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Original Article

Fed and fasted bioequivalence assessment of two formulations of extended-release fixed-dose combination dapagliflozin/metformin (10/1,000 mg) tablets in healthy subjects

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ABSTRACT

Two open-label, randomized, two-period crossover studies were conducted to investigate the pharmacokinetic (PK) properties, safety, and bioequivalence of the test formulation (KD4004), a new fixed-dose combination (FDC) formulation of dapagliflozin and metformin extended release (XR) tablets, relative to the reference formulation (10 mg dapagliflozin/1,000 mg metformin XR FDC tablet) in healthy subjects under fasting (Part A) and fed (Part B) conditions. After giving the dose, serial blood samples were collected for a period of 48 hours. Primary PK parameters (AUC_{0-t} and C_{max}) were used to assess bioequivalence between two dapagliflozin/metformin XR (10/1,000 mg) FDC formulations under fed and fasting conditions. Safety and tolerability were also evaluated. Part A and Part B were completed by 32 and 37 subjects, respectively. Bioequivalence of the two FDC formulations of dapagliflozin and metformin XR tablets was established in both the fasted and the fed conditions as the 90% confidence interval of the ratios of adjusted geometric means for AUC_{0-t} and C_{max} were contained within the predefined range of 0.800–1.250 bioequivalence criteria. Single-dose administration of dapagliflozin and metformin XR was safe and well tolerated as the two FDC formulations. In conclusion, both FDC formulations of dapagliflozin and metformin XR tablets were bioequivalent in fed and fasted subjects. All treatments were well tolerated.

Trial Registration: Clinical Research Information Service Identifier: KCT0004026

Keywords: Bioequivalence; Fixed-Dose Combination; Dapagliflozin; Metformin Extended Release; Type 2 Diabetes

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Conflict of Interest

- Authors: Nothing to declare
- Reviewers: Nothing to declare
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Author Contributions

Conceptualization: Lee HW; Data curation: Kang WY, Yang DH, Seong SJ; Formal analysis: Lee HW, Seong SJ; Investigation: Kang WY, Lee HW; Methodology: Kang WY, Lee HW, Kim EH; Resources: Gwon MR, Lee JH, Park JS, Park SJ; Supervision: Yoon YR; Writing - original draft: Lee HW, Kang WY; Writing - review & editing: Yoon YR, Seong SJ.

INTRODUCTION

Glycemic management in individuals with type 2 diabetes is crucial for preventing complications and maintaining quality of life [1]. According to current guidelines, lifestyle modification is recommended as well as the use of metformin as the first-line antihyperglycemic agent for the treatment of type 2 diabetes [2]. Metformin works primarily by improving insulin sensitivity in peripheral tissues and inhibiting hepatic gluconeogenesis [3]. Most patients with type 2 diabetes require the addition of add-on therapy to achieve additional glycemic control as their condition progresses overtime [4]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonist, dipeptidyl peptidase-4 inhibitors, thiazolidinedione, sulfonylureas, and basal insulin are the second-line drug alternatives added to metformin monotherapy [2,5].

Dapagliflozin, a SGLT2 inhibitor, lowers blood glucose by inhibiting SGLT2 from reabsorbing glucose in the renal proximal tubule, which leads to glycosuria, resulting in the decrease in plasma glucose levels [6,7]. This drug improves glycemic control independent of insulin, with a low risk of hypoglycemia [7,8]. Dapagliflozin has other beneficial effects, which include body weight loss, natriuresis, and blood pressure reduction [3,7,8].

Because metformin and dapagliflozin have complementary mechanisms of action in the liver and in the kidneys, respectively, a combination therapy with metformin and dapagliflozin may benefit patients with type 2 diabetes, with a low risk of hypoglycemia [9]. Because there is no pharmacokinetic (PK) interaction between dapagliflozin and metformin and the combination is well tolerated, dapagliflozin can be safely coadministered with metformin without a dose adjustment of either medication [10]. In two randomized, double-blind, three-arm 24-week trials comparing dapagliflozin plus metformin, dapagliflozin alone, and metformin alone in treatment-naive individuals, a combination therapy significantly decreased the levels of HbA1c compared to either monotherapy [11]. The addition of dapagliflozin to the treatment regimen of patients with type 2 diabetes whose condition was poorly controlled by metformin alone significantly improved glycemic control, according to the findings of a randomized, double-blind, placebo-controlled study [12]. Compared to dapagliflozin or metformin monotherapy, dapagliflozin and metformin combination therapy showed more significant improvements in any of the components of the metabolic syndrome [13].

Dapagliflozin and metformin in a fixed-dose combination (FDC) formulation may require fewer pills to be taken by the patient, reduce the frequency of dosage, and improve relative adherence and glycemic control, all of which may improve effectiveness in patients with type 2 diabetes [5,14]. A pharmaceutical company in the Republic of Korea has recently developed a novel FDC formulation of the drugs dapagliflozin and metformin. The objective of this study was to investigate the PK characteristics, safety, and bioequivalence of the test formulation (KD4004, a 10 mg dapagliflozin/1,000 mg metformin extended release (XR) FDC tablet, KyungDong Pharmaceutical Corp. Ltd., Seoul, Korea) and the reference formulation in healthy volunteers in both the fasting and fed states.

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METHODS

Study subjects

Participants included in the study were healthy male volunteers over the age of 19 with a body mass index of 18.0–29.0 kg/m^2. The following were key exclusion criteria: a history of hypersensitivity to dapagliflozin and metformin, or any excipient of the study drugs; clinically significant medical disorders; abnormal laboratory findings for creatinine clearance, aspartate aminotransferase, alanine aminotransferase, or total bilirubin; and a history of diabetes mellitus; any major surgery, acute illness, blood transfusion, or plasma donation within 4 weeks of first dosing of the study drug.

Study design and blood sampling

The Institutional Review Board of Kyungpook National University Hospital (KNUH, Daegu, Korea) and the Korea Ministry of Food and Drug Safety (MFDS) both gave their approval to the study protocol. The Declaration of Helsinki's ethical principles and Korean Good Clinical Practice guidelines were followed in conducting this study at KNUH Clinical Trial Center. Each subject received written and oral information about the study before to participation, and they provided their written informed consent.

This study consisted of two independent parts: Part A and Part B used the same crossover designs, and there was a 7-day washout period between the two treatment periods. During each study period, the subjects received a single oral dose of the test formulation (KD4004) or a single dose of the reference formulation (dapagliflozin and metformin HCl XR 10 mg/1,000 mg; Xigduo® XR, AstraZeneca Korea, Seoul, Korea).

Subjects were admitted to the Clinical Trial Center of the KNUH before receiving the study drug. The subjects were administered the study medication in the fasted state in Part A, and in the fed state in Part B. After a 10-hour overnight fast, the study drug was given in Part A along with 150 mL of water on day 1. In Part B, the study drug was given to participants who had previously consumed a high-fat breakfast (approximately 900 calories, 35% of which were from fat). The subjects began eating 30 minutes before dosing and finished in 20 minutes. All subjects fasted for 4 hours before consuming a standardized lunch and dinner provided at 4 and 9 hours after dosing, respectively. The subjects who completed the PK sampling for 24 hours were discharged on day 2, and additional visit for the last PK sampling was made on day 3.

Blood samples were collected up to 48 hours after dosing (at 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, and 48 hours in Part A; at 0, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, and 48 hours in Part B). Following centrifugation (3,000 rpm) for 15 minutes at 4°C, the plasma was transferred to two polypropylene tubes and frozen at –70°C before analysis.

Measurement of plasma dapagliflozin and metformin

Dapagliflozin and metformin plasma concentrations were measured by BioInfra Co., Ltd. (Yongin, Korea) using validated ultra-performance liquid chromatography (UPLC) methods (Waters ACQUITY™ UPLC system, Waters Corp., Milford, MA, USA) in conjunction with tandem mass spectrometry (MS/MS) (Waters Xevo™ TQ-S MS for dapagliflozin; Waters Micromass Quattro micro API for metformin).

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Chromatographic separation was performed on an ACQUITY™ UPLC® BEH C18 column (1.7 μm, 2.1 × 50 mm) for dapagliflozin and on a Waters ACQUITY UPLC® BEH HILIC column (130Å, 1.7 μm, 2.1 × 50 mm) for metformin. The mobile phase consisted of 0.1% (w/v) ammonium acetate in DW (A) and methanol (B) for dapagliflozin and 0.1% (w/v) ammonium formate in DW (A) and acetonitrile (B) (10:90, v/v) for metformin. Multiple reaction monitoring transitions were performed at mass-to-charge (m/z) ratios of 426.20 → 167.05 and 431.20 → 167.05 for dapagliflozin and dapagliflozin-d_5 (the internal standard [IS]), respectively, and 130.12 → 59.90 and 136.17 → 59.90 for metformin and metformin-d_6 (IS), respectively.

The linear calibration curves ranged between 1 and 400 ng/mL for dapagliflozin ($r \geq 0.9989$) and between 20 and 5,000 ng/mL for metformin ($r \geq 0.9950$). The overall intraday accuracy (% DMT, percentage of deviation of mean from theoretical) ranged from 2.4% to 4.5% at concentrations of 1, 3, 200, and 300 ng/mL for dapagliflozin, while for metformin it ranged from −1.4% to 1.4% at concentrations of 20, 60, 1,500, and 3,750 ng/mL. The overall inter-day accuracy ranged from 3.6% to 4.5% for dapagliflozin and from −0.3% to 2.4% for metformin. The intraday precision (% RSD) ranged from 1.1% to 2.3% for dapagliflozin and from 1.9% to 8.2% for metformin. The inter-day precision (%RSD) ranged from 1.6% to 4.3% for dapagliflozin and from 1.4% to 7.0% for metformin. The lower limit of quantification was 1 ng/mL for dapagliflozin and 20 ng/mL for metformin.

PK and statistical analysis

Plasma concentration-time curves were used to calculate the PK parameters for dapagliflozin and metformin, using noncompartmental methods with the Phoenix™ WinNonlin® software, version 8.1 (Certara, St. Louis, MO, USA). The single-dose PK parameters that were assessed to establish bioequivalence between the two FDC formulations include maximum plasma concentration (C_{max}); time to C_{max} (t_{max}); area under the plasma concentration-time curve from time 0 to the last measurement (AUC_{0-t}); AUC from time 0 to infinity ($AUC_{0-\infty}$); and terminal half-life ($t_{1/2}$).

Descriptive statistics were used to produce the PK data for dapagliflozin and metformin, which included mean values and standard deviations (SDs). The SAS software (ver. 9.4.; SAS Institute Inc., Cary, NC, USA) was used to run the statistical analyses. The geometric mean ratio (GMR) and its 90% confidence interval (CI) of the test formulation to the reference formulation were calculated using a generalized linear mixed-effects model for primary PK parameters (AUC_{0-t} and C_{max}). According to the standard used by the Korea MFDS, in Part A, bioequivalence between the test and reference formulations in the fasted state was established if the 90% CIs for AUC_{0-t} and C_{max} of dapagliflozin and metformin were in the range of 0.8000–1.2500. In Part B, the bioequivalence between the two formulations in the fed state was proven if the 90% CIs for the GMRs of AUC_{0-t} and C_{max} of metformin were within the range of 0.8000–1.2500.

Safety assessments

During the study period, every subject who received at least one or more doses of the study drugs had their safety assessed. Clinical adverse events (AEs) or vital signs, physical examination findings, and clinical laboratory results were included in the assessment. All laboratory tests were performed at the Department of Laboratory Medicine, KNUH.

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RESULTS

Demographic data

Of the subjects enrolled in each part of the study, 32 and 37 subjects completed the study in Part A and Part B, respectively. The demographic characteristics of the study population are summarized in **Table 1**.

The PK analysis only included subjects who completed the blood sampling as scheduled (Part A, 32; Part B, 37), and the safety evaluation only included subjects who had at least one dose of the study drug administered to them (Part A, 37; Part B, 40).

PK parameters

Fig. 1 illustrates the mean (SD) plasma concentration versus time profiles of dapagliflozin and metformin after single oral administration of the test and reference formulations of a dapagliflozin/metformin (10/1,000 mg) FDC tablet in the fasted state (a, dapagliflozin; b, metformin). **Fig. 2** shows the mean (SD) plasma concentration versus time profiles of

Table 1. Demographics characteristics of the subjects who completed the study

Demographic variables	Part A (n = 32)	Part B (n = 37)
Age (yr)		
Mean ± SD	27.9 ± 6.3	27.2 ± 6.6
Range	20–49	20–48
Height (cm)		
Mean ± SD	176.0 ± 6.2	175.2 ± 6.0
Range	160.9–186.7	160.0–187.4
Weight (kg)		
Mean ± SD	72.9 ± 11.2	75.5 ± 10.4
Range	53.0–98.7	54.0–94.8
BMI (kg/m^2)		
Mean ± SD	23.4 ± 2.7	24.6 ± 2.8
Range	18.0–28.4	18.0–29.9

Data are given as the mean ± SD and range.
Part A = under fasted condition; Part B = under fed condition.
SD, standard deviation; BMI, body mass index.

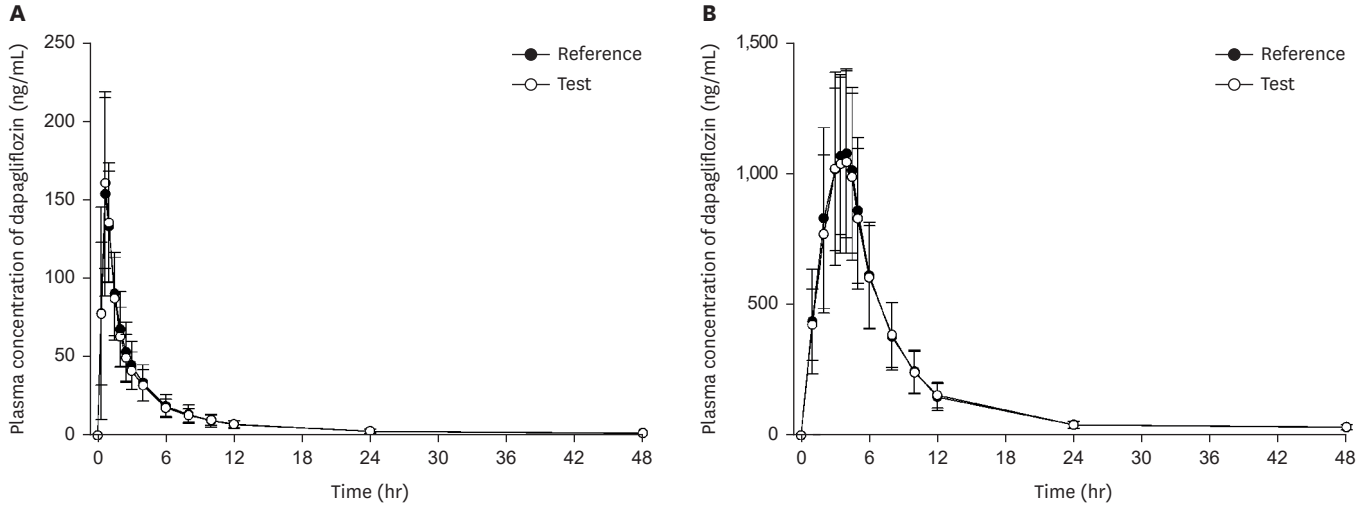

Figure 1. Mean (standard deviation) plasma concentration-time profiles of (A) dapagliflozin and (B) metformin after single oral administration of two formulations of dapagliflozin/metformin 10/1,000 mg FDC tablet under the fasted condition, in 32 healthy subjects (test formulation, ○; reference formulation, ●). Note: Error bars represent standard deviation.

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metformin following a single oral administration of two formulations in the fed state. **Tables 2** and **3** summarizes the PK parameters for the two formulations of dapagliflozin and metformin.

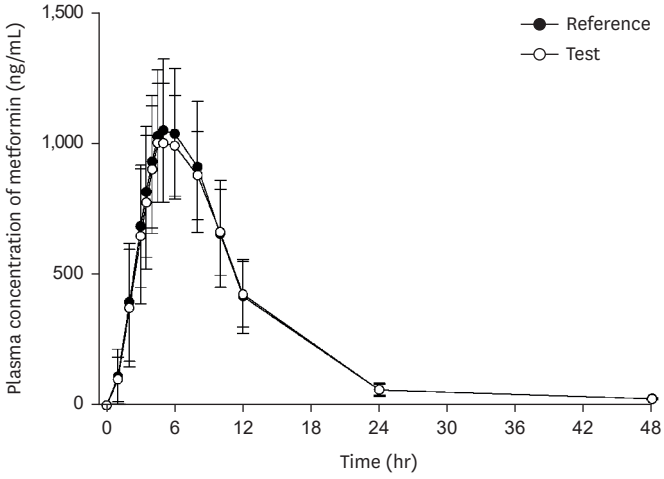

Figure 2. Mean (standard deviation) plasma concentration-time profiles of metformin after the administration of two formulations of dapagliflozin/metformin 10/1,000 mg FDC tablet under the fed condition, in 37 healthy subjects (test formulation, ○; reference formulation, ●). Note: Error bars represent standard deviation.

Table 2. Pharmacokinetic parameters following administration of the test and reference formulations of danagliflozin/metformin 10/1,000 mg FDC tablet in the fasted (Part A) conditions

PK parameter	Test (n = 32)	Reference (n = 32)	GMR (90% CI)
Dapagliflozin			
C_{max}, ng/mL	170.83 ± 42.85	166.88 ± 53.28	1.0440 (0.9489–1.1486)
AUC_{0-t}, ng×h/mL	475.38 ± 122.51	480.66 ± 147.52	0.9985 (0.9624–1.0359)
$AUC_{0-\infty}$, ng×h/mL	501.20 ± 129.25	509.59 ± 153.19	
$t_{1/2}$, hr	8.75 ± 3.88	8.94 ± 3.77	
t_{max}, hr	0.67 (0.33–1.50)	0.67 (0.33–1.50)	
Metformin			
C_{max}, ng/mL	1,183.72 ± 378.92	1,235.03 ± 319.71	0.9449 (0.8342–1.0702)
AUC_{0-t}, ng×h/mL	7,453.69 ± 2,012.66	7,435.50 ± 1,824.21	0.9956 (0.9045–1.0958)
$AUC_{0-\infty}$, ng×h/mL	7,798.04 ± 2,028.24	7,801.86 ± 1,796.19	
$t_{1/2}$, hr	5.22 ± 1.62	4.93 ± 2.46	
t_{max}, hr	3.00 (2.00–4.50)	3.50 (1.00–5.00)	

Data are presented as arithmetic means ± standard deviation, except for t_{max} values as median (range). GMR, geometric mean ratio; CI, confidence interval; C_{max}, maximum plasma concentration; AUC_{0-t}, area under the plasma concentration versus time curve (AUC) from time 0 to the last quantifiable time point; $AUC_{0-\infty}$, AUC from time 0 to infinity; $t_{1/2}$, elimination half-life; t_{max}, time to reach C_{max}.

Table 3. Pharmacokinetic parameters following administration of the test and reference formulations of danagliflozin/metformin 10/1,000 mg FDC tablet in the fed (Part B) conditions

PK Parameter	Test (n = 37)	Reference (n = 37)	GMR (90% CI)
Metformin			
C_{max}, ng/mL	1,054.86 ± 206.34	1,105.70 ± 276.09	0.9626 (0.9294–0.9969)
AUC_{0-t}, ng×h/mL	11,067.98 ± 2,206.75	11,208.16 ± 2,709.68	0.9937 (0.9529–1.0363)
$AUC_{0-\infty}$, ng×h/mL	11,410.66 ± 2,241.06	11,579.60 ± 2,737.48	
$t_{1/2}$, hr	4.53 ± 1.25	4.40 ± 1.38	
t_{max}, hr	5.00 (3.50–8.00)	5.00 (3.50–8.00)	

Data are presented as arithmetic means ± standard deviation, except for t_{max} values as median (range). GMR, geometric mean ratio; CI, confidence interval; C_{max}, maximum plasma concentration; AUC_{0-t}, area under the plasma concentration versus time curve (AUC) from time 0 to the last quantifiable time point; $AUC_{0-\infty}$, AUC from time 0 to infinity; $t_{1/2}$, elimination half-life; t_{max}, time to reach C_{max}.

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In both the fasted and fed states, the 90% CIs for the ratio (test formulation/reference formulation) of the geometric means for C_{max} and AUC_{0-t} of dapagliflozin and metformin were within the 0.8000–1.2500 limit for concluding bioequivalence of the test formulation and reference formulation (**Tables 2** and **3**).

Safety and tolerability assessments

In Part A, 12 AEs were observed in 11 subjects (29.7% of 37 subjects) during the study, and 11 AEs were determined to be adverse drug reactions (ADRs). Increased levels of blood triglycerides (three events) and protein urine present (three events) were the most common ADRs, followed by diarrhea (two events).

In Part B, 16 AEs were observed in 13 subjects (32.5% of 40 subjects), and 15AEs were determined to be ADRs. The most common ADRs include nausea (three events) and protein urine present (three events), followed by increased levels of aminotransferase (two events), blood urine present (two events), and blood bilirubin present (two events).

In both the fed and fasted studies, there were no significant differences in the AE rates of the two formulations. All AEs reported in this study were resolved spontaneously with no specific treatment. No serious or severe AEs occurred during the treatment with the test formulation or the reference formulation.

DISCUSSION

KD4004, which is the test formulation used in this study, is a new FDC formulation of dapagliflozin (10 mg) and metformin HCl (1,000 mg) XR tablet that is developed by KyungDong Pharmaceutical Corp. Ltd. (Seoul, Republic of Korea). Dapagliflozin propanediol hydrate, one of the main ingredients of the brand (reference) FDC formulation (Xigduo® XR, dapagliflozin and metformin HCl XR 10 mg/1,000 mg), was substituted by dapagliflozin bis(L-proline) for the test formulation.

In these two-part, open-label, randomized, two-period crossover studies, the PK properties and safety profiles of the test formulation and the reference formulation were compared in healthy subjects. In this study, bioequivalence between the two formulations was established under fasted (Part A) and fed (Part B) conditions. The single-dose administration of dapagliflozin and metformin XR as the two FDC formulations in both the fasted and fed states was safe and well tolerated, and there were no serious or severe AEs reported during the study. This finding supports the development and the use of the new FDC tablet as an alternative formulation for the brand dapagliflozin/metformin XR FDC tablet.

Dapagliflozin and metformin (as XR tablets) are both given orally once daily to treat type 2 diabetes, at doses of 5–10 mg for dapagliflozin and 500–2000 mg for metformin [15,16]. Xigduo® XR FDC tablets are currently offered in the following strengths and dosage forms: 2.5 mg/1,000 mg, 5 mg/500 mg, 5 mg/1,000 mg, 10 mg/500 mg, and 10 mg/1,000 mg [17]. The strengths of KD4004 evaluated in this study were dapagliflozin 10 mg and metformin 1,000 mg XR, the highest marketed strength of each active ingredient, as recommended by the US Food and Drug Administration guidance [18].

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The dapagliflozin and metformin XR FDC tablet should be taken once daily in the morning with food and gradually increased to lessen the metformin's gastrointestinal side effects, according to the dapagliflozin and metformin XR label [17]. The bioequivalence study for fed state is also conducted in this study because the dapagliflozin/metformin FDC tablet under evaluation is in XR form and is intended to be taken with food [19]. When taking metformin XR with food, the amount of metformin absorption increased by up to 50%, with no impact on the drug's C_{max} or T_{max} [17,20]. In comparison to the fasting state, a high-fat meal increased mean dapagliflozin Tmax by 1 h and decreased mean dapagliflozin Cmax by 31%, but had no effect on systemic exposure (AUC) [21]. Dapagliflozin can be taken with or without food as these changes are not thought to have clinical significance [17]. In fed participants, Boulton et al. observed that the 10 mg dapagliflozin and 1,000 mg metformin XR FDC were bioequivalent to the corresponding separate agents [20]. As a result, in this study, a PK assessment of metformin alone was performed in the fed state.

In conclusion, the two dapagliflozin/metformin 10 mg/1,000 mg XR FDC tablets were shown to be bioequivalent to each other in both the fed and fasted phases. No apparent safety or tolerability issues were observed when the XR FDC tablets were administered to healthy subjects who were either fed or fasting.

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