. Orthostatic hypotension was defined as a decrease in systolic blood pressure (SBP) (>20 mmHg) or diastolic blood pressure (DBP) (>10 mmHg) after standing for at least 2 min, and which was associated with an increase in pulse rate compared with supine measurements after baseline.

To determine if glucose malabsorption occurs with canagliflozin treatment, a hydrogen breath test was conducted. Subjects were administered 75 g of anhydrous glucose after an overnight fast on days −2 and 26. Breath samples were collected at baseline and at 5-min intervals through 20 min after ingestion, and then at 10-min intervals through 120 min after ingestion of the glucose load. An increase in the concentration of the breath hydrogen and methane excretion of at least 10 parts per million within a 2-h period is indicative of glucose malabsorption [5].

Statistical Methods

Previous experience in subjects with T2DM receiving canagliflozin suggested that the intersubject coefficient of variation for canagliflozin $AUC_{0-24\,h}$ and C_{max} at steady state is ≤35%. A sample size of 10 subjects would be sufficient for the point estimate of the geometric mean $AUC_{0-24\,h}$ and C_{max} of canagliflozin at steady state to fall within 77.9 and 128.4% of the true value with 95% confidence.

All pharmacokinetic, pharmacodynamic and safety analyses were performed in all subjects who received at least one dose

of study drug. Safety, pharmacokinetic and pharmacodynamic parameters were summarized with descriptive statistics (for continuous endpoints) or frequency tabulations (for categorical variables). The main pharmacodynamic endpoints were change from baseline (day −1) for UGE, RT_G, mean 24-h PG, FPG, A1C and body weight on day 27. An analysis of covariance model was fitted on these endpoints with the value at baseline as a continuous covariate and treatment as a factor. Only data from subjects completing the study were included to fit this model. On the basis of this model, the least square means (LSM) and intersubject variance were estimated for each dose group. Using the estimated LSM and intersubject variance, 90% confidence intervals (CIs) for the difference between each dose of canagliflozin and placebo were constructed. As this was an exploratory study, no adjustments for multiple comparisons were made.

Results

Subjects and Demographics

A total of 29 subjects were randomized and received at least one dose of study drug (10 each in the canagliflozin 100 mg QD and canagliflozin 300 mg BID groups, and 9 in the placebo group). Twenty-seven subjects completed the study; two subjects in the placebo group withdrew consent. Due to the limited number of placebo subjects in each cohort and prior to unblinding of the randomization codes, it was decided to pool the placebo data of both cohorts. Visual inspection of baseline characteristics in the placebo subjects of both cohorts did not reveal differences that were deemed to impact interpretation of pharmacokinetic, pharmacodynamic or safety results. The groups were generally well matched at baseline for demographic and anthropometric characteristics, except that there were more men in the canagliflozin 100 mg QD group and more women in the canagliflozin 300 mg BID group; the median age was lower in the canagliflozin 300 mg BID group compared with the canagliflozin 100 mg QD or placebo groups. Groups were generally well matched for baseline disease characteristics, with the exception that subjects in the canagliflozin 100 mg QD group had more than a twofold higher daily dose of insulin at baseline (Table 1). At baseline, all subjects were taking insulin: basal, mealtime or both; and 12 subjects (41%) were also taking metformin (Table 1). Mean baseline A1C was similar (8.3–8.4%) across treatment groups.

Pharmacokinetics

At steady state conditions (sampling performed on day 27), maximum plasma canagliflozin concentrations were reached within 2.75–4.0 h of dosing (figure 1). The maximum canagliflozin plasma concentration following the second daily 300-mg dose was similar to that achieved following the morning dose. The pharmacokinetics of canagliflozin were characterized by dose-dependent increases in C_{max} and $AUC_{0-24\ h}$ (Table 2). Elimination half-lives of 14.7 and 11.8 h were observed with canagliflozin 100 mg QD and 300 mg BID, respectively.

Pharmacodynamics

PG levels were reduced compared with baseline following single and multiple doses of canagliflozin, with maximal lowering

Table 1. Baseline characteristics and demographics.

	Placebo (n = 9)	Canagliflozin 100 mg QD (n = 10)	Canagliflozin 300 mg QD (n = 10)
Race, n (%)			
White	8 (89)	9 (90)	7 (70)
Black/African-American	1 (11)	1 (10)	1 (10)
Asian	0	0	1 (10)
Other	0	0	1 (10)
Gender, n (%)			
Female	4 (44)	3 (30)	7 (70)
Male	5 (56)	7 (70)	3 (30)
Age (years)			
Mean (s.d.)	52.8 (8.18)	50.5 (9.58)	42.7 (6.24)
Range	40–65	35–63	34–54
Weight (kg)			
Mean (s.d.)	95.1 (13.96)	107.8 (23.34)	94.1 (16.17)
Range	83–120	85–151	74–120
Body mass index (kg/m^2)			
Mean (s.d.)	32.4 (5.11)	34.5 (4.81)	33.6 (5.61)
Range	27–41	27–42	25–45
FPG (day 1 predose) (mmol/l)			
Mean (s.d.)	8.7 (2.43)	9.0 (1.49)	9.6 (2.38)
Range	5–12	6–11	6–14
A1C (day −3) (%)			
Mean (s.d.)	8.3 (0.83)	8.4 (0.88)	8.4 (1.02)
Range	7–10	7–10	7–10
Type of insulin, n (%)			
Basal insulin only	4 (44)	2 (20)	4 (40)
Basal and mealtime insulin	5 (56)	8 (80)	5 (50)
Mealtime insulin only	0	0	1 (10)
Total daily insulin dose (units/day)			
Mean (s.d.)	38.4 (18.84)	114.6 (66.60)	51.4 (23.71)
Oral antihyperglycaemic agents, n (%)			
Metformin	3 (33)	4 (40)	5 (50)

BID, twice daily; FPG, fasting plasma glucose; QD, once daily.

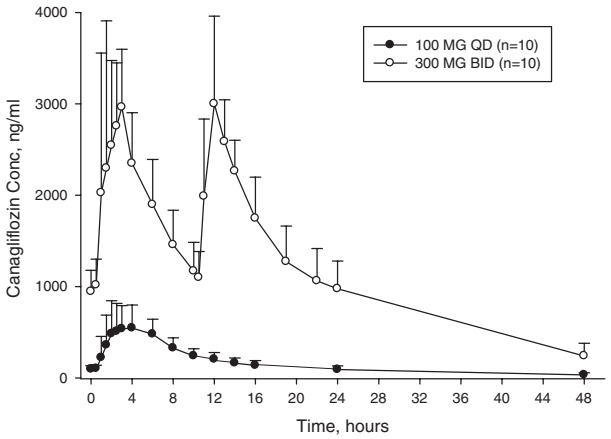

Figure 1. Mean (s.d.) plasma canagliflozin concentration-time profiles on day 27.

Table 2. Canagliflozin plasma pharmacokinetic parameters.

Mean (s.d.)	Canagliflozin 100 mg QD (n = 10)	Canagliflozin 300 mg BID (n = 10)
AUC_{0-24}, ng.h/ml	5957 (1580)	42308 (6461)
C_{max}, ng/ml	773 (213)	3556 (945)*
$t_{½\lambda}$, h	14.7 (4.1)	11.8 (2.9)
t_{max}, h†	4.00 (1.5–6.0)	2.75 (1.5–3.0)*

AUC_{0-24}, AUC over the time interval 0–24 h; BID, twice daily; C_{max}, maximum plasma concentration; QD, once daily; s.d., standard deviation; t $t_{½\lambda}$, terminal slope of the semilogarithmic drug concentration-time curve; t_{max}, time to reach the maximum observed plasma concentration.
*morning dose.
† Median (range).

achieved on day 1 and with similar reductions observed on day 27 (figure 2). In the placebo group, 24-h mean PG and FPG levels were relatively unchanged from baseline on days 1 and 27. Table 3 summarizes the means of the pharmacodynamic parameter values at baseline with the change from baseline for each treatment group. In addition, the differences in LSM changes from baseline between each canagliflozin dose and placebo is displayed with the associated 90% CI. FPG and 24-h mean PG decreased from baseline relative to placebo with both canagliflozin 100 mg QD and 300 mg BID doses (Table 3). A1C and body weight decreased from baseline relative to placebo with both canagliflozin 100 mg QD and 300 mg BID doses, with a numerically greater reduction at the higher dose (Table 3). $UGE_{24\ h}$ increased from baseline relative to placebo for both canagliflozin 100 mg QD and 300 mg BID doses, with a numerically greater increase for 300 mg BID (Table 3). Both doses of canagliflozin decreased RT_G with maximal reduction observed on day 1, which was sustained on day 27 (Table 3, figure 3).

Safety

There were no deaths or serious treatment-emergent adverse events (TEAEs). TEAEs reported in at least 20% of subjects in one treatment group are shown in Table 4. All TEAEs were considered by the investigator to be mild or moderate in severity. Two subjects had TEAEs that were considered by the investigators as possibly related to study drug (nausea and headache in subjects in the placebo and 300 mg BID canagliflozin groups, respectively). No subject discontinued the study because of an adverse event.

Twelve (41.4%) subjects experienced at least one symptomatic treatment-emergent hypoglycaemic episode, including six (60%) in the canagliflozin 100 mg QD group, three (30%) in the canagliflozin 300 mg BID group and three (33%) in the placebo group. None of the hypoglycaemic episodes were classified as severe or serious and no subjects discontinued from the study as a result of hypoglycaemia. Insulin dose was not reduced in any subject, and one placebo subject required an increase in insulin dose as a result of hyperglycaemia.

Except for the following, routine safety laboratories were generally not affected by canagliflozin treatment. The mean

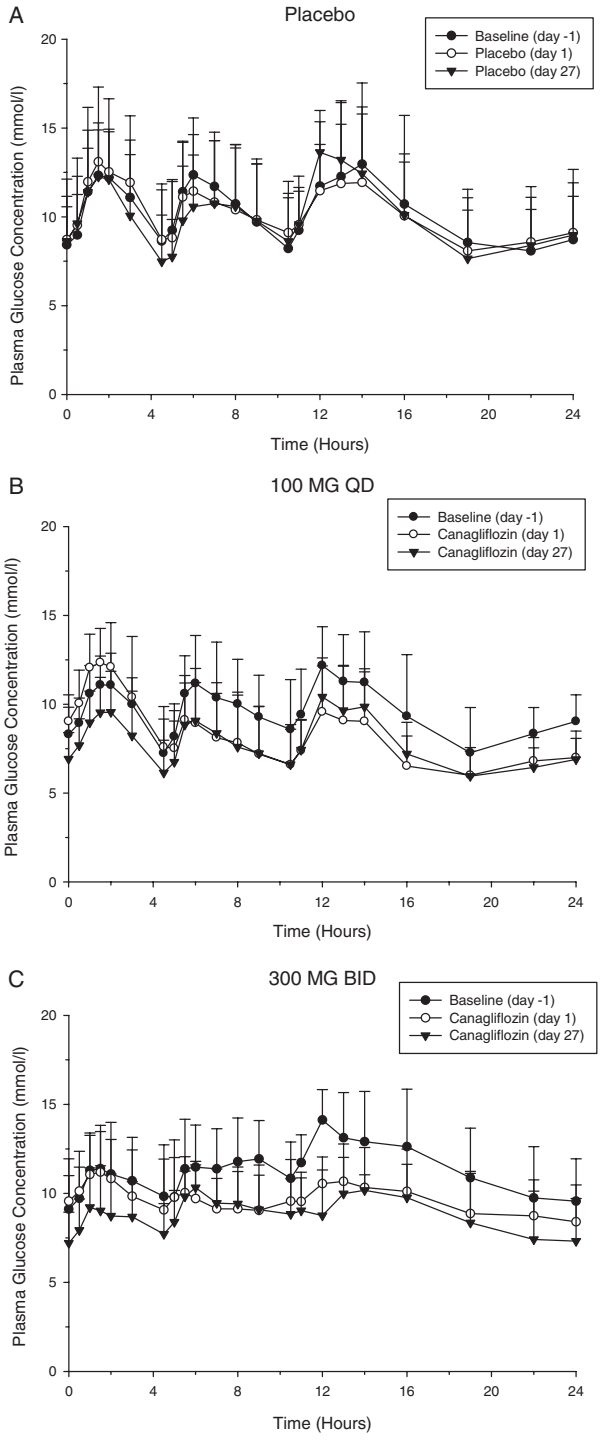

Figure 2. Mean (s.d.) plasma glucose (PG) concentration-time profiles on days −1, 1 and 27. Mean (s.d.) PG concentration-time profiles on days −1, 1 and 27 in subjects treated with (A) placebo, (B) canagliflozin 100 mg once daily (QD) and (C) canagliflozin 300 mg twice daily (BID).

(s.d.) change in blood urea nitrogen (BUN) from baseline at day 27 was 1.50 (1.11) and 1.11 (1.33) mmol/l for canagliflozin 100 mg QD and 300 mg BID, respectively, compared with 0.31 (1.23) mmol/l for the placebo group. Serum creatinine tended to increase from baseline at day 27 in a non-dose-related

Table 3. Pharmacodynamic assessments at baseline, change from baseline and the differences in LSM changes from baseline between each canagliflozin dose and placebo with the associated 90% CI.

Parameter	Mean (s.d.)			LSM difference (90% CI)	
	Placebo (n = 7)*	Canagliflozin 100 mg QD (n = 10)	Canagliflozin 300 mg BID (n = 10)	Canagliflozin 100 mg QD vs. placebo	Canagliflozin 300 mg BID vs. placebo
Baseline 24-h PG (mmol/l)	9.82 (2.19)	9.30 (1.67)	11.29 (1.62)		
Δ 24-h PG (mmol/l)	0.07 (2.09)	−1.64 (1.47)	−2.46 (1.51)	−1.96 (−3.18, −0.74)†	−1.81 (−3.09, −0.53)†
Baseline FPG (mmol/l)	8.14 (2.38)	9.03 (1.49)	9.55 (2.38)		
ΔFPG (mmol/l)	0.48 (2.29)	−2.11 (1.26)	−2.35 (1.59)	−2.37 (−3.77, −0.97)†	−2.48 (−3.91, −1.04)†
Baseline HbA1c (%)	7.99 (0.52)	8.38 (0.88)	8.42 (1.02)		
ΔHbA1c (%)	−0.19 (0.49)	−0.73 (0.50)	−0.92 (0.66)	−0.37 (−0.74, −0.003)	−0.55 (−0.92, −0.17)†
Baseline UGE (g/day)	11.30 (15.88)	5.21 (9.89)	27.50 (38.48)		
ΔUGE (g/day)	−3.2 (15.64)	71.9 (33.85)	129.2 (65.89)	67.20 (39.64, 94.77)†	153.60 (125.19, 181.91)†
Baseline 24-h RT_G (mmol/l)	12.70 (1.64)‡	12.40 (1.77)	12.35 (0.85)		
Δ24-h RT_G (mmol/l)	0.62 (1.19)‡	−6.62 (1.59)	−8.94 (0.66)	−6.62 (−8.59, −6.35)†	−8.94 (−10.07, −7.82)†
Baseline body weight (kg)	97.97 (14.01)	108.80 (23.33)	94.41 (15.73)		
Δbody weight (kg)	0.03 (0.61)	−0.73 (0.89)	−1.19 (1.40)	−0.68 (−1.62, 0.25)	−1.24 (−2.15, −0.33)†

Δ, difference from baseline (day −1) to day 27; BID, twice daily; CI, confidence interval; FPG, fasting plasma glucose; LSM, least square means; PG, plasma glucose; QD, once daily; RT_G, renal threshold for glucose excretion; s.d., standard deviation; UGE, urinary glucose excretion.
LSM difference (90% CI)results are based on ANCOVA with treatment as factor and baseline as covariate included.
*Data from subjects completing the study were included in the analysis.
†p-value <0.05.
‡n = 6.

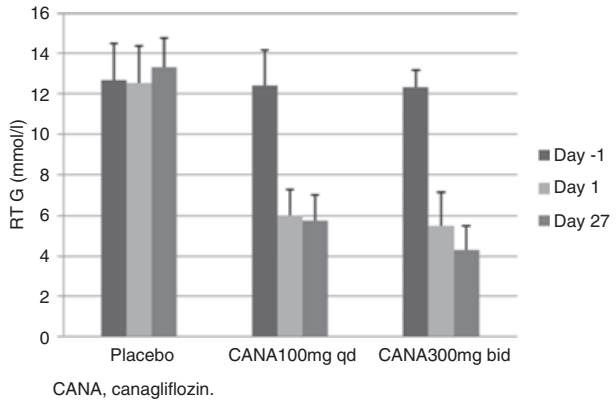

Figure 3. Mean (s.d.) 24-h renal threshold for glucose excretion (RT_G). For placebo, results are for eight subjects on days −1 and 1, and for six subjects on day 27. One subject had urinary glucose excretion (UGE) too low (<100 mg) to reliably calculate RT_G on all 3 days and was not included. For canagliflozin 100 mg once daily (QD), results are for 10 subjects on days −1 and 1, and for 9 subjects on day 27. One subject did not have UGE reported in the overnight period on day 27 and was not included. For canagliflozin 300 mg twice daily (BID), results are for 10 subjects.

manner in canagliflozin groups relative to placebo, with values returning to baseline with discontinuation of treatment. The mean (s.d.) change in serum creatinine from baseline on day 27 was 5.30 (4.56) and 5.66 (11.44) μmol/l for canagliflozin 100 mg QD and 300 mg BID, respectively, compared with −3.03 (7.77) μmol/l for the placebo group. Urinary sodium excretion (mmol) increased from baseline on day 1 in the canagliflozin groups relative to placebo, with values returning to baseline with discontinuation of treatment. The mean (s.d.) change in urinary sodium excretion from baseline on day 1 was 54.6 (72.4) mmol and 105.4 (204.2) mmol for canagliflozin 100 mg QD and 300 mg BID, respectively, compared with 1.1 (118.1) mmol for the placebo group. On day 27, urinary sodium excretion returned to baseline or slightly below baseline values. The mean (s.d.) change in urinary sodium excretion from baseline on day 27 was −34.1 (99.2) mmol and −72.6 (236.8) mmol for canagliflozin 100 mg QD and 300 mg BID, respectively, compared with −5.14 (121.0) mmol for the placebo group. Urinary urate decreased from baseline on day 27 in a dose-related manner in canagliflozin groups compared with placebo. The mean (s.d.) changes in urinary urate from baseline on day 27 were −93.8 (385.5) mg and −212.8 (656.1) mg in the canagliflozin 100 mg QD and 300 mg BID groups, respectively, compared with 48.0 (86.6) mg for the placebo group.

Table 4. Treatment-emergent adverse events in at least 20% of subjects in any treatment group (n, %).

Adverse event	Placebo (n = 9)	Canagliflozin 100 mg QD (n = 10)	Canagliflozin 300 mg BID (n = 10)
Total number of subjects with adverse events	8 (88.9)	9 (90.0)	8 (80.0)
Headache	2 (22.2)	3 (30.0)	6 (60.0)
Nausea	2 (22.2)	2 (20.0)	2 (20.0)
Diarrhoea	1 (11.1)	0	3 (30.0)
Pain in extremity	0	2 (20.0)	1 (10.0)
Dizziness	2 (22.2)	1 (10.0)	0
Nasal congestion	0	0	3 (30.0)
Feeling hot	0	2 (20.0)	0
Peripheral oedema	0	2 (20.0)	0
Contusion	0	2 (20.0)	0

BID, twice daily; QD, once daily.

Following administration of 75 g of oral glucose, there were no consistent increases of hydrogen breath content from baseline to day 26 in canagliflozin group [mean (s.e.) differences in change from baseline at the 2-h value: 100 mg QD canagliflozin dose vs. placebo was −8.19 (10.256) ppm and 300 mg BID canagliflozin dose vs. placebo was −5.79 (9.3) ppm], and maximum values with canagliflozin did not exceed the cut-off (i.e. criterion for glucose malabsorption) of 10 ppm during the 2-h time period of the test.

No clinically relevant mean changes in heart rate or ECG measurements were noted across canagliflozin groups compared with placebo. Changes from baseline in the 24-h urine volume were minimal across treatment groups [mean (s.d.) changes: −143.1 (433.8) ml for placebo, −47.2 (739.0) ml for canagliflozin 100 mg QD and 97.0 (874.4) ml for canagliflozin 300 mg BID).

While variable, blood pressure reductions seen in the canagliflozin groups tended to increase over time with the maximal decreases generally seen at end of the treatment period. Canagliflozin treatment was associated with modest reductions in SBP and DBP, which were more notable on supine blood pressure. Mean (s.d.) changes from baseline on day 27 (predose) in supine SBP and DBP were −10.7 (9.0) and −7.1 (4.5) mmHg, respectively, in the canagliflozin 100 mg QD group, and −8.8 (12.4) and −3.3 (6.1) mmHg, respectively, in the 300 mg BID group, compared with −2.1 (11.8) and −0.9 (4.7) mmHg, respectively, in the placebo group. For standing SBP and DBP, mean (s.d.) changes from baseline on day 27 (predose) were −8.0 (14.6) and −3.8 (7.8) mmHg, respectively, in the canagliflozin 100 mg QD group and −10 (10.3) and −5.4 (7.2), respectively, in the 300 mg BID group, compared with −6.3 (11.7) and −3.4 (1.3) mmHg for the placebo group. Asymptomatic orthostatic hypotension determined at routine blood pressure testing occurred in two and one subjects in the canagliflozin 100 mg QD and 300 mg BID groups, respectively, and in one in the placebo group.

Small increases from baseline to day 27 in standing and supine pulse were observed in canagliflozin treatment groups compared with placebo. Mean (s.d.) changes from baseline on day 27 (predose) in standing pulse were 0.5 (5.9) and 7.1 (8.3) beats/min in the canagliflozin 100 mg QD and 300 mg BID groups, respectively, compared with −0.4 (3.3) beats/min in the placebo group. Mean (s.d.) changes from baseline at day 27 (predose) in supine pulse were −0.7 (4.1) and 1.6 (4.4) beats/min in the canagliflozin 100 mg QD and 300 mg BID groups, respectively, compared with 0.7 (4.7) beats/min in the placebo group.

Discussion

With progression of disease, patients with T2DM often require insulin therapy to control glucose levels. Despite this, many patients on insulin do not achieve glycaemic goals. Regimens that combine oral agents and insulin are commonly used to improve glycaemic control. SGLT2 inhibitors are a new class of agents in clinical development for the treatment of T2DM; these agents inhibit SGLT2 activity in the proximal tubule of the kidney, significantly reducing glucose reabsorption into the bloodstream, thereby increasing UGE and decreasing blood glucose levels [6].

Canagliflozin is a potent, orally administered SGLT2 inhibitor in development for treatment of patients with T2DM [3,4]. As SGLT2 inhibition is a glucose-lowering mechanism distinct from that of current AHA classes, it would be expected to provide efficacy in combination with other AHA classes, including insulin. This study was conducted to provide an initial evaluation of the safety and tolerability of the addition of canagliflozin to ongoing insulin therapy (alone or in combination with another oral agent), and to provide an early assessment of the pharmacodynamic activity and the pharmacokinetics of canagliflozin in this combination setting.

Canagliflozin was generally well tolerated, with a low incidence of hypoglycaemia in this group of subjects with T2DM receiving insulin therapy. While mean RT_G values on canagliflozin treatment are above the level at which symptoms of hypoglycaemia typically occur, RT_G values in individual subjects at certain time points decreased below the threshold for the development of hypoglycaemic symptoms. As the insulin-independent mechanism of action of canagliflozin preserves the glucose-responsiveness of β-cell insulin secretion, the intrinsic risk of hypoglycaemia is limited. However, AHAs can increase the risk of insulin-induced hypoglycaemia by improving glycaemic control, thereby reducing the 'cushion' above the hypoglycaemic threshold. Larger and longer-term studies will be needed to fully evaluate the risk of hypoglycaemia with the use of canagliflozin in combination with insulin therapy.

Overall, few abnormal laboratory findings were associated with canagliflozin treatment. In subjects treated with canagliflozin, slight increases in BUN and serum creatinine that reversed with discontinuation of canagliflozin were seen. These findings could be consistent with slight intravascular volume contraction, possibly because of a small osmotic diuresis; notably, no meaningful increase in heart rate or occurrence of orthostatic hypotension was observed, suggesting that the extent of such a diuresis, and any attendant volume reduction, was probably small.

The high, local concentrations of canagliflozin that occur in the proximal gut lumen after drug administration may lead to transient gut SGLT1 inhibition, despite the selectivity of canagliflozin for SGLT2. The hydrogen breath test was used to assess whether canagliflozin administration caused glucose malabsorption; however, it should be noted that other factors such as altered gastrointestinal transit time can influence results from this test. Canagliflozin treatment with doses up to 300 mg BID was not associated with a significant increase in hydrogen breath content following oral glucose administration, suggesting that glucose malabsorption is unlikely. However, this does not exclude the potential for canagliflozin to provide a transient moderate delay in gut glucose absorption through local gut SGLT1 inhibition, leading to delayed glucose absorption, without inducing malabsorption.

Canagliflozin was rapidly absorbed and showed dose-dependent exposure. The elimination half-life of 12–15 h indicates that once-daily dosing of canagliflozin is appropriate.

As expected, based on the mechanism of canagliflozin action, marked reductions in the RT_G were observed. It is notable that at baseline, the RT_G was approximately 12.4–12.7 mmol/l. These levels are higher than have been previously observed in healthy subjects [7–9]; however, elevations in RT_G have been reported in patients with T2DM, consistent with the present observation [10].

With canagliflozin treatment, marked reductions in the 24-h PG were present on day 1, with similar reductions observed after 27 days of treatment. The reduction in the 24-h profile showed reductions both in the post-absorptive and post-meal time periods.

Due to the limited sample size and treatment duration of this study, conclusions regarding the safety and efficacy of canagliflozin as an AHA and when used in combination with insulin therapy are limited. Larger and longer-term studies will be required to determine the safety and efficacy of canagliflozin when used in combination with insulin.

Nonetheless, results from this study warrant the further investigation of adding canagliflozin in subjects with T2DM not optimally controlled on insulin therapy.

Acknowledgements

Some of these data were previously presented at American Diabetes Association 70th Scientific Sessions, 25–29 June 2010, Orlando, FL, USA. Canagliflozin is being developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation. Editorial assistance was provided by Phase Five Communications Inc., New York, NY, USA funded by Janssen Global Services, LLC.

Conflict of Interest

D. D. designed, analysed, wrote drafts and approved the final manuscript. L. M. and M. H. designed, conducted and collected data; analysed, reviewed drafts and approved the final manuscript. D. S. and S. S. designed, analysed, reviewed drafts and approved the final manuscript. A. V. designed, carried out statistical analysis, wrote drafts and approved the final manuscript. J. M. designed, analysed, revised drafts and approved the final manuscript. K. W. designed, analysed, wrote drafts and approved the final manuscript.

D. D., D. S., J. M. and K. W. are employees of Janssen Research & Development, LLC. A. V. is an employee of Janssen Pharmaceutica NV, Beerse, Belgium. Both companies are the sponsor of canagliflozin. L. M. and M. H. are employees of Profil Institute for Clinical Research, a private research institute that has received grants from a number of pharmaceutical companies, including Janssen Research & Development, LLC, the sponsor of the studies described in this manuscript. S. S. is an investigator in the DIA 2001 trial.

References

1. Liang Y, Arakawa K, Martin T et al. JNJ-28431754/TA-7284, an SGLT inhibitor, lowers blood glucose and reduces body weight in obese and type 2 diabetic animal models, New Orleans, LA, Poster presented at the American Diabetes Association 69th Scientific Session, June 5–9, 2009.
2. Liang Y, Du F, Conway J et al. Effect of canagliflozin on renal threshold for glucose excretion in diabetic animals, San Diego, CA, Poster presented at the American Diabetes Association 71st Scientific Session, June 24–28, 2011.
3. Sha S, Devineni D, Ghosh A et al. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. Diabetes Obes Metab 2011; **13**: 669–672.
4. Sha S, Devineni D, Ghosh A et al. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, improved glucose control in subjects with type 2 diabetes and was well tolerated (Abstract #568-P). American Diabetes Association, 70th Scientific Sessions, 2010; Orlando, FL.
5. Urita Y, Ishihara S, Akimoto T et al. Seventy-five gram glucose tolerance test to assess carbohydrate malabsorption and small bowel bacterial overgrowth. World J Gastroenterol 2006; **12**: 3092–3095.
6. Isaji M. SGLT2 inhibitors: molecular design and potential differences in effect. Kidney Int 2011; **79**: S14–S19.
7. Nair S, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. J Clin Endocrinol Metab 2010; **95**: 34–42.
8. Bays H. From victim to ally: the kidney as an emerging target for the treatment of diabetes mellitus. Curr Med Res Opin 2009; **25**: 671–681.
9. Rave K, Nosek L, Posner J, Heise T, Roggen K, van Hoogdalem EJ. Renal glucose excretion as a function of blood glucose concentration in subjects with type 2 diabetes–results of a hyperglycaemic glucose clamp study. Nephrol Dial Transplant 2006; **21**: 2166–2171.
10. Mogensen C. Maximum tubular reabsorption capacity for glucose and renal hemodynamics during rapid hypertonic glucose infusion in normal and diabetic subjects. Scand J Clin Lab Invest 1971; **28**: 101–109.