Effects of Hydrochlorothiazide on the Pharmacokinetics, Pharmacodynamics, and Tolerability of Canagliflozin, a Sodium Glucose Co-transporter 2 Inhibitor, in Healthy Participants

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ABSTRACT

Background: Many patients with type 2 diabetes mellitus (T2DM) also have hypertension, which is commonly treated with thiazide diuretics, including hydrochlorothiazide (HCTZ). Canagliflozin, a sodium glucose cotransporter 2 inhibitor developed for the treatment of T2DM, lowers plasma glucose by inhibiting renal glucose reabsorption, thereby increasing urinary glucose excretion and mild osmotic diuresis. Because patients with T2DM are likely to receive concurrent canagliflozin and HCTZ, potential interactions were evaluated.

Objective: This study evaluated the effects of HCTZ on the pharmacokinetic and pharmacodynamic properties and tolerability of canagliflozin in healthy participants.

Methods: This Phase I, single-center, open-label, fixed-sequence, 2-period study was conducted in healthy participants. During period 1, participants received canagliflozin 300 mg once daily for 7 days, followed by a 14-day washout period. During period 2, participants received HCTZ 25 mg once daily for 28 days, followed by canagliflozin 300 mg + HCTZ 25 mg once daily for 7 days. Blood samples were taken before and several times after administration on day 7 of period 1 and on days 28 and 35 of period 2 for canagliflozin and HCTZ pharmacokinetic analyses using LC-MS/MS. Blood and urine samples were collected for up to 24 hours after canagliflozin administration on day 1 of period 1 and day 35 of period 2 for pharmacodynamic glucose assessment. Tolerability was also evaluated.

Results: Thirty participants were enrolled (16 men, 14 women; all white; mean age, 43.7 years). Canagliflozin AUC during a dosing interval (T) at steady state ($AUC_{\tau,ss}$) and C_{max} at steady state ($C_{max,ss}$) were increased when canagliflozin was coadministered with HCTZ, with geometric mean ratios (90% CI) of 1.12 (1.08–1.17) and 1.15 (1.06–1.25), respectively. $AUC_{\tau,ss}$ and $C_{max,ss}$ for HCTZ were similar with and without canagliflozin coadministration. The 24-hour mean renal threshold for glucose and mean plasma glucose were comparable for canagliflozin alone and coadministered with HCTZ. The change in 24-hour urine volume from baseline was −0.1 L with canagliflozin alone and 0.4 L with HCTZ alone and with canagliflozin + HCTZ. The overall incidence of adverse events (AEs) was higher with canagliflozin + HCTZ (69%) than with canagliflozin (47%) or HCTZ (50%) alone; most AEs were of mild severity. Overall, minimal changes in serum electrolytes (eg, sodium, potassium) were observed after coadministration of canagliflozin + HCTZ compared with individual treatments.

Conclusions: Adding canagliflozin treatment to healthy participants on HCTZ treatment had no notable pharmacokinetic or pharmacodynamic effects; canagliflozin coadministered with HCTZ was generally well tolerated, with no unexpected tolerability concerns. ClinicalTrials.gov identifier: NCT01294631. (*Clin Ther.* 2014;▮:▮▮▮–▮▮▮) © 2014 The Authors. Published by Elsevier HS Journals, Inc. All rights reserved.

Key words: canagliflozin, diuretic, drug–drug interaction, hydrochlorothiazide, pharmacodynamics, pharmacokinetics, sodium glucose co-transporter 2 (SGLT2) inhibitor, type 2 diabetes mellitus.

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INTRODUCTION

Inhibiting renal glucose reabsorption by sodium glucose co-transporter (SGLT2) is a novel therapeutic approach to treating patients with type 2 diabetes mellitus (T2DM).[1,2] Canagliflozin is an SGLT2 inhibitor developed for the treatment of adults with T2DM[3–10]; canagliflozin doses of 100 and 300 mg have been approved in the United States.[11] Canagliflozin reduces plasma glucose by lowering the renal threshold for glucose excretion (RT_G) and increasing urinary glucose excretion (UGE).[12] The increase in UGE results in a mild osmotic diuresis and a loss of calories[1,2,4,6,7]; the osmotic diuretic effect of canagliflozin is also associated with a reduction in intravascular volume, which attenuates over time.[11,13] In clinical studies in patients with T2DM, canagliflozin treatment improved glycemic control and reduced body weight and systolic/diastolic blood pressure (BP).[4–10,14]

Hypertension is a common comorbidity in patients with T2DM.[15,16] Hydrochlorothiazide (HCTZ) is a thiazide diuretic indicated for the treatment of mild to moderate hypertension. Thiazides work, at least in part, by inhibiting sodium reabsorption in the distal convoluted tubule (DCT).[17,18] Oral administration of HCTZ results in diuresis within 2 hours,[19] indirectly leading to an initial reduction in plasma volume that attenuates with long-term treatment.[20] The SGLT2 transporters targeted by canagliflozin, in contrast, are located in the proximal convoluted tubule (PCT).[1,2] Inhibition of SGLT2 by canagliflozin is predicted to reduce both glucose and sodium resorption in the PCT, leading to increased sodium delivery to the DCT. Because both canagliflozin and HCTZ may contribute to decreased sodium reabsorption via 2 different mechanisms targeting the PCT and the DCT, the effects of the combined administration of canagliflozin + HCTZ on sodium concentration in the blood and on fractional excretion (FE) of sodium in the urine are of interest. Moreover, it is of interest whether these effects of the 2 drugs on sodium excretion lead to greater reductions in systolic and diastolic BP when the agents are administered together relative to when each agent is administered alone.

These questions are clinically relevant, given the high prevalence of hypertension in patients with T2DM and the common use of thiazide therapy in this population, because it is likely that patients with T2DM receive concurrent treatment with canagliflozin + HCTZ. Thus, it is important to evaluate whether a pharmacodynamic interaction could occur between these 2 agents. In addition, because canagliflozin and HCTZ are each associated with plasma volume reductions, it is also important to evaluate the tolerability of canagliflozin + HCTZ coadministration. The primary objective of this Phase I study was to examine the effects of HCTZ on the pharmacodynamic properties of canagliflozin; secondary objectives were: (1) to examine the effects of HCTZ on the pharmacokinetic properties of canagliflozin; (2) to evaluate the effects of canagliflozin on the pharmacokinetic properties of HCTZ; and 3) to assess the tolerability of canagliflozin coadministered with HCTZ in healthy participants.

PARTICIPANTS AND METHODS

Participants

Eligible participants were healthy men and women aged 18 to 55 years. Participants were required to have a body mass index of 18 to 30 kg/m^2, body weight $\geq$50 kg, and a creatinine clearance (estimated using the Cockcroft-Gault formula[21]) $\geq$80 mL/min.

Exclusion criteria included, but were not limited to, a history of or current clinically significant medical illness (including cardiac disease, hematologic disease, lipid abnormalities, and/or diabetes mellitus); clinically significant abnormal values on hematology, clinical chemistry, urinalysis, physical examination, vital sign measurement, or 12-lead ECG as assessed by the investigator at screening or on day −3 of the first treatment period; and current history of overactive bladder with excessive urination frequency.

Study Design

This Phase I, single-center, open-label, fixed-sequence, 2-period study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and other applicable regulatory requirements. Participants provided their written consent to participate in the study before the performance of any study-related activity. The consent form was approved by both the sponsor and the reviewing independent ethics committee.

The study consisted of 3 phases: (1) a screening phase of up to 19 days; (2) two open-label treatment periods, period 1 and period 2, with a 14-day washout period between the 2 periods; and (3) a post-treatment phase of up to 6 days (Figure 1). During period 1,

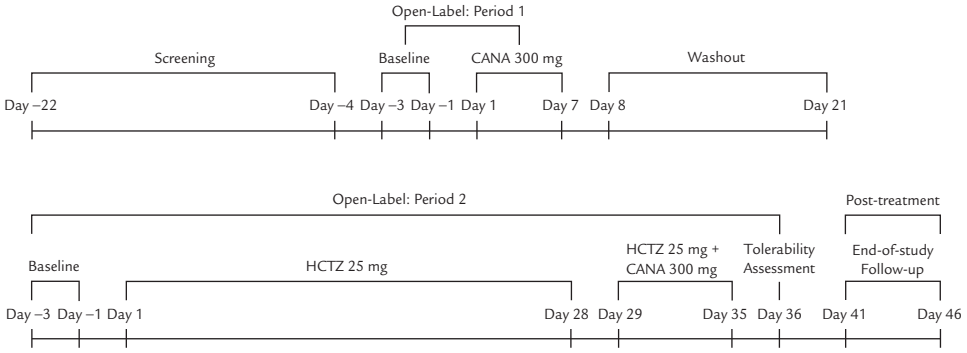

Figure 1. Study design. CANA = canagliflozin; HCTZ = hydrochlorothiazide.

participants received canagliflozin 300 mg once daily on days 1 to 7; during period 2, participants received HCTZ 25 mg once daily for 28 days (days 1–28), followed by the combination of canagliflozin 300 mg + HCTZ 25 mg once daily for 7 days (days 29–35). Participants were domiciled at the study center during days −3 to 8 of period 1, and days −3 to 1 and days 26 to 36 of period 2. Participants received standardized meals while at the study center; the meals contained sodium not exceeding 2.5 g/d and calcium content ~1 g/d.

Pharmacokinetic Evaluations

The pharmacokinetic profiles of canagliflozin and HCTZ were obtained using blood samples (4 mL for canagliflozin and 2 mL for HCTZ) taken before and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after the administration of study drug. These profiles were obtained for canagliflozin on day 7 of period 1, for HCTZ on day 28 of period 2, and for both canagliflozin and HCTZ on day 35 of period 2. In addition, predose blood samples were obtained on days 5 and 6 of period 1 and on days 7, 14, and 21 of period 2.

EDTA plasma samples were analyzed to determine the concentrations of canagliflozin with a validated LC-MS/MS method (Frontage Company Ltd, Shanghai, People's Republic of China).[22,23] A $^{13}C_6$ analogue of canagliflozin was used as the internal standard (IS). Briefly, the sample was processed using a liquid-liquid extraction with *tert*-butyl methyl ether. The LC phase used a 5 cm × 4.6 mm column packed with XBridge C18 (Waters Corporation, Milford, Massachusetts) with a mobile phase of ammonium acetate 0.01 M (30%) and methanol (70%) and a flow rate of 1.2 mL/min. Quantification was achieved by MS/MS detection with an API 4000, equipped with TurboIonSpray (TIS) interface (AB Sciex, Framingham, Massachusetts) in the positive ion multiple reaction monitoring mode. Canagliflozin and IS were monitored at mass transitions *m/z* 462.1 → 267.0 and *m/z* 468.1 → 273.0, respectively. The quantitation range was 5.00 to 10,000 ng/mL. The in-study performance of the quality-control samples ranged from 94.5% to 114.8% intrarun accuracy, with an inter-run %CV ranging from 3.9% to 9.9%. HCTZ samples were assayed with a validated assay using Isolute SLE+ 96-well plates (Biotage LLC, Charlotte, North Carolina) with *tert*-butyl methyl ether.[22,23] As the IS, a $^{15}N_2^{13}CD_2$ analogue of HCTZ was used. Quantitation was done using a LC-MS/MS method on the AB Sciex 5000, in negative TIS mode at Pharmaceutical Product Development, LLC, Richmond, Virginia. A Synergi Polar-RP column (80 Å, 2.0 × 75 mm, 4 μm) (Phenomenex, Inc, Torrance, California) was used. Mobile phase consisted of an ammonium formate/acetonitrile gradient from 74/26 to 26/74 (vol/vol) over 3 minutes with a flow rate of 0.25 mL/min. HCTZ and IS were monitored at mass transitions *m/z* 296.0 → 269.1 and *m/z* 301.0 → 271.3, respectively. The quantitation range was 2.00 to 200 ng/mL. The in-study performance of the quality-control samples ranged from 95.7% to 115.0% intrarun accuracy, with an inter-run %CV ranging from 4.0% to 5.4%.

The following pharmacokinetic parameters were evaluated based on the individual plasma concentration–time data, using actual sampling times via non-compartmental analysis with validated WinNonlin® version 5.2.1 (Pharsight Corporation, Mountain View, California): C_{max} during a dosing interval at steady state ($C_{max,ss}$); trough plasma concentration before

dosing or at the end of the dosing interval, except first dose (C_{trough}); time to $C_{max,ss}$ ($t_{max,ss}$); and area under the plasma concentration versus time curve during a dosing interval (τ) at steady state ($AUC_{\tau,ss}$).

Pharmacodynamic Evaluations

Plasma glucose was assessed using blood samples (2 mL each) obtained before and at 0.5, 1, 1.5, 2, 3, 4.5, 5, 6, 7, 8, 9.5, 10.5, 11, 12, 12.5, 14, 16, and 24 hours after administration of canagliflozin on day 7 of period 1 and on day 35 of period 2. Urinary glucose was evaluated using urine samples collected over 4 separate intervals (0–4, 4–8, 8–12, and 12–24 hours) after administration of canagliflozin on day 7 of period 1 and day 35 of period 2. Plasma samples and 1-mL aliquots collected from each urine collection interval were analyzed to determine glucose concentrations based on spectrophotometry using the Roche hexokinase method (Pacific Biomarkers Inc, Seattle, Washington).

The following pharmacodynamic parameters were evaluated: RT_G, calculated for each scheduled urine collection interval and for each 24-hour urine collection period; UGE, calculated for each scheduled urine collection interval and cumulatively for each 24-hour urine collection period ($UGE_{0-24\ h}$); and mean plasma glucose concentration during 24 hours postdose ($MPG_{0-24\ h}$) in periods 1 and 2. RT_G during each collection interval was calculated using the measured plasma glucose profiles, UGE, and estimated glomerular filtration rate (obtained from the Modification of Diet in Renal Disease formula[24]) as previously described,[12,25] and the 24-hour mean RT_G was calculated as the weighted mean of the values obtained over the different collection intervals. Values of RT_G were calculated only during canagliflozin or canagliflozin + HCTZ treatment because participants treated with HCTZ alone had virtually no UGE. $MPG_{0-24\ h}$ was determined from the measured plasma glucose profiles by calculating the AUC and dividing by 24 hours (calculations performed using WinNonlin version 5.2.1 [Pharsight Corporation]); all samples collected within the 24-hour postdose time period were included in the calculation.

Tolerability Assessment

Tolerability evaluations included reports of adverse events (AEs), physical examination findings, vital sign measurements, 12-lead ECG, hematology, clinical chemistry, urinalysis, and specific renal function tests, as described later. Vital signs included triplicate supine and 1-time standing systolic/diastolic BP and pulse rate assessments, which were measured at several time points on day −1 of both study periods (baseline) as well as on day 7 in period 1 and on days 28 and 35 in period 2. Orthostatic hypotension was defined as a decrease in standing versus supine systolic BP >20 mm Hg or a decrease in standing versus supine diastolic BP >10 mm Hg combined with an increase in standing versus supine pulse rate >0 beats/min (bpm). Clinical chemistry parameters were assessed in period 1 on day 1 predose (baseline) and day 8, and in period 2 on day 1 predose (baseline), day 29, and day 36, as well as at the final follow-up visit; the following serum chemistry parameters were included: sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen (BUN), urate, calcium, phosphate, and magnesium.

Measures of renal tubular function were also evaluated; for each urine collection interval, parameters included: total urine volume; urine pH; measured creatinine clearance; and 24-hour excretion and FE of urinary analytes, including sodium, potassium, calcium, chloride, inorganic phosphate, and magnesium. Measured creatine clearance was calculated from measured serum and urine creatinine concentrations as follows:

$$\mathrm{CrCl}\ (\mathrm{mL/min}) = \frac{10^6 \times U_{Cr}\ (\mathrm{mmol})}{S_{Cr} \times 1440\ \mathrm{min}}$$

where U_{Cr} is the measured 24-h cumulative excretion of creatinine and S_{Cr} is the serum creatinine concentration. Measured creatinine clearance was then adjusted for body surface area (BSA) to obtain CrCl in units of mL/min/1.73m^2 by multiplying the CrCl value in mL/min by (1.73m^2/BSA), where BSA is calculated using Mosteller formula:

$$\mathrm{BSA}\ (\mathrm{m}^2) = (\mathrm{weight\ [kg]} \times \mathrm{height\ [cm]}/3600)^{1/2}$$

The evaluation of FE for the different analytes was performed using the following equation:

$$FE_{analyte} = 100 \times (Analyte_{urine} \times Creatinine_{serum}) / (Analyte_{serum} \times Creatinine_{urine})$$

Statistical Analyses

The study was primarily designed as an estimation study to evaluate the effects of HCTZ on the RT_G with canagliflozin. Thus, sample size was based on the precision of the estimate of RT_G. Based on data from a

previous study of canagliflozin in healthy participants, the intersubject %CV for 24-hour mean RT_G was estimated to be 21% after multiple doses of canagliflozin 300 mg. Assuming an estimated intrasubject %CV of 20% for 24-hour mean RT_G, 24 participants were considered sufficient for the point estimate of the ratio of 24-hour mean RT_G for canagliflozin + HCTZ and canagliflozin alone to fall between 91% and 110% of the true value, with 90% confidence. Therefore, the current study planned to enroll 30 participants to ensure that 24 participants completed the study.

Pharmacokinetic parameters were determined from individual plasma concentration–time data for canagliflozin and HCTZ, and were summarized using descriptive statistics. The effects of HCTZ at steady state on the pharmacokinetic properties of canagliflozin were evaluated using data from days 7 to 8 (canagliflozin) of period 1 and days 35 to 36 (canagliflozin + HCTZ) of period 2; the effects of canagliflozin on the steady-state pharmacokinetic properties of HCTZ were evaluated using data from days 28 to 29 (HCTZ) and days 35 to 36 (canagliflozin + HCTZ) of period 2. Linear mixed-effects models were fit to the log-transformed pharmacokinetic parameters ($AUC_{\tau,ss}$ and $C_{max,ss}$) using SAS® version 9.2 (SAS Institute Inc, Cary, North Carolina), with treatment as a fixed effect and participant as a random effect. Least squares (LS) means and intraparticipant variance were estimated from the mixed-effects models and used to determine the geometric mean ratio (GMR) of $AUC_{\tau,ss}$ and $C_{max,ss}$ of canagliflozin at steady state with or without HCTZ, and the GMR of $AUC_{\tau,ss}$ and $C_{max,ss}$ of HCTZ with and without canagliflozin, as well as the associated 90% CIs.

All pharmacodynamic parameters were summarized using only descriptive statistics for each day of measurement. To evaluate the effects of HCTZ on the pharmacodynamic properties of canagliflozin, the primary end point, 24-hour mean RT_G, was analyzed on a log scale, and $UGE_{0-24\ h}$ was analyzed untransformed, using original units (g), because UGE is often close to zero in patients not treated with canagliflozin. A mixed-effects model was fit to the 24-hour mean RT_G (on a log scale) and $UGE_{0-24\ h}$ data from periods 1 and 2, with treatment as a fixed effect and participant as a random effect. LS means were estimated based on the mixed-effects model and used to calculate the difference in 24-hour mean RT_G (on a log scale) and $UGE_{0-24\ h}$ between coadministration of canagliflozin + HCTZ and administration of canagliflozin alone, as well as the associated 90% CIs. Estimated LS mean differences (on a log scale) and associated 90% CIs for 24-hour mean RT_G were back-transformed to estimate the ratio of means and associated 90% CIs for canagliflozin + HCTZ and canagliflozin alone, along with the difference in 24-hour mean RT_G. The analysis of MPG_{0-24h} was similar to that of 24-hour mean RT_G.

RESULTS

Participants

A total of 30 healthy participants (16 men and 14 women; all white) were enrolled and received ≥1 dose of study drug; 28 participants (93%) completed the study, and 2 participants were withdrawn due to AEs. Mean (SD) age of the participants was 43.7 (8.4) years, mean weight was 75.6 (9.4) kg, and mean body mass index was 25.7 (2.2) kg/m^2.

Pharmacokinetic Results

After repeated once-daily dosing alone, plasma canagliflozin concentrations achieved steady state by day 7. After administration of canagliflozin alone and after coadministration with HCTZ, plasma canagliflozin concentrations increased rapidly (median t_{max}, 1.0 hour with both treatments) (Figure 2). Plasma HCTZ concentrations increased rapidly when HCTZ was dosed alone and in combination with canagliflozin (median t_{max}, 1.5 hours with both treatments) (Figure 3). Coadministration of canagliflozin + HCTZ was associated with increases versus canagliflozin alone of ~12% in geometric LS mean canagliflozin $AUC_{\tau,ss}$ (27,942 and 24,896 ng · h/mL, respectively; GMR [90% CI], 1.12 [1.08–1.17]) and 15% in geometric LS mean canagliflozin $C_{max,ss}$ (4350 and 3787 ng/mL; GMR [90%CI], 1.15 [1.06–1.25]) (Table I). Similar geometric LS mean HCTZ $AUC_{\tau,ss}$ (1049 and 1055 ng · h/mL; GMR [90% CI], 0.99 [0.95; 1.04]) and $C_{max,ss}$ (141 and 151 ng/mL; GMR [90% CI], 0.94 [0.87; 1.01]) were observed when HCTZ was administered with canagliflozin or alone.

Pharmacodynamic Results

The geometric LS mean RT_G was 3.48 mmol/L (62.6 mg/dL) with canagliflozin + HCTZ and 3.22 mmol/L (58.0 mg/dL) with canagliflozin alone. With canagliflozin + HCTZ and canagliflozin alone, LS mean UGE_{0-24h} values were 41.34 and 42.34 g,

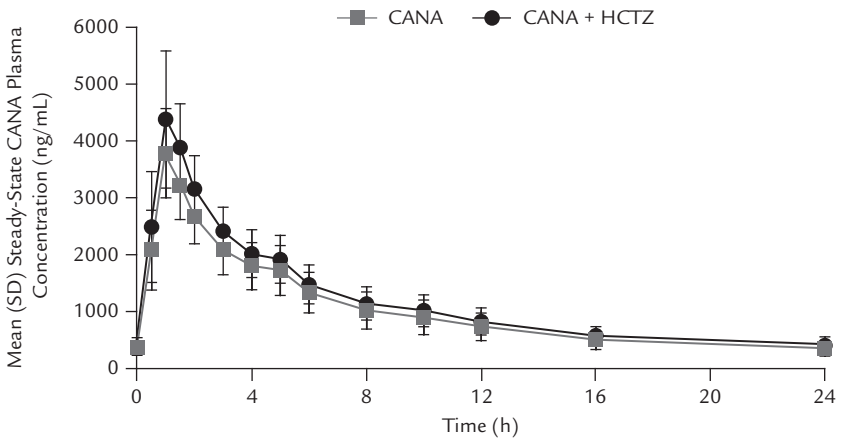

Figure 2. Canagliflozin (CANA) plasma concentration–time profiles following the administration of CANA with and without hydrochlorothiazide (HCTZ).

respectively, and geometric LS mean MPG_{0-24h} values were 5.46 mmol/L (98.2 mg/dL) and 5.16 mmol/L (93.0 mg/dL), respectively (Table II).

Tolerability

Adverse Events

Treatment-emergent AEs (TEAEs) were reported in 23 of 30 participants (77%); 14 participants (47%) had TEAEs during treatment with canagliflozin alone in period 1, 15 participants (50%) during treatment with HCTZ alone in period 2, and 20 participants (69%) during coadministration of canagliflozin and HCTZ in period 2. Two serious AEs were reported (lymphadenopathy [assessed by investigator as doubtfully related to study drugs] and tonsillitis [assessed by investigator as not related to study drugs], in the same participant during canagliflozin + HCTZ treatment), both of which resolved.

There were 2 discontinuations due to AEs (1 during treatment with HCTZ alone [forearm fracture after a fall; participant denied dizziness or lightheadedness at the time of this event and it was considered by the investigator as unrelated to study drug], and the other during canagliflozin + HCTZ treatment [lymphadenopathy]).

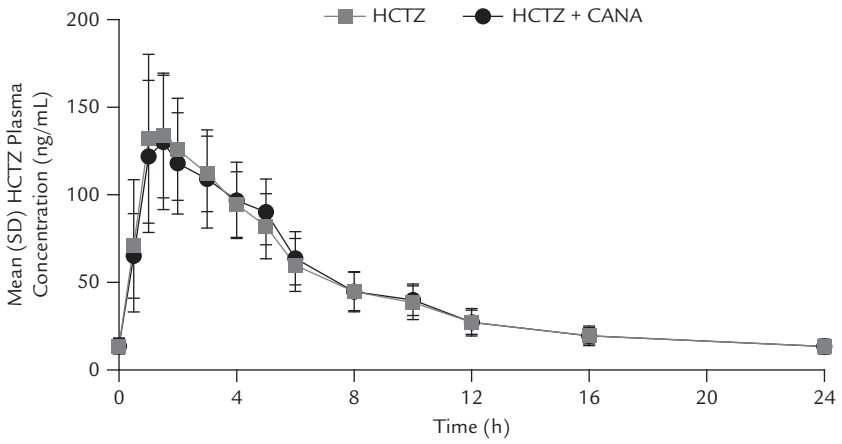

Figure 3. Hydrochlorothiazide (HCTZ) plasma concentration–time profiles following the administration of HCTZ with and without CANA.

Table I. Plasma pharmacokinetic properties of canagliflozin (CANA) and hydrochlorothiazide (HCTZ) alone and in combination.

	Geometric Least Squares Mean			Arithmetic Mean (SD)	
	CANA 300 mg (n = 28)	CANA 300 mg + HCTZ 25 mg (n = 28)	GMR (90% CI)*	CANA 300 mg (n = 30)	CANA 300 mg + HCTZ 25 mg (n = 28)
Canagliflozin					
$AUC_{\tau,ss}$, ng · h/mL	24,896	27,942	1.12 (1.08–1.17)	25,112 (6071)	28,552 (6016)
$C_{max,ss}$, ng/mL	3787	4350	1.15 (1.06–1.25)	3820 (767)	4490 (1143)
$t_{max,ss}$, h	—	—	—	1.00 (1.00–1.50)†	1.00 (0.62–2.00)†
HCTZ					
$AUC_{\tau,ss}$, ng · h/mL	1055	1049	0.99 (0.95–1.04)	1056 (184)	1068 (208)
$C_{max,ss}$, ng/mL	151	141	0.94 (0.87–1.01)	154 (33.6)	144 (32.1)
$t_{max,ss}$, h	—	—	—	1.50 (0.50–3.00)†	1.50 (0.62–5.00)†

GMR = geometric mean ratio; $AUC_{\tau,ss}$ = AUC during a dosing interval (τ) at steady state; $C_{max,ss}$ = C_{max} during a dosing interval during steady state; $t_{max,ss}$ = time to $C_{max,ss}$.
*GMR and 90% CI for CANA + HCTZ relative to CANA alone or HCTZ alone.
†For $t_{max,ss}$, arithmetic mean (range) is provided.

There were no reports of hypoglycemia. Pollakiuria was reported in 2 participants (both during treatment with HCTZ alone); 1 participant had an AE related to volume depletion (orthostatic hypotension, reported during canagliflozin + HCTZ treatment). Five participants reported rash during treatment with canagliflozin alone (all episodes were localized and mild in severity). Three participants reported mild, localized fungal infection of the skin during treatment with canagliflozin alone. There were 2 reports of

Table II. Pharmacodynamic properties of canagliflozin (CANA) alone and in combination with hydrochlorothiazide (HCTZ).

	Geometric Least Squares Mean		
	CANA 300 mg (n = 28)	CANA 300 mg + HCTZ 25 mg (n = 28)	GMR (90% CI)*
24-h mean RT_G			
mmol/L	3.22	3.48	1.08 (1.05–1.11)
mg/dL	58.0	62.6	
$UGE_{0-24\ h}$, g†	42.34	41.34	−1.00 (−3.09–1.09)‡
$MPG_{0-24\ h}$			
mmol/L	5.16	5.46	1.06 (1.04–1.07)
mg/dL	93.0	98.2	

GMR = geometric mean ratio; $MPG_{0-24\ h}$ = mean plasma glucose during 24 hours postdose; RT_G = renal threshold for glucose excretion; $UGE_{0-24\ h}$ = urinary glucose excretion during 24 hours postdose.
*GMR and 90% CI for CANA + HCTZ relative to CANA alone.
†Values are least squares mean.
‡Difference in least squares means between CANA + HCTZ relative to CANA alone.

syncope that occurred during coadministration of canagliflozin + HCTZ, both mild in severity; 1 of the events was considered by the investigator as doubtfully related to study drugs, and the other event was considered possibly related to study drugs. All AEs resolved by the end-of-study visit or last follow-up visit.

Laboratory Parameters

Mean serum sodium, potassium, and chloride concentrations were relatively unchanged during treatment with canagliflozin alone and were slightly decreased during administration of HCTZ alone and of canagliflozin + HCTZ (Table III). Mean serum urate and bicarbonate concentrations were decreased with canagliflozin alone and increased with HCTZ treatment. Other serum chemistry parameters, including calcium, phosphate, and magnesium concentrations, changed minimally during the study period.

Renal Function

Small increases in serum creatinine were seen with canagliflozin alone and with canagliflozin coadministered with HCTZ, and increases in BUN were observed during each treatment period (Table III); serum creatinine and BUN returned to baseline levels by the end-of-study visit. No notable changes in measured creatinine clearance were observed after any treatment (Table IV).

The change from baseline in mean 24-hour urine volume was ~+0.4 L with HCTZ alone and with coadministration with canagliflozin, and was −0.1 L with canagliflozin alone (Table IV). Changes from baseline in urine pH during treatment with canagliflozin alone, HCTZ alone, and coadministration of canagliflozin + HCTZ were +0.5, +1.7, and +0.7, respectively. During treatment with canagliflozin alone, HCTZ alone, and canagliflozin + HCTZ, changes from baseline in the amount of urinary sodium excretion were +3.6, −8.9, and −24.8 mmol/24 h, respectively; changes in FE_{sodium} were +0.02%, −0.04%, and −0.09%, respectively. Changes from baseline in the 24-hour excretion of potassium were +2.4, +17.5, and +3.7 mmol/24 h during treatment with canagliflozin alone, HCTZ alone, and canagliflozin + HCTZ, respectively, with changes in

Table III. Summary of serum laboratory parameters.[*]

	CANA 300 mg (n = 30)		HCTZ 25 mg (n = 29)		CANA 300 mg + HCTZ 25 mg (n = 28)	
Parameter	Baseline, Mean	Δ,[†] Mean (SE)	Baseline, Mean	Δ,[‡] Mean (SE)	Baseline, Mean	Δ,[§] Mean (SE)
Bicarbonate	28.0	−1.3 (0.3)	27.8	+1.9 (0.4)	27.7	+4.1 (0.5)
BUN	5.7	+0.7 (0.1)	5.5	+0.7 (0.1)	5.5	+1.7 (0.2)
Calcium	2.3	0.00 (0.01)	2.4	−0.02 (0.01)	2.4	−0.01 (0.02)
Chloride	101.8	−0.03 (0.27)	101.8	−4.4 (0.4)	101.9	−7.1 (0.4)
Creatinine[‖]	80.4	+2.1 (0.9)	79.2	−0.5 (1.0)	79.1	+5.9 (0.9)
Magnesium	0.8	+0.03 (0.01)	0.8	+0.02 (0.01)	0.8	+0.09 (0.01)
Phosphate	1.2	+0.01 (0.02)	1.2	+0.01 (0.02)	1.2	−0.03 (0.02)
Potassium	4.5	−0.03 (0.06)	4.5	−0.5 (0.1)	4.5	−0.9 (0.1)
Sodium	137.7	−0.3 (0.3)	137.6	−1.7 (0.4)	137.5	−2.1 (0.4)
Urate[‖]	294.4	−76.1 (5.6)	283.7	+57.2 (4.0)	282.7	+2.3 (8.0)

CANA = canagliflozin; HCTZ = hydrochlorothiazide; SE = standard error; BUN = blood urea nitrogen.
[*]Values are mmol/L unless otherwise noted.
[†]Mean change from baseline at day 8 (period 1).
[‡]Mean change from baseline at day 29 (period 2).
[§]Mean change from baseline at day 36 (period 2).
[‖]Values are μmol/L.

Table IV. Summary of renal function parameters.

Parameter	CANA 300 mg			HCTZ 25 mg			CANA 300 mg + HCTZ 25 mg		
	No. of Participants	Baseline, Mean	Δ, Mean (SE)	No. of Participants	Baseline, Mean	Δ, Mean (SE)	No. of Participants	Baseline, Mean	Δ, Mean (SE)
24-h urine volume, L[*]	30	3.0	−0.1 (0.1)	29	2.5	+0.4 (0.1)	28	2.5	+0.4 (0.2)
Urine pH[†]	30	5.5	+0.5 (0.2)	29	5.5	+1.7 (0.1)	28	5.5	+0.7 (0.2)
Measured CrCl, mL/min/1.73 m^2[*,‡]	29	108.8	+1.5 (2.1)	29	108.0	+4.7 (2.1)	28	107.6	−3.8 (2.6)
Urinary analytes									
Calcium, n	29			29			28		
Amount, mmol/24 h		3.4	+0.02 (0.15)		3.6	−1.3 (0.2)		3.5	−1.1 (0.3)
Fractional excretion, %		0.9	+0.00 (0.03)		0.9	−0.3 (0.05)		0.9	−0.3 (0.07)
Chloride, n	29			28			20		
Amount, mmol/24 h		42.9	+2.2 (2.9)		66.4	+3.2 (3.8)		67.1	−12.0 (3.5)
Fractional excretion, %		0.3	+0.02 (0.02)		0.4	+0.03 (0.03)		0.4	−0.01 (0.03)
Magnesium, n	29			29			28		
Amount, mmol/24 h		4.2	−0.2 (0.2)		4.2	+1.0 (0.2)		4.2	+0.1 (0.2)
Fractional excretion, %		3.0	−0.2 (0.1)		3.0	+0.6 (0.1)		3.0	−0.1 (0.1)
Phosphate, n	29			29			28		
Amount, mmol/24 h		30.1	+0.9 (0.9)		29.9	+3.3 (0.9)		29.6	+2.9 (1.0)
Fractional excretion, %		15.4	+0.4 (0.4)		15.4	+1.3 (0.4)		15.4	+3.2 (0.5)
Potassium, n	29			29			28		
Amount, mmol/24 h		74.8	+2.4 (3.0)		74.1	+17.5 (2.3)		73.8	+3.7 (2.7)
Fractional excretion, %		10.0	+0.4 (0.3)		9.9	+3.7 (0.5)		9.9	+4.4 (0.5)
Sodium, n	29			29			28		
Amount, mmol/24 h		45.2	+3.6 (3.5)		77.0	−8.9 (4.4)		77.2	−24.8 (4.7)
Fractional excretion, %		0.2	+0.02 (0.02)		0.3	−0.04 (0.02)		0.3	−0.09 (0.02)

CANA = canagliflozin; CrCl = creatinine clearance; HCTZ = hydrochlorothiazide; SE = standard error.
[*]Baseline is day −1 for all treatment groups.
[†]Baseline is day −2 for all treatment groups.
[‡]Calculated based on 24-hour urine collection in period 1 and period 2.

$FE_{potassium}$ of +0.4%, +3.7%, and +4.4%, respectively. $FE_{calcium}$ was decreased and $FE_{magnesium}$ was increased with HCTZ alone; these FE values did not change with the addition of canagliflozin.

Vital Signs

Overall, small or no changes in systolic/diastolic BP and pulse were observed, and none were considered clinically adverse. In period 1, after canagliflozin treatment alone (on day 7), slight decreases from baseline were observed in mean supine (range, −1.0 to −5.4 mm Hg) and standing (range, −2.5 to −10.7 mm Hg) systolic BP values, and mean supine (range, –0.3 to −4.5 mm Hg) and standing (range, −0.9 to −4.0 mm Hg) diastolic BP values. Mean supine and standing pulse rates showed minimal changes on day 7 of period 1 relative to baseline values. In period 2, after treatment with HCTZ alone (on day 28), mean supine and standing systolic and diastolic BP values were minimally changed relative to baseline values. Mean supine pulse rates also showed minimal changes on day 28 of period 2 compared with baseline, but mean standing pulse rates were slightly increased (range, −1.0 to 9.1 bpm). After further treatment with canagliflozin + HCTZ for 7 days in period 2 (on day 35), mean supine and standing systolic BP values were slightly decreased relative to baseline values (ranges, −0.4 to −3.4 mm Hg and −0.7 to −8.2 mm Hg, respectively). Mean supine diastolic BP showed no notable changes, whereas mean standing diastolic BP was slightly decreased (range, −0.3 to −3.4 mm Hg). Mean supine pulse rates did not notably change, but mean standing pulse rates were increased relative to baseline values (range, 6.5 to 16.1 bpm).

A single event of orthostatic hypotension, as defined by measurement of vital signs (see Methods), occurred during canagliflozin treatment alone in period 1; 5 events of orthostatic hypotension were reported in 4 participants during treatment with HCTZ alone in period 2; and 7 events of orthostatic hypotension were reported in 5 participants during coadministration of canagliflozin + HCTZ.

DISCUSSION

Hypertension affects ~70% of patients with diabetes,[26] so it is likely that some individuals will receive concurrent therapy with canagliflozin and an antihypertensive medication such as HCTZ. A pharmacodynamic interaction between canagliflozin and HCTZ could occur because both target the kidney and have a diuretic effect.[4–6,17,18] In the present study, potential pharmacodynamic interactions as well as the tolerability of canagliflozin coadministered with HCTZ were assessed in healthy adults; pharmacokinetic properties with canagliflozin + HCTZ coadministration were also evaluated.

The 300-mg canagliflozin dose was chosen because this is the maximal dose evaluated in the Phase III program and the maximal dose approved in the United States.[11] HCTZ is effective over the range of 12.5 to 50 mg once daily; therefore, a dose of 25 mg was chosen for this study. Plasma concentrations of canagliflozin were assessed 7 days after initiation of dosing (on day 7 of period 1 and day 35 of period 2) because plasma canagliflozin concentrations have been shown to achieve steady state within 6 days with the 300-mg dose.[27] HCTZ treatment has been associated with a decrease in extracellular fluid volume and thus takes several weeks to achieve steady-state levels.[20] HCTZ was administered alone for 28 days so that acute extracellular volume changes were attenuated. Although a fixed-sequence study design has limitations (ie, potential period and crossover effects), it was used in the current study due to the required 28-day administration of HCTZ in period 2 and to allow for the evaluation of each study drug alone and in combination within the same participant group. The 14-day washout between periods was sufficient because the half-life of canagliflozin is ~12 hours,[11] and in previous studies pharmacodynamic activity of canagliflozin returned to baseline within 5 days after the last dose was administered (unpublished observations, Janssen, 2012).

Coadministration of canagliflozin + HCTZ resulted in ~12% and 15% increases in mean canagliflozin $AUC_{\tau,ss}$ and $C_{max,ss}$, respectively, relative to canagliflozin alone. Plasma canagliflozin concentrations achieved with 300 mg/d were sufficient to provide near-maximal lowering of RT_G throughout the full 24-hour period in patients with T2DM.[28] Furthermore, in other studies, twice-daily doses of canagliflozin 300 mg achieved mean plasma $AUC_{\tau,ss}$ that was ~68% higher than that with the canagliflozin 300-mg once-daily dose + HCTZ in this study (unpublished data, Janssen, 2012), but glycemic efficacy was comparable between canagliflozin 300 mg once- and twice-daily doses in a previous study.[3] Based on the efficacy and tolerability results observed in prior Phase I and II studies[3,25,27,28] and the pharmacodynamic findings presented here, the small increases in canagliflozin $AUC_{\tau,ss}$ and $C_{max,ss}$ when canagliflozin is coadministered with HCTZ are unlikely to be clinically important. Repeated doses of canagliflozin 300 mg/d had minimal effects on the steady-state pharmacokinetic properties of HCTZ.

Values of RT_G are reported to be ~10 to 11 mmol/L (180–200 mg/dL) in healthy participants without any pharmacologic intervention[29–31]; as anticipated based on results from other clinical canagliflozin trials,[12,25,28] mean RT_G was lowered to ~3.3 mmol/L (60 mg/dL) with canagliflozin treatment in the present study. Although plasma canagliflozin levels increased during coadministration with HCTZ, only a slight change in the direct pharmacodynamic effect of canagliflozin (ie, further RT_G lowering) was observed. The difference in RT_G lowering by canagliflozin with and without coadministration with HCTZ was ~0.3 mmol/L (5 mg/dL), and this difference is unlikely to have an impact on the efficacy of canagliflozin. Consistent with this, $UGE_{0–24\ h}$ and 24-hour MPG were generally similar between canagliflozin + HCTZ coadministration and canagliflozin alone in this study.

No unanticipated tolerability concerns were identified during coadministration of canagliflozin + HCTZ. Three cases of fungal infection were reported during treatment with canagliflozin alone, were considered mild, and were resolved by the end-of-study visit. Five cases of rash were reported during treatment with canagliflozin alone, all of which were mild; rash and urticaria were observed with a low prevalence across Phase III studies of canagliflozin.[32] TEAEs related to the diuretic effects of each drug (eg, orthostatic hypotension) were of particular interest, but were not greatly increased in prevalence or severity during combined treatment compared with either drug alone. However, 2 participants experienced syncope during coadministration of canagliflozin + HCTZ; both episodes were mild and reflected volume depletion during combined therapy.

The reductions observed in mean systolic and diastolic BP values (supine and standing) following

canagliflozin treatment for 7 days were generally comparable to placebo-subtracted BP reductions reported in other canagliflozin studies[4,5,7,9,10]; however, these changes may not be entirely attributable to canagliflozin because the present study did not include a placebo control group. HCTZ treatment alone for 1 month led to minimal changes in mean systolic and diastolic BP values (supine and standing), consistent with the effects of HCTZ in normotensive individuals.[33,34] After coadministration of canagliflozin + HCTZ for 7 days, mean standing and supine systolic BP values were slightly lower than baseline values. Of note, the conditions of this study were designed to amplify any potential interactions between canagliflozin and HCTZ related to BP effects. Taken together, findings related to BP and pulse rate during canagliflozin and HCTZ monotherapy periods, and during the combined canagliflozin + HCTZ treatment period, do not suggest any major hemodynamic interactions.

As anticipated, HCTZ treatment alone increased potassium excretion without significant changes in serum potassium levels. Coadministration of canagliflozin + HCTZ led to a slight increase in potassium excretion and had little effect on serum potassium compared with HCTZ treatment alone. Unexpectedly, sodium excretion was relatively unchanged with either canagliflozin or HCTZ administered alone, which may be related to low sodium content in the diet or to an underlying low baseline sodium excretion. Coadministration of canagliflozin + HCTZ resulted in a greater increase in sodium excretion. Serum sodium and potassium levels were unchanged with canagliflozin treatment alone, and both were slightly decreased after treatment with HCTZ alone, as expected based on the known effects of HCTZ.[35] Even though FE_{sodium} increased with the coadministration of canagliflozin + HCTZ, the combined treatment did not appear to influence serum sodium and potassium levels beyond those observed with HCTZ alone. Serum urate was markedly decreased with canagliflozin alone and increased with HCTZ alone, consistent with the known effect of HCTZ to inhibit uric acid excretion. The observed changes from baseline in 24-hour creatinine clearance or serum creatinine were minimal after any treatment and are not expected to have a clinical impact. Increases in BUN seen in each period were reflective of the independent effects of each drug. Mean daily urine volumes, mean urinary sodium excretion, and FE_{sodium} were only slightly affected by treatment with canagliflozin, HCTZ, or the combination. HCTZ alone increased $FE_{potassium}$ and $FE_{magnesium}$ and decreased $FE_{calcium}$, consistent with the known effects of thiazides on these electrolytes[36,37]; however, the total and fractional excretion of these electrolytes were largely unaffected by the addition of canagliflozin to HCTZ.

A limitation of this study was that it was conducted in healthy participants and not in patients with T2DM, the intended treatment population. Although data describing the combined effects of canagliflozin and diuretics in patients with T2DM have not been published, unpublished data from Phase III studies of canagliflozin describing findings in patients with T2DM who were taking both canagliflozin and diuretics are described to provide context. Changes from baseline in systolic BP and the prevalence of AEs related to volume depletion have been evaluated in patients with T2DM using pooled data from patients enrolled in Phase III studies of canagliflozin who were on background therapy with a diuretic (eg, thiazides, furosemide). In a pooled, placebo-controlled population (N = 4158), reductions in systolic BP observed with canagliflozin relative to placebo were not notably different between subgroups of patients who were on (35.9%) or not on (64.1%) diuretics at baseline (unpublished data, Janssen, 2012). Among patients on diuretics (35.2%) in a larger pooled population (N = 9439), which included more patients with comorbidities such as cardiovascular and renal disease compared with the placebo-controlled population, those who received canagliflozin had a higher incidence of volume-depletion AEs (eg, orthostatic hypotension, postural dizziness) compared with those who received control (2.7%, 5.4%, and 2.1% with canagliflozin 100 and 300 mg and controls, respectively) (unpublished data, Janssen, 2012). The increased risk for volume-depletion AEs was primarily noted with canagliflozin 300 mg relative to canagliflozin 100 mg and controls in patients on loop diuretics (eg, furosemide; 8.8%, 3.2%, and 4.7%, respectively)[32]; a smaller increase in the incidence of volume-depletion AEs was observed with canagliflozin versus controls in patients on nonloop diuretics, such as thiazide diuretics (2.6%, 4.4%, and 1.4% for canagliflozin 100 and 300 mg and controls, respectively) (unpublished data, Janssen, 2012). These results from Phase III studies are generally consistent with findings from the present study demonstrating no notable interactions between canagliflozin and HCTZ.

CONCLUSION

This study in healthy participants showed that coadministration of canagliflozin + HCTZ had no notable pharmacokinetic or pharmacodynamic interactions, and there was no evidence of any unexpected drug–drug interactions based on clinical laboratory or other tolerability end points.

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Dr. Devineni, Ms. Vaccaro, Dr. Polidori, Ms. Rusch, and Dr. Wajs participated in the research and design of the manuscript. Ms. Vaccaro, Dr. Polidori, Ms. Rusch, and Dr. Wajs performed the data analysis. Dr. Devineni, Ms. Vaccaro, Dr. Polidori, Ms. Rusch, and Dr. Wajs wrote or contributed to the writing of the manuscript.

CONFLICTS OF INTEREST

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