

Bioequivalence of Canagliflozin/Metformin Immediate Release Fixed-Dose Combination Tablets Compared with Concomitant Administration of Single Components of Canagliflozin and Metformin in Healthy Fed Participants

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Abstract

Background: A fixed-dose combination (FDC) tablet formulation of canagliflozin, a selective inhibitor of sodium glucose co-transporter 2 (SGLT2), and metformin can potentially provide complimentary mechanism of action to improve glycemic control in adults with type 2 diabetes mellitus.

Objectives: To assess the bioequivalence of immediate release (IR) FDC tablets containing canagliflozin and metformin relative to co-administration of individual tablets of IR canagliflozin and metformin in healthy fed participants.

Methods: The six studies were randomized, open-label, single-center, single-dose, 2-treatment, 2-period crossover trials conducted in healthy male and female participants under fed conditions. Pharmacokinetics of canagliflozin and metformin were investigated following administration of 2 canagliflozin/metformin IR FDC tablets (test) at 50 mg/500 mg, 50 mg/850 mg, 50 mg/1,000 mg, 150 mg/500 mg, 150 mg/850 mg, or 150 mg/1,000 mg compared with co-administration of equivalent doses of single-component IR tablets (reference).

Results: Across the six studies, a total of 64 to 83 participants were randomized to each treatment sequence and 57 to 68 were analyzed. The median t_{max} , mean $t_{1/2}$, and mean plasma canagliflozin and metformin concentration-time profiles were similar after administration of IR FDC and individual components. Bioequivalence criteria for the FDC with respect to $AUC_{0-\infty}$, AUC_{last} , and C_{max} of both canagliflozin and metformin met the 90% CI for the test-to-reference geometric mean ratios of these parameters and were contained within the bioequivalence limits of 80% to 125%. Both treatments were well-tolerated with similar adverse events and the most common were gastrointestinal events generally attributed to metformin.

Conclusions: When administered as IR FDC tablets or individual component IR tablets, the pharmacokinetics of canagliflozin and metformin across six dose levels were bioequivalent and were well-tolerated.

Keywords: Bioequivalence; Canagliflozin; Metformin; Fixed-dose combination; Pharmacokinetics

Abbreviations: FDC: fixed-dose combination; SGLT2: sodium glucose co-transporter 2; IR: immediate release; AUC_{∞} : area under the plasma concentration-time curve from time 0 to infinite time; AUC_{last} : area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max} : maximum observed plasma concentration; t_{max} : maximum observed plasma concentration; $t_{1/2}$: terminal elimination half-life; CI: confidence interval; CV: coefficient of variation; GMR: geometric mean ratio; T2DM: type 2 diabetes mellitus; QD: once daily; DPP-4: dipeptidyl peptidase-4 inhibitors; PPAR: peroxisome proliferator-activated receptor agonists; K2EDTA: dipotassium ethylenediaminetetraacetic acid; LC-MS/MS: liquid chromatography-tandem mass spectrometry; MRM: multiple reaction monitoring; IS: internal standard; ISR: incurred sample reproducibility; BMI: body mass index; TEAE: treatment-emergent adverse event; ECG: electrocardiograms

Introduction

Type 2 diabetes mellitus (T2DM) is the most prevalent metabolic disease worldwide. Inadequate management and control of hyperglycemia in patients with T2DM may lead to risk of developing complications over long term due to chronic and progressive nature of the disease arising from pathophysiology of beta-cell dysfunction,

insulin resistance and increased hepatic glucose output. Patients with T2DM often require a combination of therapeutic agents in order to achieve glycemic control over the long term [1-5]. Recent position statement by the American Diabetes Association and the European Association for the Study of Diabetes has recommended that for patients who are inadequately controlled with metformin, additional antihyperglycemic agents be used that have complimentary mechanisms of action [2].

Metformin is the most commonly prescribed oral antidiabetic agent recommended as a first-line therapy in management of T2DM whose

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hyperglycemia is not satisfactorily managed by diet alone. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization [6,7]. Metformin immediate release (IR) tablets are available at 500, 850, and 1,000 mg strengths of metformin hydrochloride (HCl) and are administered 2 or 3 times daily up to a maximum recommended daily dose of 2,550 mg in adults [8,9].

Canagliflozin (Invokana[®]; Janssen Pharmaceuticals, Inc.) belongs to a novel class of orally active inhibitors of renal sodium glucose co-transporter 2 (SGLT2) that decrease extent of glucose reabsorption from the proximal tubules of the kidney, thereby increasing urinary glucose excretion (UGE) and decreasing plasma glucose levels in patients with hyperglycemia [10-20]. Canagliflozin is approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in numerous countries worldwide. The recommended dose of canagliflozin is 100 or 300 mg once daily (QD) [21-23].

Canagliflozin's novel and distinct mechanism of action from other classes of oral antidiabetic agents such as dipeptidyl peptidase-4 inhibitors (DPP-4), sulfonylureas, and peroxisome proliferator-activated receptor agonists (PPAR) makes canagliflozin an ideal candidate for add-on combination therapy with metformin and other antidiabetic agents. In Phase 3 studies of canagliflozin (100 and 300 mg QD) in participants with T2DM who were inadequately controlled with metformin monotherapy, or dual therapy with metformin plus sulphonylurea, or metformin plus pioglitazone, the addition of canagliflozin significantly improved glycemic control and was associated with a low incidence of hypoglycaemia and clinically meaningful weight loss at all doses [24-26].

A combined formulation consisting of both metformin and canagliflozin in a single tablet would potentially offer increased patient convenience and subsequent potential for increased therapy compliance [27,28]. Vokanamet[™] (Janssen Pharmaceuticals, Inc.) is an immediate release (IR) fixed-dose combination (FDC) tablet of canagliflozin (50 or 150 mg) and metformin (500, 850, or 1,000 mg) that has received regulatory approval in the European Union for the treatment of adults with T2DM to improve glycemic control in patients not adequately controlled on their maximally tolerated doses of metformin alone or combined with other glucose lowering medicinal products including insulin, and patients already treated with combination of canagliflozin and metformin as separate IR tablets [29].

Differences in the formulation of a fixed-dose combination (FDC) tablet relative to individual tablets may affect performance of the FDC tablet in the gastrointestinal tract and hence influence bioavailability of its components [30]. Six dose strengths of canagliflozin/metformin IR FDC tablets consisting of canagliflozin at 50 or 150 mg and metformin at 500, 850, or 1,000 mg were evaluated in six separate single-dose Phase 1 bioequivalence studies. The studies evaluated bioequivalence of canagliflozin/metformin IR FDC tablets compared to co-administration of canagliflozin and metformin individual single-component IR tablets in healthy fed participants. The FDC tablets at different dose strengths were based on the same qualitative composition and the same manufacturing process.

Participants and Methods

Study population

Men and women with a minimum age of 18 (or 19 in Studies 1, 2, 6; minimum age of consent for the research center) to 55 years who were considered healthy based on medical history, physical

examination, and clinical laboratory evaluations, were enrolled in these studies. Participants had a body mass index (BMI) of 18.5 to 30 kg/m², a body weight \geq 50 kg, and blood pressure between 90 and 140 mmHg. Pregnant or breast feeding women were excluded from the study. Participants with history of drug or alcohol abuse were excluded. Participants refrained from taking any over-the-counter or prescription medications (with the exception of acetaminophen, oral contraceptives, and hormonal replacement therapy) for at least 14 days prior to first drug administration and throughout the study.

The protocol for each of the studies was approved by an Institutional Review Board at each study site. The studies were conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the protocol. All participants provided written informed consent to participate in the studies.

Study design

All six studies were randomized, open-label, single-center, single-dose, 2-treatment, 2-period crossover trials consisting of 3 phases: a screening phase of approximately 3 weeks (day-22 through day-2); a treatment phase up to 20 days (including a washout period of 10 to 15 days between day 1 of each of treatment period), and a follow-up phase 7-10 days after day 4 of period 2 or at early withdrawal. The total planned duration of the study for each participant was approximately 7 weeks.

During the treatment phase, eligible participants were admitted to the clinical research center on day-1 of each treatment period. On day 1 of treatment period 1, all participants were randomized (1:1) to receive either Treatment A in period 1, followed by Treatment B in period 2 (sequence AB) or vice versa (sequence BA). For Treatment B (test), participants received 2 tablets of to-be-marketed canagliflozin/metformin IR FDC tablets of 50 mg/500 mg, 50 mg/850 mg, or 50 mg/1,000 mg in Studies 1, 2 and 3, respectively; and 2 tablets of 150 mg/500 mg, 150 mg/850 mg, or 150mg/1,000 mg in Studies 4, 5, and 6, respectively. For Treatment A (reference), participants received equivalent doses of single component tablets of to-be-marketed canagliflozin and metformin IR: 1 canagliflozin tablet of 100 mg (Studies 1, 2, and 3) or 300 mg (Studies 4, 5, and 6), and 2 metformin tablets of 500 mg (Studies 1, 4), 850 mg (Studies 2, 5) or 1,000 mg (Studies 3,6). Metformin IR tablets were supplied as commercially available Glucophage[®] IR tablets sourced from United States [8,9]. (ClinicalTrials.gov identifiers: Study 1: NCT01508195; Study 2: NCT01463774; Study 3: NCT01454622; Study 4: NCT01508182; Study 5: NCT01518712, Study 6: NCT01463228).

Following an overnight fast of at least 10 hours, study drug administration occurred at approximately the same time each morning under fed conditions. Fluids were restricted beginning 1 hour before and lasting until 1 hour after dosing, except for the milk with breakfast and water administered with the study drug. Approximately 30 minutes before study drug administration, participants were given a standardized high-fat breakfast consisting of 2 strips of fried bacon, 2 eggs fried in butter, 4 ounces (120 gram) hash brown potatoes, 2 buttered pieces of white toast, and 240 mL whole milk [30]. Participants were to consume the entire meal in 30 minutes. Study drug was administered 30 minutes after the start of the meal with 240 mL of noncarbonated water. Study drug was to be swallowed whole. No additional food was allowed for at least 4 hours postdose.

Pharmacokinetic evaluations

Sample collection: Venous blood samples (2 mL for canagliflozin and 2 mL for metformin) for determination of canagliflozin and metformin plasma concentrations were collected at predose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48 (canagliflozin only) and 72 (canagliflozin only) hours postdose on day 1 of each treatment period (for all studies) through an indwelling catheter into collection tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) as anticoagulant. The samples were centrifuged at room temperature (10 minutes at 1,300 g) to obtain plasma. All plasma samples were stored at or below $-20^{\circ}C$ until transferred to a bioanalytical facility.

Analytical methods: K_2EDTA plasma canagliflozin concentrations were determined with $^{13}C_6$ -canagliflozin as internal standard (IS) using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method at PRA (Assen, The Netherlands). The HPLC system consisted of a Shimadzu LC-10Advp pump (PRA) with Shimadzu SIL-HTC autosampler (Shimadzu Corporation, Japan). An API4000 mass spectrometer with a Turbo-IonsprayTM Interface (AB SCIEX, MA, USA) in the positive ion mode was used for MS determination. Multiple reaction monitoring (MRM) transitions were m/z 462.1 \rightarrow 267.0 and 468.1 \rightarrow 273.0 for canagliflozin and IS, respectively. The method for canagliflozin plasma determination used a liquid-liquid extraction with tert-butylmethylether, followed by chromatography with 30% ammonium acetate (0.01 M) and 70% methanol as the mobile phase. The flow rate was 0.25 mL/min on a Waters XBridgeTMC18 column (5 cmx2.1 mm, 3.5- μ m particle size), kept at $30^{\circ}C$. The validated quantification range was 5.0 to 5,000 ng/mL.

K_2EDTA plasma metformin concentrations were determined with 2H_6 -metformin as IS. The same LC-MS/MS system as for the canagliflozin assay was used, but with an API3000 mass spectrometer, also in the positive ion mode. MRM transitions were m/z 130.1 \rightarrow 70.9 and 136.0 \rightarrow 77.0 for metformin and metformin IS, respectively. The sample preparation consisted of a protein precipitation with acidic (formic acid) acetonitrile, followed by gradient ion-pair chromatography with 0.02M hexafluorobutyric acid in 0.01M ammonium acetate (A) and acetonitrile (B), from 5% to 27.5 % B in 3 minutes. The flow rate was 0.3 mL/min over a Waters XBridgeTM Shield RP18 column (5 cmx2.1 mm, 3.5- μ m particle size), kept at $40^{\circ}C$. The validated quantification range was 5.0 to 2,500 ng/mL.

The validation was performed according to Food and Drug Administration (FDA) guidance for bioanalysis [31,32]. This included within- and between-run precision and accuracy, selectivity, matrix effect, recovery, incurred sample reproducibility (ISR) and stability (blood, plasma, processed sample). All validation results were within predefined acceptance criteria. The storage period between sample collection and analysis was covered by the available long-term stability data for the analytes in the presence of the other analyte (for canagliflozin 762 days and for metformin 190 days at $-20^{\circ}C$).

Pharmacokinetic analyses: The following plasma pharmacokinetic parameters were determined for canagliflozin and metformin based on the individual subject plasma concentration-time data, using actual sampling times via non-compartmental methods using validated WinNonlin[®] software Version 5.2.1 (Pharsight Corporation, Mountain View, CA): maximum observed plasma concentration (C_{max}), time to reach maximum observed plasma concentration (t_{max}), terminal elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve from time 0 to infinite time (AUC_{∞}), and area under the plasma

concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).

Safety Assessments: In all studies, safety evaluations were based upon the type, incidence, and severity of treatment-emergent adverse events (TEAEs) reported throughout the study, and on clinical laboratory tests, vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECG) assessed at pre-defined time points.

Statistical analyses

Sample size: In all studies, the intra-participant coefficient of variation (CV) of AUC_{last} , AUC_{∞} , and C_{max} was estimated to be $\leq 23\%$. Using an estimated intra-participant CV of 23% and a 5% level of significance, a sample size of 56 participants was considered to be sufficient to conclude bioequivalence between 2 FDC tablets and the individual components at equal doses with an overall power of 80% (90% power for the individual components), when the true ratio of the treatment means equalled 91% or 110%. For each study, planned enrollment was 64 participants with the option of enrolling additional participants if needed to ensure that at least 56 participants completed the study.

Statistical comparison: The primary pharmacokinetic parameters of interest for the statistical analysis were the log-transformed canagliflozin and metformin AUC_{∞} , AUC_{last} and C_{max} values.

Only the data from participants who completed all required open-label assessments, up to and including day 4 of treatment period 2, were included in the statistical analysis. If one of the pharmacokinetic parameters of interest was not estimable for a given participant in one or more periods, that participant's data was not included in the statistical analysis of that particular pharmacokinetic parameter.

A mixed-effect analysis of variance model that included treatment, period, and treatment sequence as fixed effects, and participant as a random effect, was used to estimate the least squares means and intra-participant variance. Using these estimated least squares means and intra-participant variance, the point estimates and 90% confidence intervals (CIs) for the difference in means on a log scale between Treatment B (test) and A (reference) were constructed. The limits of the CIs were retransformed using antilogarithms to obtain the 90% CIs for the ratios of the geometric mean AUC_{∞} , AUC_{last} , and C_{max} of the test to reference treatments (B/A). Treatment A (reference) and B (test) were considered to be bioequivalent if the 90% CIs for the ratio of geometric means for all primary parameters (AUC_{∞} , AUC_{last} , and C_{max}) fell entirely within 80% to 125%.

In all studies, TEAEs were summarized by treatment within each body system and for each preferred term. Results of clinical laboratory tests, vital signs, and ECG parameters were summarized using descriptive statistics.

Results

Study disposition and demographics

The demographic and baseline characteristics were generally similar for all enrolled participants across the six studies (Table 1). The mean age of participants ranged from 32.9 to 37.8 years and the majority were white (80% to 97%) and male (47% to 66%). Mean baseline body weight ranged from 72.6 to 75.4 kg, and BMI from 25.2 to 26.1 kg/m².

The study completion and early withdrawal information across the six studies are summarized in Table 2. Study withdrawal due to TEAEs

Table 1: Demographic and baseline characteristics.

Characteristic	Study 1 (N=64)	Study 2 (N=74)	Study 3 (N=64)	Study 4 (N=64)	Study 5 (N=64)	Study 6 (N=83)
Age (years)						
Mean (SD)	34.7 (11.8)	32.9 (10.9)	36.6 (8.4)	36.0 (10.4)	37.8 (8.1)	34.2 (11.4)
Range	(19;54)	(19;55)	(19;54)	(18;54)	(21;55)	(20;55)
Sex, n (%)						
Female	27 (42)	31 (42)	22 (34)	27 (42)	28 (44)	44 (53)
Male	37 (58)	43 (58)	42 (66)	37 (58)	36 (56)	39 (47)
Race, n (%)						
White	59 (92)	59 (80)	61 (95)	61 (95)	62 (97)	70 (84)
Black or African American	4 (6)	10 (14)	3 (5)	2 (3)	1 (2)	11 (13)
Other	1 (2)	5 (7)	0	1 (2)	1 (2)	2 (2)
Weight (kg)						
Mean (SD)	75.3 (12.7)	75.2 (11.6)	73.1 (11.2)	72.7 (11.5)	72.6 (11.2)	75.4 (11.7)
Range	(54;106)	(54;103)	(52;106)	(50;95)	(52;97)	(54;104)
Height (cm)						
Mean (SD)	172.4 (9.6)	172.1 (9.8)	167.9 (10.1)	167.4 (9.8)	166.4 (8.7)	171.5 (9.0)
Range	(153;190)	(152;196)	(149;192)	(151;191)	(151;184)	(148;191)
BMI (kg/m²)						
Mean (SD)	25.2 (2.5)	25.3 (2.7)	25.9 (2.7)	25.8 (2.4)	26.1 (2.8)	25.5 (2.5)
Range	(21;30)	(19;30)	(20;30)	(21;30)	(20;30)	(20;30)

Note: In each study, participants received 2 canagliflozin/metformin IR FDC tablets or equivalent doses of canagliflozin and metformin as individual component IR tablets. BMI = body mass index; N = total sample size; n = size of subsample; SD = standard deviation; IR = immediate release; FDC = fixed-dose combination.

Table 2: Study completion/early withdrawal information and summary of most commonly reported treatment-emergent adverse events.

	Study 1 (N=64)	Study 2 (N=74)	Study 3 (N=64)	Study 4 (N=64)	Study 5 (N=64)	Study 6 (N=83)
Completion/withdrawal						
Enrolled, n (%)	64 (100)	74 (100)	64 (100)	64 (100)	64 (100)	83 (100)
Completed, n (%)	59 (92.2)	62 (83.8)	58 (90.6)	60 (93.8)	61 (95.3)	62 (74.7)
Withdrawn, n (%)	5 (7.8)	12 (16.2)	6 (9.4)	4 (6.3)	3 (4.7)	21 (25.3)
Adverse event	1 (1.6)	4 (5.4)	6 (9.4)	1 (1.6)	2 (3.1)	9 (10.8)
Withdrawal of consent	-	-	-	1 (1.6)	-	3 (3.6)
Other	4 (6.3)	8 (10.8)	-	3 (4.7)	1 (1.6)	9 (10.8)
Most common TEAEs						
Any adverse event, n (%)	35 (54.7)	48 (64.9)	35 (54.7)	33 (51.6)	44 (68.8)	60 (72.3)
Gastrointestinal disorders, n (%)	26 (40.6)	41 (55.4)	27 (42.2)	19 (29.7)	35 (54.7)	53 (63.9)
Diarrhea	16 (25.0)	28 (37.8)	22 (34.4)	13 (20.3)	28 (43.8)	29 (34.9)
Nausea	11 (17.2)	21 (28.4)	14 (21.9)	7 (10.9)	13 (20.3)	27 (32.5)
Nervous system disorders, n (%)	16 (25.0)	16 (21.6)	9 (14.1)	15 (23.4)	19 (29.7)	23 (27.7)
Headache	13 (20.3)	14 (18.9)	7 (10.9)	8 (12.5)	15 (23.4)	14 (16.9)

Note: Total treatment dose of canagliflozin and metformin administered as 2 IR FDC tablets or coadministered as single-component canagliflozin and metformin: 100 mg CANA, 1000 mg MET (Study 1); 100 mg CANA, 1700 mg MET (Study 2); 100 mg CANA, 2000 mg MET (Study 3); 300 mg CANA, 1000 mg MET (Study 4); 300 mg CANA, 1700 mg MET (Study 5); 300 mg CANA, 2000 mg MET (Study 6); IR = immediate release; FDC = fixed-dose combination; CANA = canagliflozin; MET = metformin; TEAE = treatment-emergent adverse events; N = total sample size; n = size of subsample.

was relatively infrequent and attributed primarily to vomiting within 8 hours after dosing (a study protocol withdrawal criterion). Withdrawal of consent occurred very infrequently and withdrawal due to other reasons was often attributed to non-compliance and the participant unable to complete the standard high-fat breakfast.

Pharmacokinetic analyses

Canagliflozin: Across the six studies, the canagliflozin pharmacokinetic parameters were generally similar when administered with metformin (Treatment A; reference) or as a FDC formulation (Treatment B, test) (Table 3). The mean plasma canagliflozin concentrations were similar following administration of both treatments across the range of doses (Figures 1 and 2). Median t_{\max} and mean $t_{1/2}$ values for canagliflozin were similar for both treatments (Table 3).

For all six studies, the FDC formulation met the predefined bioequivalence criteria with respect to AUC_{∞} , AUC_{last} , and C_{\max} of canagliflozin as the 90% CI for the test-to-reference geometric mean ratio (GMR) of these parameters were entirely contained within the prespecified bioequivalence limits of 80% to 125%, indicating that bioequivalence criteria for canagliflozin were met in each of the studies (Table 3).

Metformin: Across the six studies, the mean plasma metformin concentration-time profiles were similar after administration of the FDC formulation and the co-administered treatments (Figures 3 and 4). The median t_{\max} and mean $t_{1/2}$ values for metformin after administration were generally similar for both treatments (Table 4).

For all six studies the FDC formulation met the predefined bioequivalence criteria with respect to AUC_{∞} , AUC_{last} , and C_{\max}

Table 3: Summary statistics for geometric means and ratio of geometric means with corresponding 90% confidence intervals for canagliflozin pharmacokinetic parameters following administration of 2 IR FDC tablets (50 or 100 mg canagliflozin/500, 850, or 1,000 mg metformin) compared to coadministration of individual IR canagliflozin (100 or 300 mg) and 2 metformin (500, 850, and 1,000 mg) tablets at equivalent doses.

	Treatment A (Reference)	Treatment B (Test)	Test/Reference
STUDY 1			
Parameter	100 mg CANA + 2 X 500 mg MET IR (n=58)	2 X (50 mg CANA/500 mg MET) IR FDC (n=58)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	722.50	679.01	93.98 (86.10-102.58)
AUC _{last}	8523.60	8561.16	100.44 (98.27-102.66)
AUC _∞ (ng h/mL) ^a	8815.54	8808.21	99.92 (97.68-102.20)
t _{max} (h)	3.00 (0.98 – 12.00) ^b	3.00 (1.00 – 16.00) ^c	
t _{1/2} (h)	13.7 (2.75) ^d	13.7 (2.84) ^e	
STUDY 2			
Parameter	100 mg CANA + 2 X 850 mg MET IR (n=62)	2 X (50 mg CANA/850 mg MET) IR FDC (n=62)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	705.28	740.96	105.06 (97.89 - 112.76)
AUC _{last}	8370.97	8487.99	101.40 (99.73 – 103.10)
AUC _∞ (ng h/mL)	8632.52	8748.88	101.35 (99.62 – 103.10)
t _{max} (h)	3.52 (1.00-10.00) ^f	3.00 (1.00-10.00) ^g	
t _{1/2} (h)	14.4 (3.14) ^f	14.5 (2.89) ^g	
STUDY 3			
Parameter	100 mg CANA + 2 X 1000 mg MET IR (n=57)	2 X (50 mg CANA/1000 mg MET) IR FDC (n=57)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	803.00	775.90	96.62 (89.12-104.77)
AUC _{last}	8609.25	8752.70	101.67 (99.33-104.06)
AUC _∞ (ng h/mL) ^a	8904.71	9078.94	101.96 (99.57-104.40)
t _{max} (h)	4.00 (1.00-10.00)	3.00 (1.00-10.00) ^h	
t _{1/2} (h)	13.92 (2.96) ⁱ	14.47 (3.45) ^c	
STUDY 4			
Parameter	300 mg CANA + 2 X 500 mg MET IR (n=60)	2 X (150 mg CANA/500 mg MET) IR FDC (n=60)	Estimated Ratio, % (90% CI)
C _{max} (ng/mL)	2558.49	2673.78	104.51 (98.47-110.92)
AUC _{last}	27679.43	28125.42	101.61 (99.94-103.31)
AUC _∞ (ng h/mL) ^c	28262.76	28707.97	101.58 (99.84-103.34)
t _{max} (h)	4.00 (1.00-12.00) ^j	3.00 (1.50-10.03) ^b	
t _{1/2} (h)	13.9 (2.49) ^j	14.1 (2.79) ^d	
STUDY 5			
Parameter	300 mg CANA + 2 X 850 mg MET IR (n=61)	2 X (150 mg CANA/850 mg MET) IR FDC (n=61)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	2527.63	2606.24	103.11 (95.91 – 110.86)
AUC _{last}	30037.82	30344.32	101.02 (99.60 – 102.47)
AUC _∞ (ng h/mL) ^h	30852.23	31148.41	100.96 (99.44 – 102.50)
t _{max} (h)	3.00 (1.50-12.02) ^b	3.00 (1.00-12.00) ^d	
t _{1/2} (h)	14.80 (3.08) ^d	14.89 (3.45) ^d	
STUDY 6			

Parameter	300 mg CANA + 2 X 1000 mg MET IR (n=62)	2 X (150 mg CANA/1000 mg MET) IR FDC (n=62)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	2099.09	2225.02	106.00 (97.90-114.77)
AUC _{last}	26960.48	27560.10	102.22 (100.00-104.50)
AUC _∞ (ng h/mL)	27561.67	28234.55	102.44 (100.21-104.72)
t _{max} (h)	4.00 (0.98-24.00) ^q	3.00 (0.98-16.00) ^q	
t _{1/2} (h)	14.29 (2.68) ^k	14.47 (2.88) ^k	

Note: metformin IR tablets supplied as Glucophage® IR tablets. ^an=55; ^bn=63; ^cn=59; ^dn=62; ^en=57; ^fn=66; ^gn=68; ^hn=60; ⁱn=56; ^jn=61; ^kn=67; AUC_{last}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC_∞, area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; C_{max}, maximum observed plasma concentration; n: total number of participants; Ref=reference; t_{1/2} (h), terminal elimination half-time and represented by arithmetic mean (SD); t_{max} (h), time to reach the maximum plasma concentration and reported as median (range).

metformin as the 90% CI for the test-to-reference GMRs of these parameters were entirely contained within the prespecified bioequivalence limits of 80% to 125%, indicating bioequivalence criteria for metformin were met in each of the studies (Table 4).

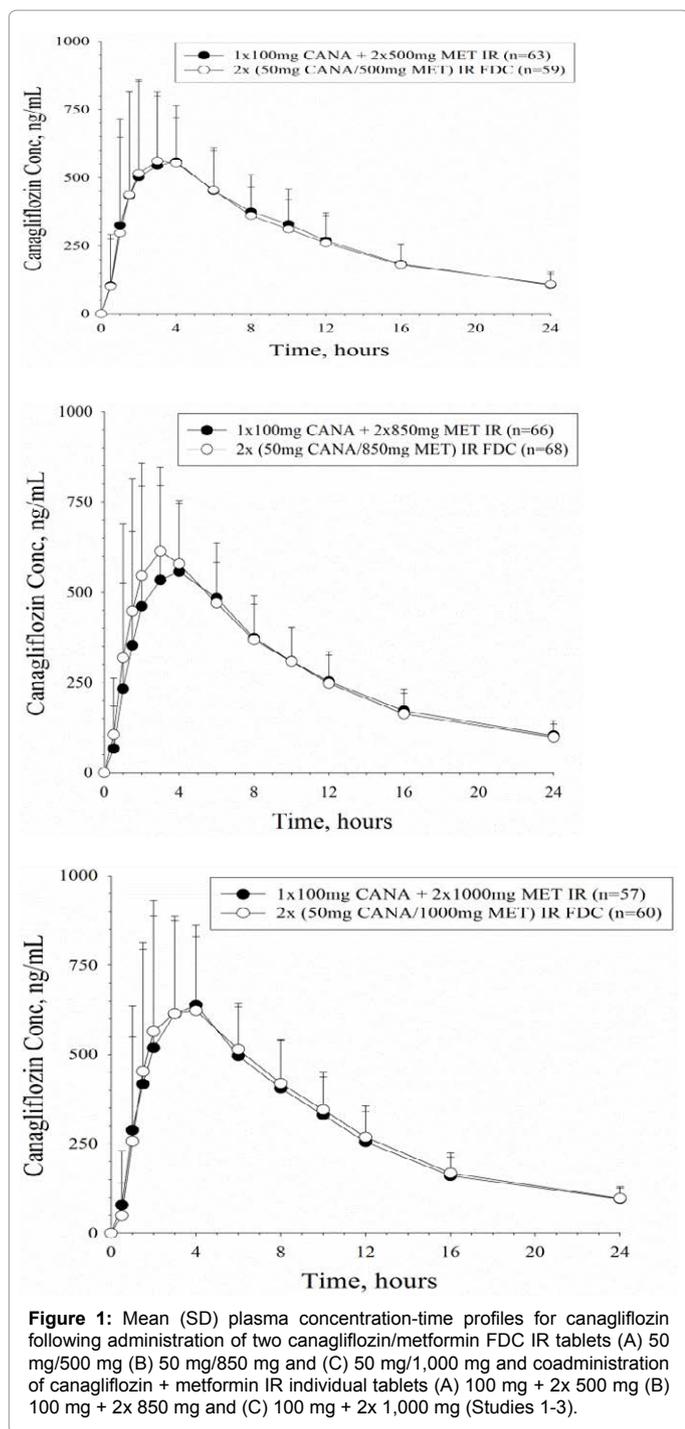
Safety and tolerability: Across the six studies, single doses of canagliflozin and metformin administered as either the FDC treatment or the co-administered treatment were generally well-tolerated, other than gastrointestinal adverse events known to be associated with metformin (Table 2). Almost all gastrointestinal TEAEs were assessed by the investigator as possibly, probably or very likely related to metformin. The incidence, type, and duration of specific TEAEs were generally similar between the two treatment formulations. The majority of the reported TEAEs were mild, transient and resolved by the end of the study, with only one serious TEAE (radiculopathy due to a herniated disc) which was assessed by the investigator as not related to study drug (FDC 300 mg/2,000 mg group). No hypoglycemic events were reported in any of the studies. No deaths were reported.

Overall, the incidence of TEAEs in the studies varied from 51.6% in Study 4 to 72.3% in Study 6. The most commonly reported TEAEs by system organ class (SOC) were gastrointestinal system disorders (incidence ranged from 29.7% in Study 4 to 63.9% in Study 6) and nervous system disorders (incidence ranged from 14.1% in Study 3 to 29.7% in Study 5). The incidence of diarrhea and nausea in the studies where canagliflozin 300 mg dose was administered tended to increase with greater metformin dose. The most commonly reported TEAEs were diarrhea, nausea, and headache. Overall, the incidence of TEAEs in Treatment A was similar to Treatment B.

For all studies, there were no treatment-related mean changes from baseline (day-1) in any of the routine clinical laboratory safety tests (i.e., hematology, chemistry, and urinalysis) that were considered to be clinically significant. There were no consistent treatment-related changes from baseline in mean vital sign measurements (i.e., pulse rate or blood pressure), ECG parameters, or physical examinations.

Discussion

Long-term Phase 3 clinical studies of canagliflozin in patients with T2DM inadequately controlled with metformin, or dual therapy with metformin plus sulphonylurea or metformin plus pioglitazone, have established efficacy of canagliflozin in achieving improvements in fasting plasma glucose and HbA_{1c} reduction with additional weight loss and reduction in blood pressure, with a favorable safety and tolerability profile. In these Phase 3 studies, patients received canagliflozin 100



and 300 mg QD and were on stable metformin therapy at $\geq 2,000$ mg/day or $\geq 1,500$ mg/day if unable to tolerate a higher dose [26,33,34]. In a drug-drug interaction study, healthy participants received single daily oral doses of canagliflozin 300 mg and metformin 2,000 mg, and no clinically meaningful interaction between the pharmacokinetics of either drug was observed suggesting that the two drugs could be combined into a single FDC tablet [35].

The present studies evaluated the bioequivalence of an IR FDC tablet of canagliflozin and metformin as compared to co-administration of individual single-component IR tablets at corresponding doses

in healthy fed participants. The bioequivalence studies used six dose strengths of the IR FDC tablets formulated to contain 50 or 150 mg canagliflozin combined with metformin at 500, 850 or 1,000 mg.

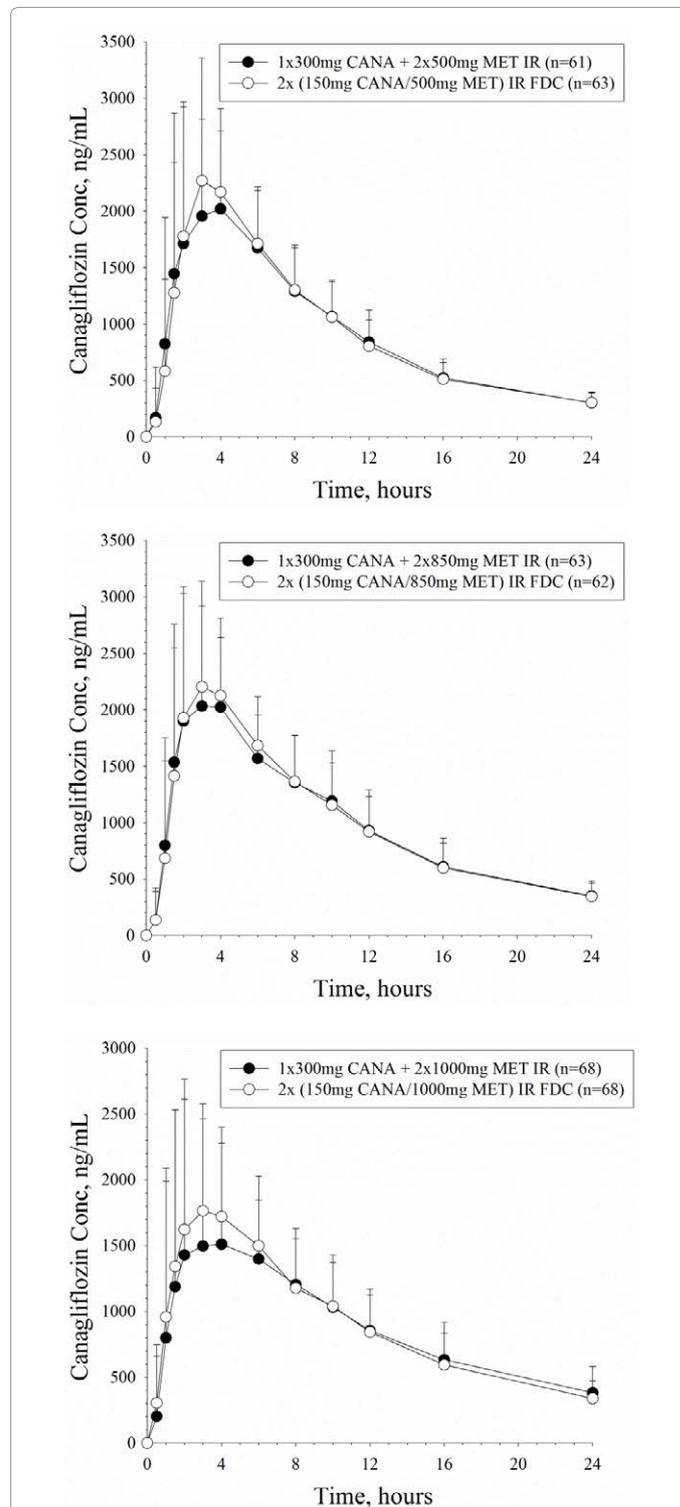
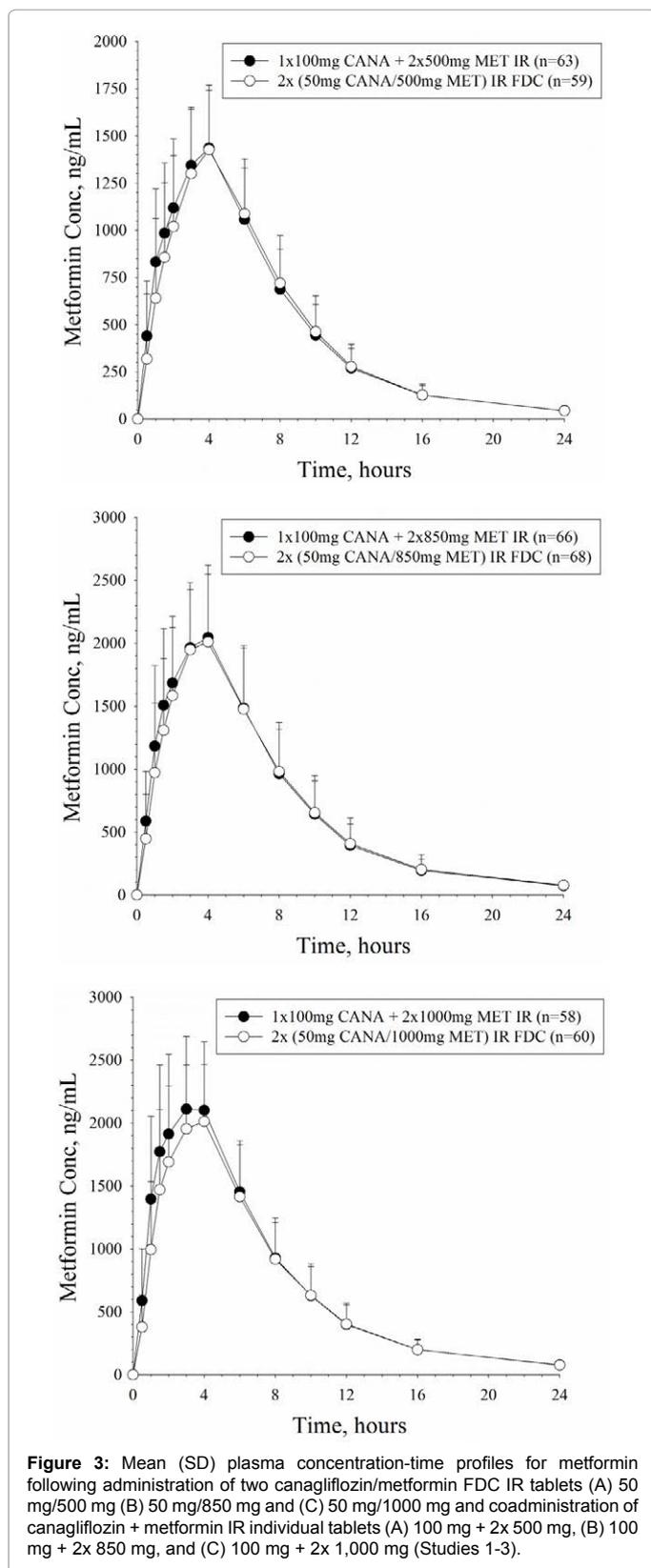


Figure 2: Mean (SD) plasma concentration-time profiles for canagliflozin following administration of two canagliflozin/metformin FDC IR tablets (A) 150 mg/500 mg (B) 150 mg/850 mg and (C) 150 mg/1,000 mg and coadministration of canagliflozin + metformin IR individual tablets (A) 300 mg + 2x 500 mg (B) 300 mg + 2x 850 mg, and (C) 300 mg + 2x 1,000 mg (Studies 4-6).



These studies involved oral administration of single doses of 100 or 300 mg of canagliflozin and 1,000, 1,700 or 2,000 mg metformin HCl (Glucophage®) either as canagliflozin/metformin IR FDC tablets or as

tablets of the individual components. As the to-be-marketed single-agent canagliflozin tablets used as reference treatment are only available in tablet strengths of 100 or 300 mg, two canagliflozin/metformin IR

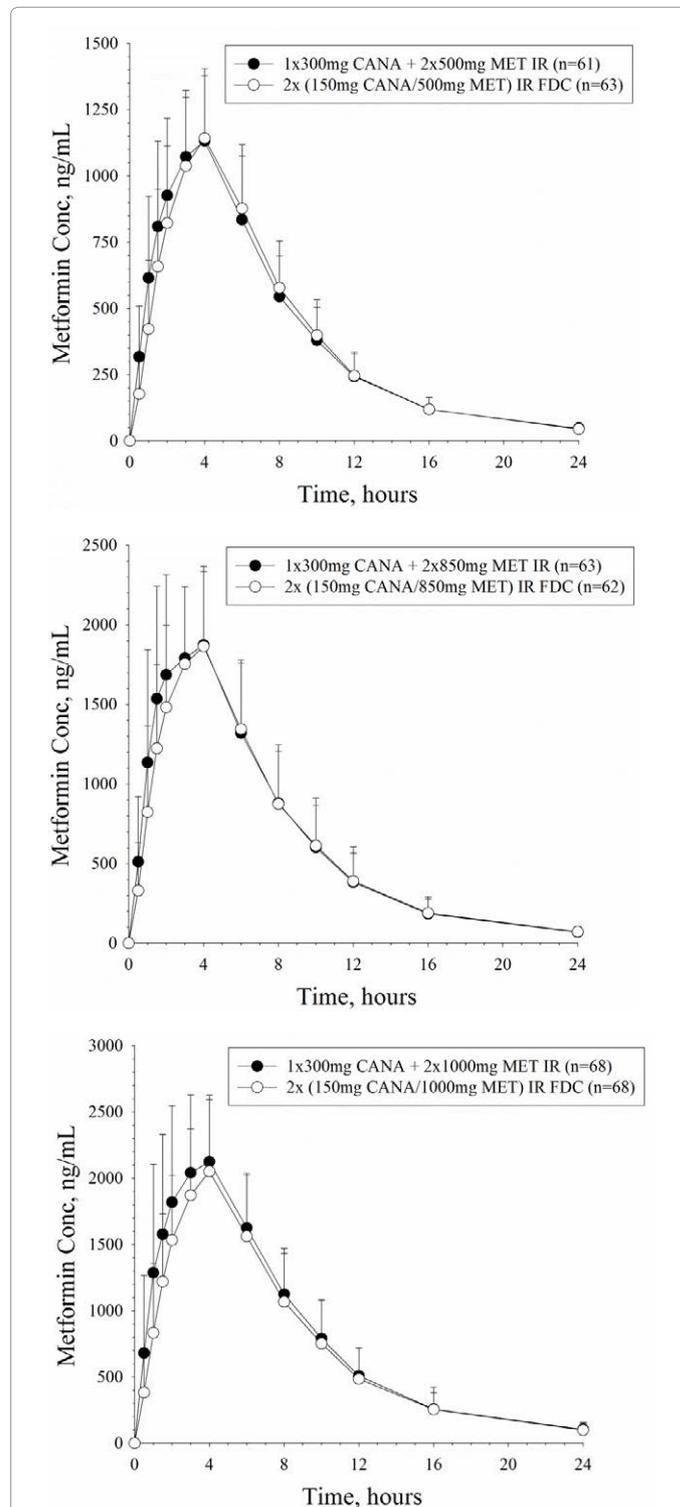


Figure 4: Mean (SD) plasma concentration-time profiles for metformin following administration of two canagliflozin/metformin FDC IR tablets (A) 150 mg/500 mg (B) 150 mg/850 mg and (C) 150 mg/1000 mg and coadministration of canagliflozin + metformin IR individual tablets (A) 300 mg + 2x 500 mg (B) 300 mg + 2x 850 mg and (C) 300 mg + 2x 1,000 mg (Studies 4-6).

Table 4: Summary statistics for geometric means and ratio of geometric means with corresponding 90% confidence intervals for metformin pharmacokinetic parameters following administration of 2 IR FDC tablets (50 or 100 mg canagliflozin/500, 850, or 1,000 mg metformin) compared to coadministration of individual IR canagliflozin (100 or 300 mg) and 2 metformin (500, 850, and 1,000 mg) tablets at equivalent doses.

	Treatment A (Reference)	Treatment B (Test)	Test/Ref
STUDY 1			
Parameter	100 mg CANA + 2 X 500 mg MET IR (n=58)	2 X (50 mg CANA/500 mg MET) IR FDC (n=58)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	1507.20	1471.39	97.62 (94.32-101.05)
AUC _{last}	11436.06	11300.29	98.81 (96.07-101.63)
AUC _∞ (ng·h/mL) ^a	11804.70	11648.74	98.68 (95.80-101.64)
t _{max} (h)	4.00 (0.98 – 6.00) ^b	4.00 (1.00 – 8.00) ^c	
t _{1/2} (h)	4.28 (0.966) ^b	4.13 (0.719)	
STUDY 2			
Parameter	100 mg CANA + 2 X 850 mg MET IR (n=62)	2 X (50 mg CANA/850 mg MET) IR FDC (n=62)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	2181.83	2145.93	98.35 (95.31-101.49)
AUC _{last}	16322.17	16098.88	98.63 (95.85-101.50)
AUC _∞ (ng·h/mL)	16775.23	16602.04	98.97 (96.18-101.84)
t _{max} (h)	4.00 (1.00-6.23) ^d	4.00 (1.50-6.00) ^e	
t _{1/2} (h)	4.54 (0.67) ^d	4.65 (1.13) ^e	
STUDY 3			
Parameter	100 mg CANA + 2 X 1000 mg MET IR (n=58)	2 X (50 mg CANA/1000 mg MET) IR FDC (n=58)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	2274.31	2141.21	94.15 (91.00-97.40)
AUC _{last}	16828.48	15899.55	94.48 (91.90-97.13)
AUC _∞ (ng·h/mL) ^f	17327.58	16447.21	94.92 (92.14-97.78)
t _{max} (h)	3.00 (1.00-6.00)	3.98 (1.50-6.00) ^g	
t _{1/2} (h)	4.68 (1.09) ^f	4.79 (1.09) ^g	
STUDY 4			
Parameter	300 mg CANA + 2 X 500 mg MET IR (n=60)	2 X (150 mg CANA/500 mg MET) IR FDC (n=60)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	1195.92	1178.57	98.55 (94.91-102.33)
AUC _{last}	9292.72	9256.26	99.61 (96.17-103.17)
AUC _∞ (ng·h/mL)	9615.39	9543.12	99.25 (95.74-102.89)
t _{max} (h)	4.00 (0.98-6.03) ^h	4.00 (1.50-7.98) ^b	
t _{1/2} (h)	4.64 (1.17) ^h	4.51 (1.01) ^b	
STUDY 5			
Parameter	300 mg CANA + 2 X 850 mg MET IR (n=61)	2 X (150 mg CANA/850 mg MET) IR FDC (n=61)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	2042.38	1910.31	93.53 (90.00-97.20)
AUC _{last}	15013.95	14537.47	96.83 (93.92-99.83)
AUC _∞ (ng·h/mL) ^c	15614.58	15184.15	97.24 (94.24-100.34)
t _{max} (h)	3.00 (0.98-6.00) ^b	4.00 (0.98-6.00) ⁱ	
t _{1/2} (h)	4.67 (1.08) ^j	4.71 (0.98)	
STUDY 6			
Parameter	300 mg CANA + 2 X 1000 mg MET IR (n=62)	2 X (150 mg CANA/1000 mg MET) IR FDC (n=62)	Estimated Ratio, % (90% CI) (Test/Ref.)
C _{max} (ng/mL)	2309.04	2099.46	90.92 (87.03-94.99)
AUC _{last}	18256.73	16873.75	92.42 (89.42-95.54)
AUC _∞ (ng·h/mL) ^j	19026.61	17471.82	91.83 (88.82-94.93)
t _{max} (h) ^d	4.00 (1.00-6.00) ^e	4.00 (1.00-10.00) ^e	
t _{1/2} (h) ^d	5.01 (0.89) ^d	5.06 (0.90) ^d	

Note: metformin IR tablets supplied as Glucophage® IR tablets. ^an=57; ^bn=63; ^cn=59; ^dn=66; ^en=68; ^fn=56; ^gn=60; ^hn=61; ⁱn=62; ^jn=58; AUC_{last}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC_∞, area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; C_{max}, maximum observed plasma concentration; n: total number of participants; Ref: reference; t_{1/2} (h), terminal elimination half-time and represented by arithmetic mean (SD); t_{max} (h), time to reach the maximum plasma concentration and reported as median (range).

FDC tablets containing 50 or 150 mg canagliflozin were administered to provide these same daily doses.

These bioequivalence studies were conducted under fed conditions because metformin HCl IR is recommended to be taken with meals to reduce the incidence of gastrointestinal side effects [8,9]. In addition, no meaningful effect of food on the pharmacokinetics of canagliflozin was observed when canagliflozin tablet was administered under fed versus fasted conditions [36].

For all doses of canagliflozin and metformin, the 90% CI for the test-to-reference GMR of AUC_∞, AUC_{last}, and C_{max} were close to 100% and entirely contained within the prespecified bioequivalence limits of 80% to 125%. This indicates that the FDC is bioequivalent to co-administration with respect to either canagliflozin or metformin pharmacokinetics with no effects on its rate and extent of absorption as well as its elimination attributed to the formulation performance factors of the FDC tablet. Canagliflozin pharmacokinetics from administration of FDC and co-administration of individual tablets

were consistent with single- and multi-dose pharmacokinetics of canagliflozin alone (50, 100, and 300 mg) in healthy participants and in adults with T2DM that showed C_{max} and AUC increased in a dose-dependent manner across all 3 doses [37,38]. The single-dose pharmacokinetics of metformin observed in the bioequivalent studies are consistent with previously reported studies of metformin alone in healthy participants [39].

The evidence for the efficacy and safety of the canagliflozin/metformin IR FDC for the target indication is primarily derived from six multinational Phase 3 studies which used locally-sourced approved metformin from each country. In the US, the patients with T2DM in Phase 3 pivotal studies received US-sourced Glucophage® or the generic equivalent. In the reported bioequivalence studies, the reference tablets were canagliflozin 100 and 300 mg and metformin was US sourced Glucophage® 500, 850 and 1000 mg tablets, thus providing support for bridging of the safety and efficacy data from prior clinical studies of canagliflozin and metformin co-administered monotherapies to the FDC tablet [25,26,33,34].

The safety findings observed in these studies are consistent with those previously reported for concomitant administration of canagliflozin (300 mg/day) with metformin (2,000 mg/day) in healthy participants in which the incidence of the most prevalent TEAEs (gastrointestinal disorders) were more common with metformin alone as compared with canagliflozin alone [35]. Findings from 52-week canagliflozin Phase 3 clinical studies in T2DM patients demonstrated favorable safety and tolerability of canagliflozin (100 or 300 mg) when administered concomitantly with metformin, metformin plus sulfonylurea, or metformin plus pioglitazone [24-26,33].

Conclusions

The results of six pivotal bioequivalence studies in healthy fed participants demonstrated that the pharmacokinetics of canagliflozin and metformin across six dose levels are bioequivalent, and unaffected by formulation of the two components whether administered as an IR FDC tablet or co-administered as individual component IR tablets. Single doses of the canagliflozin/metformin IR FDC tablet or the individual tablets of canagliflozin and metformin were generally well-tolerated, other than gastrointestinal adverse events known to be associated with metformin. These results provide support for administration of the FDC tablet as an alternative option to co-administration of the individual monotherapies with the added benefits of enhanced patient compliance and convenience.

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