Bioequivalence and Food Effect of Dapagliflozin/Saxagliptin/Metformin Extended-release Fixed-combination Drug Products Compared With Coadministration of the Individual Components in Healthy Subjects

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ABSTRACT

Purpose: Fixed-combination drug products (FCDPs) for patients with type 2 diabetes mellitus (T2DM) may show efficacy comparable to their individual components (ICs) while improving adherence to treatment. This study evaluated the bioequivalence and safety of 2 dapagliflozin/saxagliptin/metformin extended-release (XR) FCDPs relative to their ICs: saxagliptin and dapagliflozin/metformin XR.

Methods: This randomized, open-label, single-dose, single-center crossover study was conducted in 84 healthy subjects aged 18−55 years. The primary objective was to evaluate the fed-state bioequivalence of a dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP and a dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP relative to the ICs. Secondary objectives included the evaluation of the effect of food on the pharmacokinetic (PK) parameters of saxagliptin, dapagliflozin, and metformin in both FCDPs and characterization of the PK parameters of the active metabolite of saxagliptin, 5-hydroxy saxagliptin, in healthy subjects. PK parameters ($AUC_{0-\infty}$, AUC_{0-t}, and C_{max}) were used to assess the bioequivalence of the 2 FCDPs with their ICs. The C_{max} and AUC_{0-t} of the study drugs were compared between female and male subjects to assess sex differences in exposure. Safety and tolerability of both FCDPs and ICs were also assessed with adverse events, vital signs (systolic and diastolic blood pressures and pulse rate), 12-lead ECG, physical examinations, and laboratory assessments.

Findings: Both dapagliflozin/saxagliptin/metformin XR FCDPs were bioequivalent to their ICs. For the dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP, the 90% CI for the geometric mean ratio of dapagliflozin C_{max} was slightly above the 80%−125% bioequivalence limit, which is unlikely to be clinically relevant. Food delayed the absorption of the study drugs in both FCDPs, which is unlikely to have a clinically relevant impact on efficacy. In both cohorts, exposure was higher in female subjects compared with male subjects, potentially due to the lower body weight of the female subjects. The safety profile and tolerability of the FCDPs were similar to those of their ICs, and no deaths or serious adverse events were reported.

Implications: These data support the use of the dapagliflozin/saxagliptin/metformin XR FCDP in patients with T2DM. ClinicalTrials.gov identifier: NCT03169959. (*Clin Ther*. 2019;41:1545−1563)

Key Words: bioequivalence, dapagliflozin, fixed-combination drug product, metformin extended release, saxagliptin.

INTRODUCTION

It is crucial to manage hyperglycemia and reduce complications in patients with type 2 diabetes

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mellitus (T2DM).[1–3] Metformin is the recommended first-line oral glucose-lowering agent in conjunction with diet and lifestyle modifications. If the patient does not attain his or her individualized glycated hemoglobin (HbA_{1c}) target after metformin monotherapy at the maximum tolerated dose, use of a second glucose-lowering agent (eg, sodium–glucose cotransporter-2 inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist) is recommended. After dual combination therapy, intensification to a triple drug combination is recommended in patients who fail to reach target HbA_{1c} values.

Dapagliflozin is a selective sodium–glucose cotransporter-2 inhibitor that reduces glucose resorption in the proximal tubule of the kidney and promotes glucosuria.[4,5] Dapagliflozin has shown long-term reductions in HbA_{1c} values, fasting plasma glucose levels, blood pressure, and body weight, with a low risk of hypoglycemia in patients with T2DM.[5–7] Saxagliptin is a selective, competitive dipeptidyl peptidase-4 inhibitor that slows inactivation of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, thereby improving glycemic control with a low risk of hypoglycemia in patients with T2DM.[8,9] When treatment intensification is required in patients with T2DM, the insulin-independent action of dapagliflozin provides a complementary mechanism of action when used in combination with other glucose-lowering drugs.[5] For example, dapagliflozin plus metformin combination therapy capitalizes on their distinct renal and hepatic mechanisms of action, respectively, to achieve glycemic control in patients with T2DM.[10] Moreover, in patients with T2DM with poor glycemic control, the addition of dapagliflozin plus saxagliptin to metformin monotherapy shows greater improvements in glycemic control versus the addition of saxagliptin or dapagliflozin to metformin alone.[11] The addition of saxagliptin to dapagliflozin plus metformin therapy, or of dapagliflozin to saxagliptin plus metformin therapy, is well tolerated and produces improvements in glycemic control in patients with T2DM.[12,13]

Personalized treatment intensification strategies for patients with T2DM typically follow a stepwise approach, with new therapies added sequentially until glycemic control is achieved.[1–3] Fixed-combination drug products (FCDPs) that combine different classes of glucose-lowering agents have become popular.[14–16] FCDPs offer distinct advantages compared with individual therapies, such as enhancing adherence to therapy by reducing treatment burden, improving glycemic control, increasing patient satisfaction, and reducing health care costs.[16–18]

A dapagliflozin/saxagliptin/metformin extended-release (XR) FCDP is currently in clinical development, based on saxagliptin[8] and a dapagliflozin/metformin hydrochloride XR FCDP.[19] The formulation design principle is a bilayer tablet core containing dapagliflozin and metformin hydrochloride, surrounded by a 3-layer film coating containing saxagliptin. In the bilayer tablet, the dapagliflozin layer is formulated for immediate release, whereas the metformin hydrochloride layer is formulated to provide XR.

To support regulatory approval, FCDPs must show bioequivalence to their individual components (ICs).[20] The current Phase I study aimed to assess the fed-state bioequivalence and safety of 2 tablet strengths of a dapagliflozin/saxagliptin/metformin XR FCDP—dapagliflozin 5 mg/saxagliptin 2.5 mg/metformin 1000 mg XR and dapagliflozin 10 mg/saxagliptin 5 mg/metformin 1000 mg XR—relative to their ICs, saxagliptin and dapagliflozin/metformin XR FCDP,[8,19] in healthy subjects.

SUBJECTS AND METHODS

Study Population

Healthy male or female subjects aged 18–55 years with a body mass index of 18–32 kg/m^2 and body weight of ≥50 to ≤100 kg were eligible to participate in the study. Women of non-childbearing potential (postmenopausal or surgically sterile) were also considered; women of childbearing potential could not be pregnant or breastfeeding for the duration of the study, and a negative result on a pregnancy test at the screening visit and within 24 h of study drug administration was required. All subjects had to use effective birth control from at least 4 weeks before dosing, throughout the entire study, and for 90 days after the last dose of the study drug.

Key exclusion criteria included the following: history of any clinically significant disease or disorder which, in the opinion of the investigator, could have either put the volunteer at risk because of

participation in the study or could have influenced the results or the volunteer's ability to participate in the study; current or recent (within 3 months of first dosing of the study drug) gastrointestinal disease that could have influenced drug absorption and affected the pharmacokinetic (PK) parameters of the study drug, or any gastrointestinal surgery including cholecystectomy that could have affected drug absorption; any major surgery, blood transfusion, or plasma donation within 4 weeks of first dosing of the study drug; a history of diabetes mellitus, heart failure, or chronic or recurrent urinary tract infection; use of nicotine-containing products or excessive consumption of caffeine-containing products; use of dapagliflozin, saxagliptin, and/or metformin within 3 months before the first administration of the study drug; and a history of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity as judged by the investigator, or a history of hypersensitivity to drugs with a similar chemical structure or class to dapagliflozin, saxagliptin, and/or metformin.

Study Design

This randomized, open-label, single-dose, single-center crossover study was conducted in 84 healthy subjects aged 18−55 years. After a screening period of a maximum 28 days, 2 parallel cohorts of 42 subjects each were randomized to 1 of 6 treatment sequences in which the study drugs were administered over 3 successive treatment periods (Figure. 1A and B). The ICs were administered in a fed state. The respective FCDPs were administered under both fed and fasted conditions (within 5 min of completing a light-fat, low-calorie meal in the morning or after a 10-h fast, respectively). Discharge was on the morning of day 4, and a follow-up visit occurred within 5−7 days after the last administration of the study drug. The treatment periods were separated by a minimum washout period of 7−14 days between each study drug dose. Each subject was involved in the study for ~7−9 weeks.

This study conformed to the Declaration of Helsinki (version 1996) and the International Council for Harmonisation Good Clinical Practice Guideline, and followed applicable regulatory requirements. The study also conformed to the AstraZeneca policy on Bioethics and Human Biological Samples. All eligible subjects provided written informed consent before study participation.

Assessments

PK parameters were assessed for dapagliflozin, saxagliptin, the major active metabolite of saxagliptin (5-hydroxy [5-OH] saxagliptin), and metformin in plasma concentrations. The primary PK parameters assessed were $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}. The secondary PK parameters assessed were T_{max} and the half-life associated with the terminal slope of a semi-logarithmic concentration−time curve. The C_{max} and AUC_{0-t} of dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin were compared between female and male subjects. Additional PK parameters were determined where appropriate.

Safety and tolerability variables assessed during the study included adverse events (AEs) and vital signs (systolic and diastolic blood pressures and pulse rate). Twelve-lead ECGs, physical examinations, and laboratory assessments (hematology, clinical chemistry, and urinalysis) were also performed.

Bioanalytical Analyses

The method used to determine dapagliflozin concentrations in plasma samples was based on a previous method that was further modified and independently validated.[21] Plasma samples for dapagliflozin analysis were extracted by using protein precipitation followed by solid phase extraction. [$^{13}C_6$] Dapagliflozin was used as the internal standard. Samples were analyzed by using a Shimadzu Nexera liquid chromatography system (or equivalent) (Shimadzu Corporation, Kyoto, Japan) with an Acquity UPLC high-strength silica T3 (Waters Corporation, Milford, Massachusetts), 100 × 2.1, 1.8 μm analytical column with mobile phases of 1 M ammonium acetate, acetonitrile, and water in a 0.5:25:74.5 ratio and a 0.5:95:4.5 ratio running with a gradient method over 7.0 min. The analytes of interest were then detected by using MS/MS with a SCIEX atmospheric pressure ionization (API) 5000/5500 instrument (electrospray ionization negative) (SCIEX, Framingham, Massachusetts) using a transition of 467/329 for dapagliflozin and 473/335 for the internal standard. The lower limit of quantitation (LLOQ) for dapagliflozin was 0.2 ng/mL, with a validated calibration range of 0.2−200 ng/mL. In the study, assay performance

was acceptable with quality control (QC) demonstrating intra-assay accuracy ranging from 99.4% (high QC) to 102.2% (low QC) and intra-assay precision (%CV) ranging from 5.1% (high QC) to 10.6% (low QC).

The analytical method used to determine the concentrations of saxagliptin and 5-OH saxagliptin in plasma samples was originally developed by Tandem Laboratories (now Covance Laboratories Inc, Madison, Wisconsin). Plasma samples for

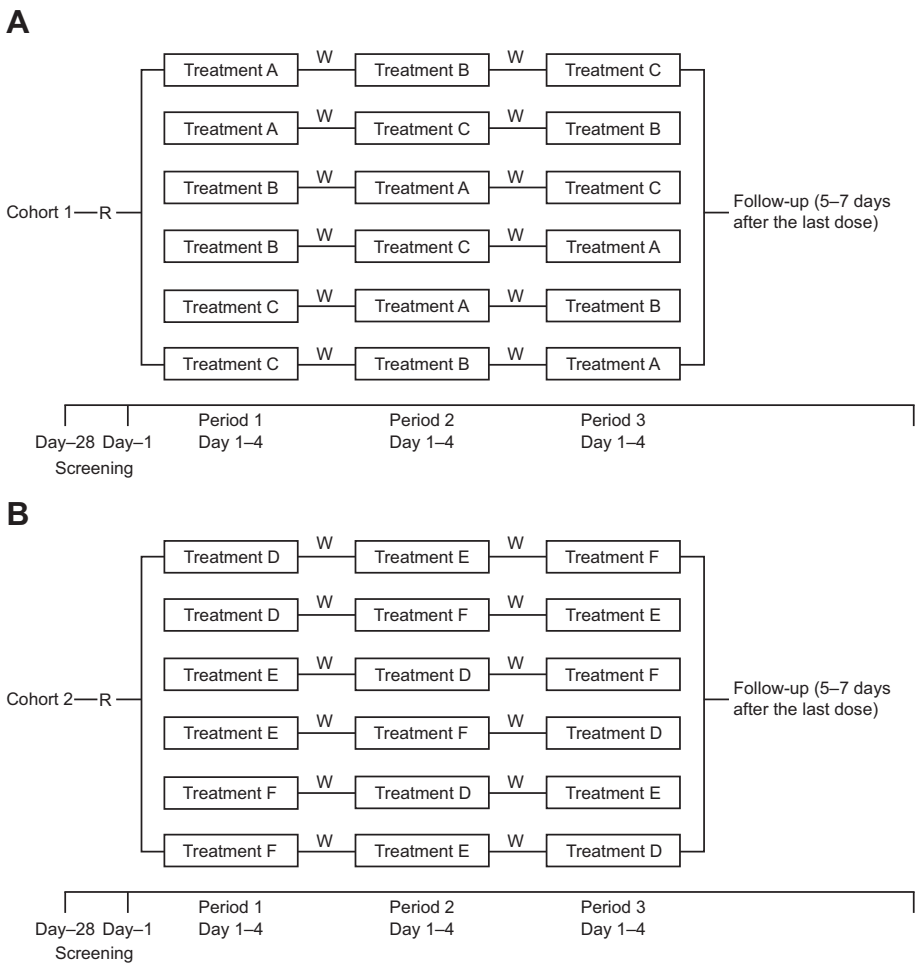

Figure. 1. Study design for (A) cohort 1 and (B) cohort 2. Treatment A (reference product, fed conditions) = single dose of saxagliptin 2.5-mg and dapagliflozin 5-mg/metformin 1000-mg extended-release (XR) tablets coadministered orally under fed conditions. Treatment B (test product, fed conditions) = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR fixed-combination drug product (FCDP) under fed conditions. Treatment C (test product, fasted conditions) = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fasted conditions. Treatment D (reference product, fed conditions) = single dose of saxagliptin 5-mg and dapagliflozin 10-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions. Treatment E (test product, fed conditions) = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fed conditions. Treatment F (test product, fasted conditions) = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fasted conditions. R = randomization; W = minimum washout period of 7—14 days between study drug administration.

saxagliptin/5-OH saxagliptin were extracted by using protein precipitation; [^{13}C,D$_2$] saxagliptin and [^{13}C,D$_2$] 5-OH saxagliptin were used as the internal standards. Samples were analyzed by using a Shimadzu Nexera liquid chromatography system (or equivalent) with an Atlantis dC18, 50 × 2.1 mm, 5 μm analytical column (Waters, Hertfordshire, United Kingdom) with mobile phases of 0.1% formic acid and acetonitrile containing 0.1% formic acid running with a gradient method over 6.01 min. The analytes of interest were then detected by using MS/MS with a SCIEX API 4000 instrument (electrospray ionization positive) using a transition of 316/180 for saxagliptin, 319/180 for its internal standard, 332/196 for 5-OH saxagliptin, and 335/196 for its corresponding internal standard. The LLOQ for saxagliptin was 0.1 ng/mL, with a validated calibration range of 0.1−50 ng/mL, whereas the LLOQ for 5-OH saxagliptin was 0.2 ng/mL with a validated calibration range of 0.2−100 ng/mL. The following assay performance was acceptable in this study: for saxagliptin, QCs demonstrated intra-assay accuracy data ranging from 101.0% (low and high QC) to 104.0% (mid QC) and intra-assay precision (%CV) ranging from 4.6% (mid and high QC) to 7.8% (low QC); for 5-OH saxagliptin, QCs demonstrated intra-assay accuracy data ranging from 100.7% (low QC) to 102.1% (high QC) and intra-assay precision (%CV) ranging from 4.2% (high QC) to 7.8% (low QC).

To determine metformin concentrations, a method developed and validated in-house by Covance was used. Plasma samples for metformin analysis were extracted by using protein precipitation. Metformin-D6 was used as the internal standard. Samples were analyzed by using a Shimadzu Nexera liquid chromatography system (or equivalent) with an Epic Silica, 50 × 3.2 mm, 3 μm analytical column (ES Industries, West Berlin, New Jersey) with mobile phases of 10 mM ammonium formate (aqueous) containing 0.1% formic acid and acetonitrile containing 0.1% formic acid, running a gradient over 4.5 min. The analytes of interest were then detected by using MS/MS with a SCIEX API 4000 instrument (electrospray ionization positive) using a transition of 130/71 for metformin and 136/77 for the internal standard. The LLOQ for metformin was 2 ng/mL, with a validated calibration range of 2−2000 ng/mL. In the study, assay performance was acceptable with QCs demonstrating intra-assay accuracy data ranging from 97.3% (high QC) to 103.5% (mid QC) and intra-assay precision (%CV) ranging from 4.9% (high QC) to 5.8% (mid QC).

Statistical Analyses

PK parameters were summarized according to treatment by using descriptive statistics. Bioequivalence was assessed from results obtained in the independent analyses of PK parameters for each cohort. Bioequivalence analyses were performed by using a repeated measures ANOVA using the natural logarithms of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin as the response variables, with terms for treatment and period and the within-subject error across study periods modeled by using an unstructured covariance structure in each model. Bioequivalence was established if the 90% CIs for the FCDP-to-IC geometric mean (GM) ratios of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were contained within the 80%−125% limit. Food effect was assessed by using the same ANOVA model, with an absence of food effect established if the 90% CIs for the GM ratios of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were contained within the 80%−125% limit. Continuous safety variables were summarized by using descriptive statistics, and categorical safety variables were summarized in frequency tables according to treatment. AEs were summarized according to Preferred Term and System Organ Class by using Medical Dictionary for Regulatory Activities definitions. Clinical laboratory data were reported in the units provided by the clinical laboratory for the Safety Review Committee meeting and in International System of Units; these data were summarized for the observed values at each scheduled assessment, together with the corresponding changes (and/or percent change) from baseline. Statistical analyses were performed by using SAS® version 9.4 (SAS Institute, Inc, Cary, North Carolina), and PK analyses were performed by using Phoenix® WinNonlin® version 6.4 (Certara USA Inc, Princeton, New Jersey).

RESULTS

Subject Disposition and Demographic Characteristics

A total of 84 subjects were enrolled in the study; 41 and 40 subjects completed the treatment in cohorts 1 and 2, respectively (Table I). Baseline characteristics were generally similar across both cohorts; the mean age of subjects in cohorts 1 and 2 was 38.1 and 33.9 years, respectively, and the majority of subjects were male (64.3% and 66.7% in cohorts 1 and 2, respectively) (Table II). In cohort 1, the mean body weight of male and female subjects was 82.7 kg and 75.0 kg, respectively; in cohort 2, it was 79.5 kg and 69.6 kg, respectively.

Nine subjects received prohibited concomitant medication (including nontherapeutic products), 8 of whom received these treatments for the management of AEs. Two subjects and 1 subject in cohorts 1 and 2, respectively, received prohibited concomitant medications, whereas 3 subjects in each cohort received other nontherapeutic products. None of the previous or concomitant medications administered during the

Table I. Subject disposition of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg extended-release (XR) fixed-combination drug product (FCDP) (cohort 1) and dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP (cohort 2) during the study period (all randomized subjects). Values are given as number (%) of subjects.

Cohort 1	ABC	ACB	BAC	BCA	CAB	CBA	All Subjects
Randomized to treatment	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	42 (100.0)
Received treatment	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	42 (100.0)
Not received treatment	0	0	0	0	0	0	0
Completed treatment	7 (100.0)	6 (85.7)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	41 (97.6)
Discontinued treatment	0	1 (14.3)	0	0	0	0	1 (2.4)
Completed study	7 (100.0)	6 (85.7)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	41 (97.6)
Withdrawn from study	0	1 (14.3)	0	0	0	0	1 (2.4)
Severe noncompliance	0	1 (14.3)	0	0	0	0	1 (2.4)

Cohort 2	DEF	DFE	EDF	EFD	FDE	FED	All Subjects
Randomized to treatment	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	42 (100.0)
Received treatment	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	42 (100.0)
Not received treatment	0	0	0	0	0	0	0
Completed treatment	6 (85.7)	6 (85.7)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	40 (95.2)
Discontinued treatment	1 (14.3)	1 (14.3)	0	0	0	0	2 (4.8)
Completed study	6 (85.7)	6 (85.7)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	40 (95.2)
Withdrawn from study	1 (14.3)	1 (14.3)	0	0	0	0	2 (4.8)
Severe noncompliance	1 (14.3)	0	0	0	0	0	1 (2.4)
Other	0	1 (14.3)	0	0	0	0	1 (2.4)

A = single dose of saxagliptin 2.5-mg and dapagliflozin 5-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions; B = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fed conditions; C = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fasting conditions; D = single dose of saxagliptin 5-mg and dapagliflozin 10-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions; E = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fed conditions; F = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fasting conditions.

Table II. Subject baseline and demographic characteristics of cohort 1 (dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg extended-release fixed-combination drug product) and cohort 2 (dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg extended-release fixed-combination drug product). Values are given as mean (SD) unless stated otherwise.

Characteristic	Cohort 1 (n = 42)	Cohort 2 (n = 42)
Age, y	38.1 (9.2)	33.9 (9.6)
Male sex, male, n (%)	27 (64.3)	28 (66.7)
Race, n (%)		
White	11 (26.2)	7 (16.7)
Black or African American	30 (71.4)	34 (81.0)
Asian	1 (2.4)	1 (2.4)
Height, cm	174.0 (10.0)	172.0 (9.0)
Weight, kg	80.0 (10.3)	76.2 (11.5)
Male	82.7 (8.1)	79.5 (10.2)
Female	75.0 (12.2)	69.6 (11.3)
Body mass index, kg/m^2	26.4 (2.6)	25.7 (3.0)
Concomitant medication, n (%)		
Prohibited concomitant medication	2 (4.8)	1 (2.4)
Other nontherapeutic products	3 (7.1)	3 (7.1)

study was considered likely to affect the outcome of the study.

PK PARAMETERS

Dapagliflozin 5-mg/Saxagliptin 2.5-mg/Metformin 1000-mg XR FCDP

Bioequivalence

The mean plasma dapagliflozin concentration−time profile in the FCDP was similar to that of the ICs in the fed state (Figure. 2A). Mean plasma concentration−time profiles for saxagliptin, 5-OH saxagliptin, and metformin in the FCDP were almost superimposable to those of the ICs (Figure. 3A, 4A and 5A). The derived mean PK parameters for dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin were similar between the FCDP and the ICs, showing a similar rate of absorption (C_{max} and T_{max}) and extent of absorption (AUCs), and thus similar bioavailability (Table III).

For dapagliflozin, the 90% CI for the GM ratio of dapagliflozin C_{max} was 100.99%−128.48%, slightly above the 80%−125% limit, and the 90% CIs for the GM ratios of dapagliflozin $AUC_{0-\infty}$ and AUC_{0-t} were entirely within the 80%−125% limit, indicating bioequivalence (Table IV). For saxagliptin, 5-OH saxagliptin, and metformin, the 90% CIs for the GM ratios were entirely within the 80%−125% limit, indicating bioequivalence.

Food Effect

For dapagliflozin, median T_{max} was delayed in the fed state versus the fasted state (2.00 vs 0.98 h, respectively) (Table III).The dapagliflozin GM ratio for the C_{max} value was ~38% lower in the fed versus fasted state (90% CI, 54.80−69.72); however, the dapagliflozin GM ratios for $AUC_{0-\infty}$ and AUC_{0-t} were 98.41% and 98.14%, respectively, and the corresponding 90% CIs were within the 80%−125% limit (Table IV). The median T_{max} values for saxagliptin and 5-OH saxagliptin were delayed under the fed state (1.52 and 3.00 h, respectively) versus the fasted state (0.50 and 1.50 h, respectively). The 90% CIs for the GM ratios of saxagliptin $AUC_{0-\infty}$ and AUC_{0-t} were slightly above the 80%−125% limit and slightly below the 80%−125% limit for saxagliptin C_{max}. The 90% CIs for the GM ratios

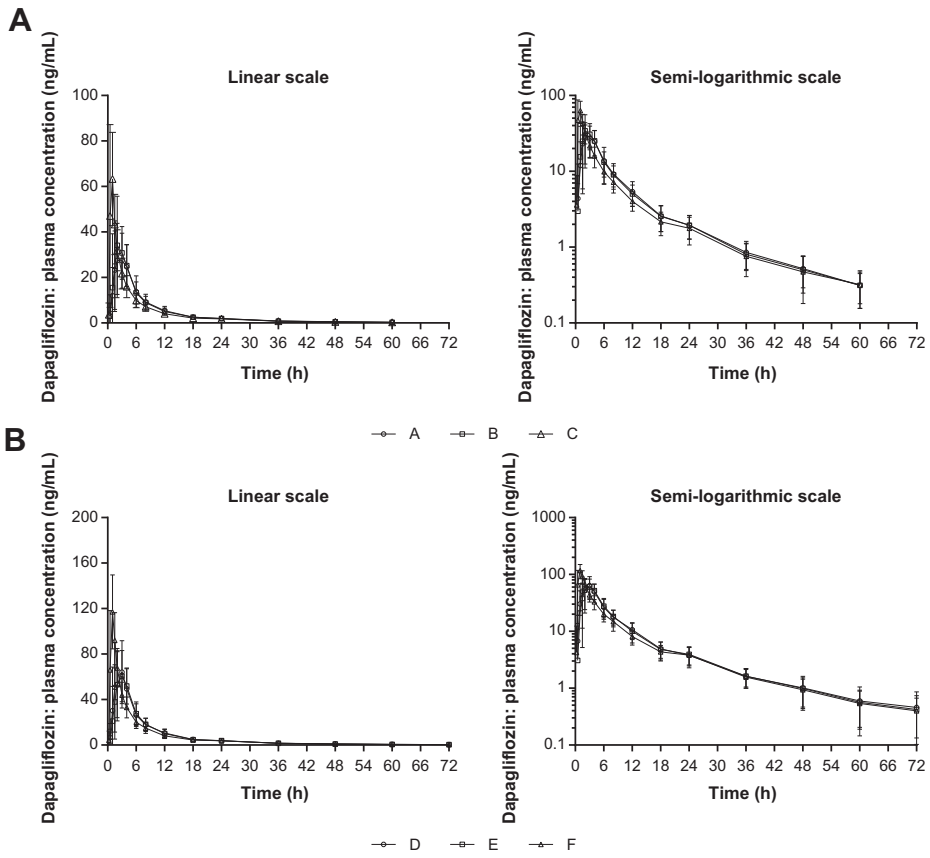

Figure. 2. Mean (SD) dapagliflozin plasma concentration−time profiles after single-dose administration of (A; top) dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg extended-release (XR) fixed-combination drug product (FCDP) and coadministered individual components in cohort 1 and (B; bottom) dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP and coadministered individual components in cohort 2. A = single dose of saxagliptin 2.5-mg and dapagliflozin 5-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions. B = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fed conditions. C = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fasting conditions. D = single dose of saxagliptin 5-mg and dapagliflozin 10-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions. E = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fed conditions. F = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fasting conditions.

of 5-OH saxagliptin $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were completely within the 80%−125% limit. The metformin median T_{max} value was slightly delayed in the fed versus fasted state (5.98 vs 4.00 h). The 90% CIs for the GM ratios of metformin $AUC_{0-\infty}$ and AUC_{0-t} were slightly above the 80%−125% limit, and the 90% CI for the GM ratio of metformin C_{max} was within the 80%−125% limit.

Exposure: Sex Comparison

The AUC_{0-t} of dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin was 8%−18%, 16%−18%, 25%−27%, and 3%−14% higher in female

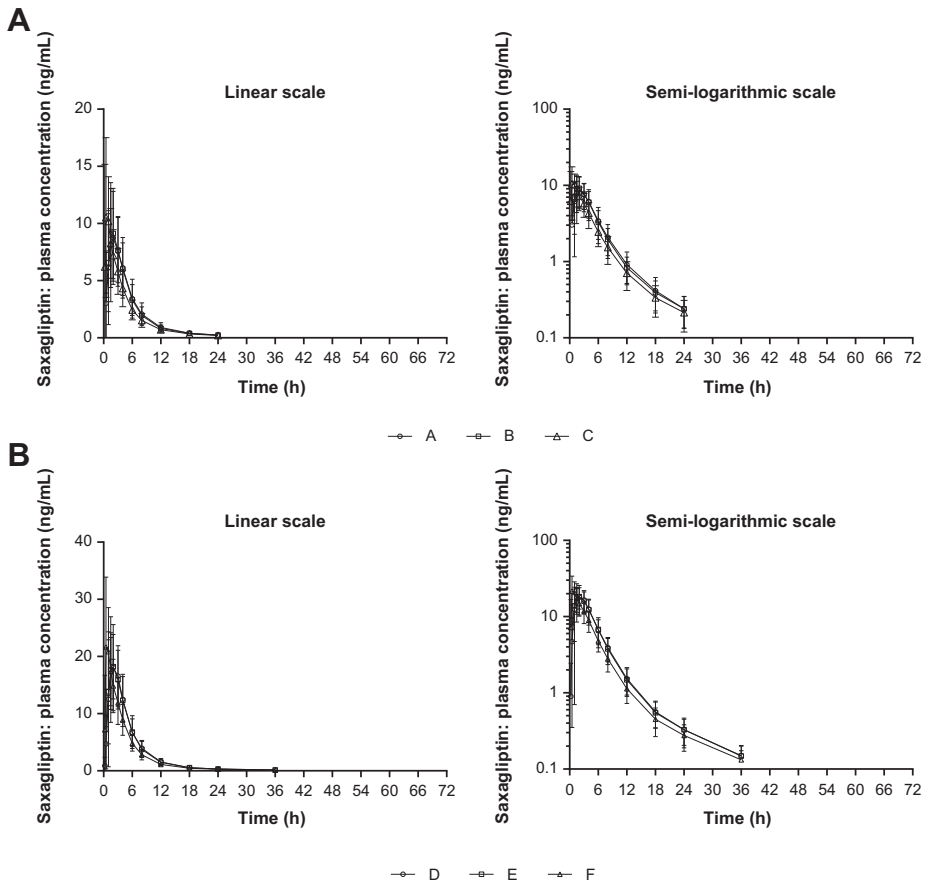

Figure. 3. Mean (SD) saxagliptin plasma concentration−time profiles after single-dose administration of (A; top) dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg extended-release (XR) fixed-combination drug product (FCDP) and coadministered individual components in cohort 1 and (B; bottom) dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP and coadministered individual components in cohort 2. A = single dose of saxagliptin 2.5-mg and dapagliflozin 5-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions. B = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fed conditions. C = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fasting conditions. D = single dose of saxagliptin 5-mg and dapagliflozin 10-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions. E = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fed conditions. F = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fasting conditions.

subjects than in male subjects, respectively. The C_{max} of dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin was 7%−17%, 24%−38%, 29%−32%, and 7%−17% higher in female subjects than in male subjects, respectively (Table V).

Dapagliflozin 10-mg/Saxagliptin 5-mg/Metformin 1000-mg XR FCDP

Bioequivalence

The mean plasma dapagliflozin concentration−time profile in the FCDP was similar to that of the ICs in the fed state (Figure. 2B). The plasma concentration−time

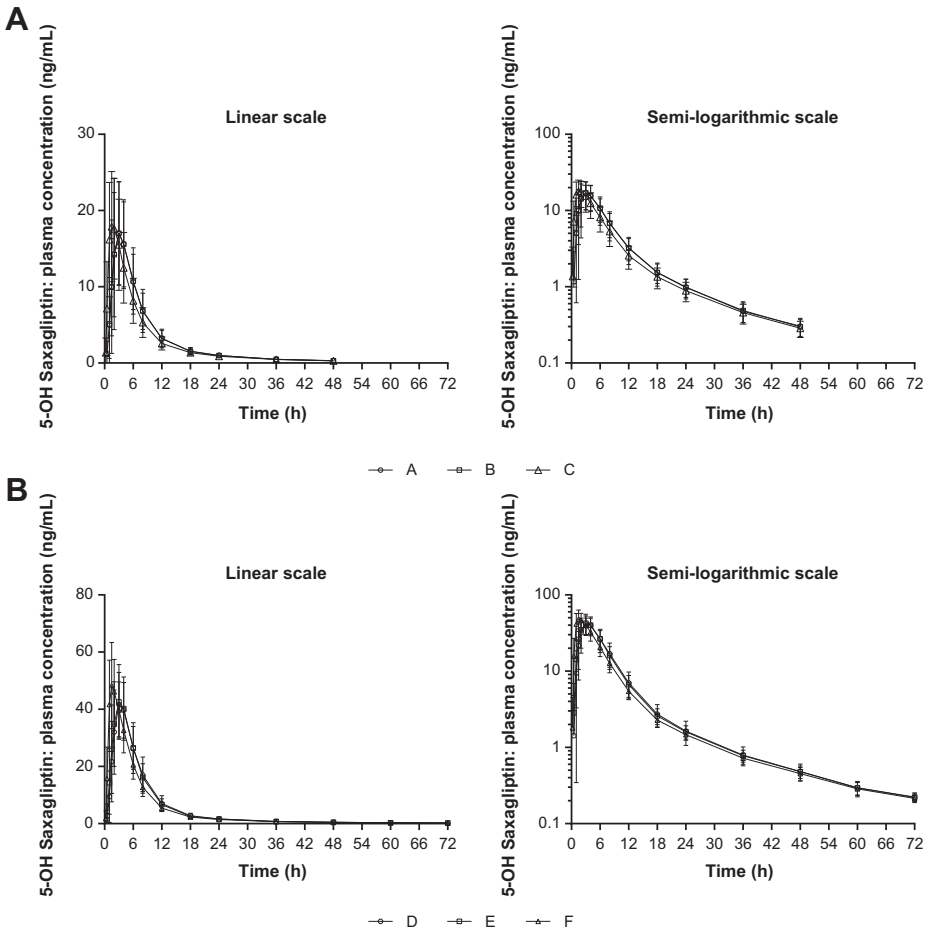

Figure. 4. Mean (SD) 5-hydroxy (5-OH) saxagliptin plasma concentration–time profiles after single-dose administration of (A; top) dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg extended-release (XR) fixed-combination drug product (FCDP) and coadministered individual components in cohort 1 and (B; bottom) dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP and coadministered individual components in cohort 2. A = single dose of saxagliptin 2.5-mg and dapagliflozin 5-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions. B = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fed conditions. C = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fasting conditions. D = single dose of saxagliptin 5-mg and dapagliflozin 10-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions. E = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fed conditions. F = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fasting conditions.

profiles for saxagliptin, 5-OH saxagliptin, and metformin in the FCDP were almost superimposable to those of the ICs in the fed state (Figure. 3B, 4B and 5B). The derived mean PK parameters for dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin were similar between the FCDP and the ICs, indicating a similar rate of absorption (C_{max} and T_{max}) and extent of absorption (AUCs), and thus similar bioavailability (Table III). For dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin, the

Table III. Plasma pharmacokinetic parameters of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg extended-release (XR) fixed-combination drug product (FCDP) (cohort 1) and dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP (cohort 2).

Variable	$AUC_{0-\infty}$ (ng/mL/h): GM (%CV)	AUC_{0-t} (ng/mL/h): GM (%CV)	C_{max} (ng/mL): GM (%CV)	T_{max} (h): Median (Minimum, Maximum)	$t_{½\lambda z}$ (h): Mean (SD)
Dapagliflozin					
Cohort 1					
A (n = 41)	233.7 (23.52)	226.3 (24.21)	37.12 (30.81)	2.00 (1.00, 5.98)	14.59 (5.85)
B (n = 41)	239.9 (23.64)	232.5 (24.38)	42.31 (39.57)	2.00 (0.98, 6.00)	14.75 (6.79)
C (n = 41)	243.8 (24.77)	236.9 (25.31)	68.30 (30.05)	0.98 (0.48, 1.50)	14.54 (6.17)
Cohort 2					
D (n = 41)	472.5 (25.21)	459.7 (24.05)	81.75 (36.82)	2.98 (1.00, 6.02)	15.45 (8.06)
E (n = 40)	463.6 (22.38)	452.4 (22.03)	75.70 (24.96)	3.00 (1.00, 6.05)	14.70 (6.07)
F (n = 41)	487.5 (22.95)	477.2 (22.72)	123.8 (27.33)	1.00 (0.50, 2.00)	14.15 (5.18)
Saxagliptin					
Cohort 1					
A (n = 41)	51.53 (36.17)	49.86 (37.41)	10.61 (44.43)	1.50 (0.50, 4.00)	7.25 (2.47)
B (n = 41)	51.57 (35.47)	50.06 (36.08)	10.61 (37.47)	1.52 (0.48, 4.00)	7.17 (2.20)
C (n = 41)	46.90 (38.53)	45.32 (39.33)	11.69 (52.61)	0.50 (0.23, 1.50)	7.53 (2.55)
Cohort 2					
D (n = 41)	102.0 (26.25)	100.2 (26.50)	22.30 (33.75)	2.00 (0.50, 4.03)	9.07 (3.66)
E (n = 40)	102.6 (26.43)	100.9 (26.70)	20.95 (26.90)	1.99 (0.48, 4.00)	8.59 (3.11)
F (n = 41)	91.56 (26.29)	89.95 (26.44)	24.80 (37.27)	0.50 (0.25, 2.03)	8.09 (3.31)
5-OH saxagliptin					
Cohort 1					
A (n = 41)	137.6 (36.72)	132.8 (37.96)	17.64 (46.59)	3.00 (1.50, 6.00)	13.28 (2.36)
B (n = 41)	136.1 (41.37)	131.0 (42.81)	17.29 (44.08)	3.00 (0.98, 6.00)	13.02 (1.99)
C (n = 41)	131.3 (38.87)	126.0 (40.38)	18.19 (43.81)	1.50 (0.98, 3.00)	13.65 (2.98)
Cohort 2					
D (n = 41)	321.2 (19.94)	315.5 (20.14)	45.83 (19.51)	3.00 (1.50, 6.03)	15.61 (2.84)
E (n = 40)	325.3 (19.84)	319.6 (20.18)	46.38 (26.11)	3.00 (1.50, 6.05)	15.32 (2.14)
F (n = 41)	318.7 (19.52)	313.1 (19.77)	49.28 (26.72)	1.50 (0.98, 4.00)	15.44 (1.81)

(*continued on next page*)

Table III. (*Continued*)

Variable	$AUC_{0-\infty}$ (ng/mL/h): GM (%CV)	AUC_{0-t} (ng/mL/h): GM (%CV)	C_{max} (ng/mL): GM (%CV)	T_{max} (h): Median (Minimum, Maximum)	$t_{½\lambda z}$ (h): Mean (SD)
Metformin					
Cohort 1					
A (n = 41)	10,980* (32.82)	10,910 (31.03)	1041 (29.47)	5.98 (3.98, 8.02)	15.37* (10.10)
B (n = 41)	10,930† (34.44)	10,780 (34.20)	1098 (26.97)	5.98 (3.98, 8.05)	17.00† (13.39)
C (n = 41)	9511‡ (26.11)	9265 (26.62)	1195 (28.04)	4.00 (1.52, 6.00)	16.72‡ (11.53)
Cohort 2					
D (n = 41)	11,090§ (31.77)	10,910 (29.72)	1104 (27.10)	6.00 (3.98, 8.10)	15.15§ (9.81)
E (n = 40)	10,470† (30.82)	10,420 (29.79)	1057 (24.43)	6.00 (3.00, 8.02)	15.29† (8.79)
F (n = 41)	9213† (26.97)	9248 (27.63)	1167 (35.46)	4.00 (2.00, 6.03)	14.49† (10.35)

5-OH = 5-hydroxy; A = single dose of saxagliptin 2.5-mg and dapagliflozin 5-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions; B = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fed conditions; C = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fasting conditions; D = single dose of saxagliptin 5-mg and dapagliflozin 10-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions; E = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fed conditions; F = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fasting conditions; GM = geometric mean; $t_{½\lambda z}$ = half-life associated with terminal slope of a semi-logarithmic concentration–time curve.

* n = 35.

† n = 37.

‡ n = 39.

§ n = 38.

Table IV. Bioequivalence and food effect for dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg extended-release (XR) fixed-combination drug product (FCDP) (cohort 1) and dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP (cohort 2).

Variable	GM Ratios (90% CI)*		
	$AUC_{0-\infty}$ (ng/mL/h)	AUC_{0-t} (ng/mL/h)	C_{max} (ng/mL)
Dapagliflozin			
Cohort 1			
Bioequivalence (B/A)	102.74 (94.17, 112.09)	102.80 (94.00, 112.42)	113.91 (100.99, 128.48)
Food effect (B/C)	98.41 (90.20, 107.37)	98.14 (89.74, 107.32)	61.81 (54.80, 69.72)
Cohort 2			
Bioequivalence (E/D)	98.19 (90.09, 107.02)	98.44 (90.52, 107.06)	92.51 (82.94, 103.18)
Food effect (E/F)	95.08 (87.24, 103.63)	94.75 (87.13, 103.05)	61.08 (54.76, 68.12)
Saxagliptin			
Cohort 1			
Bioequivalence (B/A)	100.19 (87.89, 114.22)	100.51 (87.91, 114.93)	100.07 (85.45, 117.20)
Food effect (B/C)	110.13 (96.61, 125.55)	110.62 (96.75, 126.49)	90.61 (77.37, 106.12)
Cohort 2			
Bioequivalence (E/D)	100.64 (91.41, 110.79)	100.73 (91.43, 110.98)	93.90 (83.45, 105.65)
Food effect (E/F)	112.08 (101.81, 123.39)	112.09 (101.74, 123.50)	84.35 (74.97, 94.91)
5-OH saxagliptin			
Cohort 1			
Bioequivalence (B/A)	98.92 (86.08, 113.67)	98.65 (85.45, 113.88)	98.01 (83.72, 114.74)
Food effect (B/C)	103.64 (90.19, 119.09)	103.97 (90.06, 120.03)	94.92 (81.08, 111.12)
Cohort 2			
Bioequivalence (E/D)	101.32 (94.22, 108.96)	101.34 (94.15, 109.08)	101.15 (92.55, 110.55)
Food effect (E/F)	102.04 (94.90, 109.73)	102.05 (94.81, 109.85)	94.06 (86.06, 102.79)
Metformin			
Cohort 1			
Bioequivalence (B/A)	99.48 (88.21, 112.19)	98.89 (88.51, 110.49)	105.45 (95.24, 116.76)
Food effect (B/C)	114.96 (102.26, 129.24)	116.40 (104.18, 130.06)	91.79 (82.90, 101.63)
Cohort 2			
Bioequivalence (E/D)	94.53 (84.55, 105.70)	95.66 (86.16, 106.20)	95.96 (86.36, 106.63)
Food effect (E/F)	113.61 (101.53, 127.11)	112.59 (101.41, 125.00)	90.55 (81.49, 100.61)

5-OH = 5-hydroxy; A = single dose of saxagliptin 2.5-mg and dapagliflozin 5-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions; B = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fed conditions; C = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fasting conditions; D = single dose of saxagliptin 5-mg and dapagliflozin 10-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions; E = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fed conditions; F = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fasting conditions; GM = geometric mean.

* Result based on ANOVA of log-transformed pharmacokinetic parameter with terms for treatment and period and within-subject error across study periods modeled by using an unstructured covariance structure.

Table V. Comparison of dapagliflozin, saxagliptin, 5-hydroxy (5-OH) saxagliptin, and metformin exposure between female and male subjects in both cohorts. Values are given as arithmetic mean (SD).

Cohort 1		Treatment A			Treatment B			Treatment C		
Analyte	Subject	n	C_{max} (ng/mL)	AUC_{0-t} (ng/mL/h)	n	C_{max} (ng/mL)	AUC_{0-t} (ng/mL/h)	n	C_{max} (ng/mL)	AUC_{0-t} (ng/mL/h)
Dapagliflozin	Female	15	40.6 (12.9)	244.5 (67.0)	15	50.6 (21.8)	260.3 (75.3)	15	79.2 (24.6)	273.1 (84.8)
	Male	26	37.7 (11.1)	225.7 (45.7)	26	42.8 (18.1)	227.1 (46.8)	26	66.8 (20.3)	227.6 (39.1)
Saxagliptin	Female	15	13.9 (4.1)	58.9 (16.1)	15	13.1 (4.6)	58.3 (16.1)	15	16.6 (8.0)	53.9 (17.6)
	Male	26	10.1 (3.9)	49.4 (17.2)	26	10.3 (3.4)	49.8 (16.6)	26	11.3 (5.8)	45.2 (16.5)
5-OH saxagliptin	Female	15	23.0 (6.0)	164.7 (33.3)	15	22.6 (4.4)	165.4 (35.6)	15	23.9 (6.3)	156.1 (34.8)
	Male	26	17.1 (7.9)	127.2 (45.5)	26	16.5 (7.5)	126.4 (49.4)	26	17.3 (7.1)	122.0 (44.7)
Metformin	Female	15	1135.5 (312.5)	11,641.5 (2825.0)	15	1263.8 (291.1)	11,983.4 (3093.6)	15	1363.2 (296.5)	10,466.9 (2205.3)
	Male	26	1053.6 (310.8)	11,291.8 (4075.8)	26	1062.5 (283.3)	10,984.6 (3864.7)	26	1164.8 (307.4)	9059.5 (2508.4)
Cohort 2		**Treatment D**			**Treatment E**			**Treatment F**		
Analyte	Subject		C_{max} (ng/mL)	AUC_{0-t} (ng/mL/h)	n	C_{max} (ng/mL)	AUC_{0-t} (ng/mL/h)	n	C_{max} (ng/mL)	AUC_{0-t} (ng/mL/h)
Dapagliflozin	Female	14	85.1 (34.4)	513.4 (87.7)	14	77.0 (16.5)	499.0 (100.7)	14	133.9 (38.5)	529.6 (105.2)
	Male	27	87.8 (29.6)	451.1 (116.9)	26	78.4 (19.5)	443.5 (98.0)	27	125.2 (30.3)	467.8 (105.8)
Saxagliptin	Female	14	25.8 (11.2)	114.2 (29.7)	14	24.2 (6.2)	118.0 (31.2)	14	30.2 (8.1)	105.1 (22.0)
	Male	27	22.4 (6.2)	98.0 (24.0)	26	20.3 (4.6)	96.9 (22.6)	27	24.4 (9.8)	86.6 (22.3)
5-OH saxagliptin	Female	14	51.2 (11.6)	359.9 (79.2)	14	52.8 (14.3)	355.1 (75.3)	14	58.3 (14.0)	354.4 (66.9)
	Male	27	44.4 (6.9)	302.1 (50.1)	26	45.3 (11.3)	310.1 (52.9)	27	47.2 (11.7)	300.7 (52.5)
Metformin	Female	14	1251.0 (329.3)	13,183.3 (2906.1)	14	1196.5 (325.9)	13,252.2 (3347.8)	14	1408.9 (588.1)	10,660.6 (3505.7)
	Male	27	1086.3 (272.9)	10,418.3 (3032.0)	26	1029.3 (215.0)	9567.8 (2306.5)	27	1150.8 (352.5)	9041.2 (2100.4)

A = single dose of saxagliptin 2.5-mg and dapagliflozin 5-mg/metformin 1000-mg extended-release (XR) tablets coadministered orally under fed conditions; B = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR fixed-combination drug product (FCDP) under fed conditions; C = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fasting conditions; D = single dose of saxagliptin 5-mg and dapagliflozin 10-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions; E = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fed conditions; F = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fasting conditions.

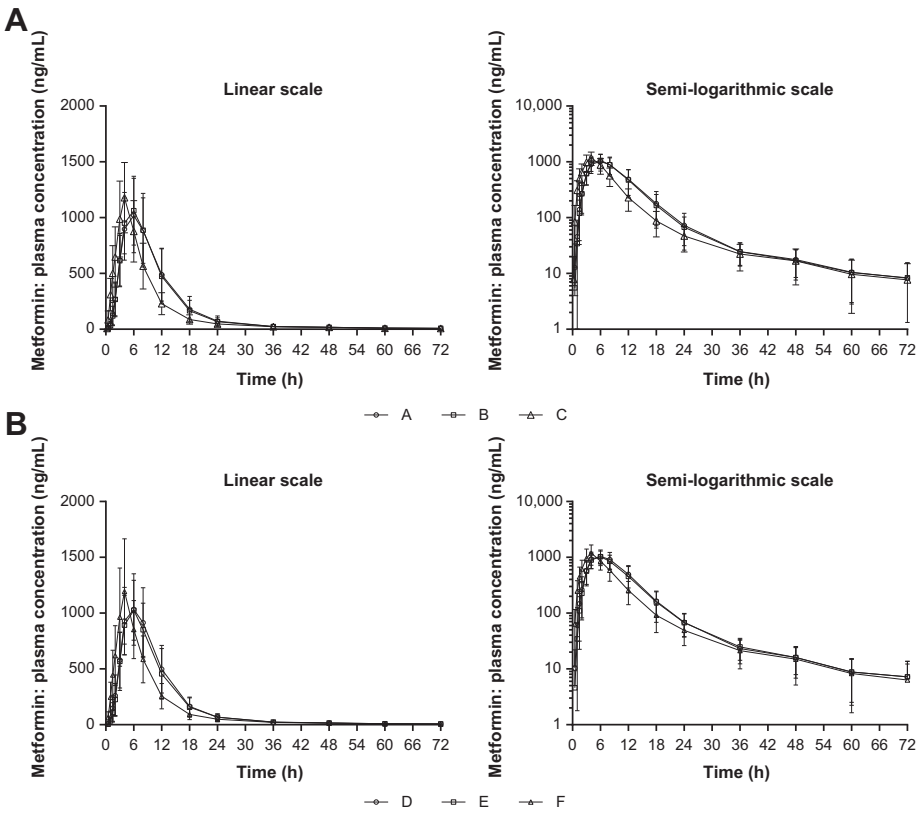

Figure. 5. Mean (SD) metformin plasma concentration−time profiles after single-dose administration of (A; top) dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg extended-release (XR) fixed-combination drug product (FCDP) and coadministered individual components in cohort 1 and (B; bottom) dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP and coadministered individual components in cohort 2. A = single dose of saxagliptin 2.5-mg and dapagliflozin 5-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions. B = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fed conditions. C = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fasting conditions. D = single dose of saxagliptin 5-mg and dapagliflozin 10-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions. E = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fed conditions. F = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fasting conditions.

90% CIs for the GM ratios of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were entirely within the 80%−125% limit, indicating bioequivalence (Table IV).

Food Effect

For dapagliflozin, the median T_{max} value was delayed in the fed state versus the fasted state (3.00 vs 1.00 h, respectively) (Table III). The dapagliflozin GM ratio for C_{max} was ~39% lower in the fed versus the fasted state (90% CI, 54.76%−68.12%); however, the GM ratios for $AUC_{0-\infty}$ and AUC_{0-t} were 95.08% and 94.75%, respectively, with the corresponding 90% CIs within the 80%−125% limit (Table IV). The median T_{max} values for saxagliptin and 5-OH saxagliptin were delayed in the fed state (1.99 and 3.00 h, respectively) versus the fasted state (0.50 h and 1.50 h, respectively). For saxagliptin, the 90% CIs for the GM ratios of $AUC_{0-\infty}$ and AUC_{0-t}

were within the 80%−125% limit and the 90% CI for the GM ratio of C_{max} was slightly below the 80%−125% limit. For 5-OH saxagliptin, the 90% CIs for the GM ratios of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were entirely within the 80%−125% limit. For metformin, the median T_{max} value was slightly delayed in the fed versus the fasted state (6.00 vs 4.00 h). The 90% CIs for the GM ratio of metformin $AUC_{0-\infty}$ were slightly above the 80%−125% limit, and the 90% CIs for the GM ratios of metformin AUC_{0-t} and C_{max} were within the 80%−125% limit.

Exposure: Sex Comparison

The AUC_{0-t} of dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin was 12%−13%, 15%−20%, 14%−18%, and 16%−32% higher in female subjects than in male subjects, respectively. The C_{max} of dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin was <2%, 14%−21%, 14%−21% and 14%−20% higher in female subjects than in male subjects, respectively (Table V).

Safety

No deaths, serious AEs, or AEs leading to discontinuation of the study drugs occurred. In total, 13 (31.0%) and 9 (21.4%) subjects experienced at least 1 AE in cohorts 1 and 2, respectively; headache and nausea were the most commonly reported AEs among subjects experiencing at least 1 AE (Table VI). AEs were judged as related to the study drug in 5 (11.9%) subjects in cohort 1 and in 3 (7.1%) subjects in cohort 2. All AEs were mild to moderate in intensity, and food did not appear to have any influence on the occurrence of AEs. For both FCDPs, AEs were similar between the fed and fasted states. Fewer AEs were reported with the higher tablet strength (cohort 2), although more of the reported AEs were considered related to the study drug versus those reported in cohort 1. Four (9.5%) subjects in cohort 1 and 3 (7.1%) subjects in cohort 2 reported AEs for the FCDPs that were not experienced after receiving the ICs; all were mild and considered not related to the study drug. Five (11.9%) subjects in cohort 1 and 2 (4.8%) subjects

Table VI. Adverse events (AEs) in cohort 1 (dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg extended-release [XR] fixed-combination drug product [FCDP]) and cohort 2 (dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP). Data are expressed as number of subjects with event (%).

AE Category	Cohort 1				Cohort 2			
	A (n = 42)	B (n = 41)	C (n = 41)	All Subjects (N = 42)	D (n = 42)	E (n = 40)	F (n = 41)	All Subjects (N = 42)
Any AE	7 (16.7)	5 (12.2)	5 (12.2)	13 (31.0)	3 (7.1)	5 (12.5)	4 (9.8)	9 (21.4)
Any AE causally related to treatment	4 (9.5)	1 (2.4)	2 (4.8)	5 (11.9)	1 (2.4)	2 (5.0)	1 (2.4)	3 (7.1)
Headache	2 (4.8)	0	1 (2.4)	3 (7.1)	1 (2.4)	2 (5.0)	0	2 (4.8)
Diarrhea	2 (4.8)	1 (2.4)	1 (2.4)	2 (4.8)	0	0	0	0
Nausea	2 (4.8)	0	0	2 (4.8)	0	0	2 (4.9)	2 (4.8)

Safety analysis set. There were no reported AEs or serious AEs with an outcome of death/including events with an outcome of death. There were no AEs or serious AEs leading to discontinuation of the study drugs as judged by the investigator. A = single dose of saxagliptin 2.5-mg and dapagliflozin 5-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions; B = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fed conditions; C = single dose of dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP under fasting conditions; D = single dose of saxagliptin 5-mg and dapagliflozin 10-mg/metformin 1000-mg XR tablets coadministered orally under fed conditions; E = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fed conditions; F = single dose of dapagliflozin 10-mg/saxagliptin 5-mg/metformin 1000-mg XR FCDP under fasting conditions.

in cohort 2 reported AEs for the ICs that were not reported for the FCDPs; all were mild to moderate in intensity and were judged by the investigator as not related to the study drug. No clinically significant results were identified for vital signs measurements, ECG evaluations, physical examinations, or laboratory data.

DISCUSSION

Personalized treatment strategies that incorporate FCDPs may simplify disease management and improve outcomes for patients with T2DM.[1–3,14–18] The current study was performed as part of the clinical development program of a dapagliflozin/saxagliptin/metformin XR FCDP. Two FCDP tablet strengths were evaluated in healthy subjects, and both showed bioequivalence with coadministration of the ICs.[8,19]

In the evaluation of the dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP in cohort 1, the upper limit of the 90% CI for the GM ratio for dapagliflozin's C_{max} was slightly above 125%. For dapagliflozin, the pharmacodynamic effect of urinary glucose excretion is mainly driven by AUC not by C_{max}.[22,23] Dapagliflozin monotherapy 100 mg has previously been established as safe and generally well tolerated in healthy volunteers.[24] This finding is therefore unlikely to have a clinically relevant impact on efficacy and safety.

Similar to previous investigations, food delayed the absorption of dapagliflozin, saxagliptin (plus 5-OH saxagliptin), and metformin.[25–28] The C_{max} for dapagliflozin was ~38%–39% lower in the fed versus the fasted state; however, the effect of food on dapagliflozin's C_{max} is unlikely to have a clinically relevant impact on efficacy, given the role of dapagliflozin's $AUC_{0-\infty}$ in driving urinary glucose excretion.[21,22] As stated in the US label, dapagliflozin can be taken with or without food.[4] Food slightly increased the overall exposure (AUC parameters) of saxagliptin and metformin, and slightly decreased the C_{max} of saxagliptin. However, considering the small magnitude of these changes, the impact of food on both saxagliptin and metformin is not considered clinically meaningful.

One subject in cohort 1 was identified as an outlier as this subject had a 3.56-fold higher dapagliflozin C_{max} for the dapagliflozin 5-mg/saxagliptin 2.5-mg/metformin 1000-mg XR FCDP compared with the ICs in the fed condition, which was the highest ratio observed of all subjects. Moreover, the C_{max} and concentration–time profile of this subject were largely equivalent between the fed and fasted states, which was not in accordance with the established effect of food on dapagliflozin PK,[23–28] suggesting the possibility that this subject may not have consumed all of the breakfast meal.

The exposure of dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin was higher in female subjects than in male subjects in both cohorts. These differences may be due to body weight, as the mean body weight of female subjects was lower than in male subjects in both cohorts. Previously, sex has been found to be a significant covariate in a dapagliflozin population PK model, in which the mean dapagliflozin $AUC_{0-\infty}$ at steady state was 22% higher in female subjects than in male subjects.[29] Furthermore, 5-OH saxagliptin exposure has been reported as ~25% higher in female subjects compared with male subjects.[30] The relatively small sex differences in dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin systemic exposure observed in the current study are unlikely to have a clinically relevant impact on the efficacy and safety of the FCDPs. Indeed, minimal sex differences in efficacy and safety have generally been observed in clinical studies of dapagliflozin,[6] saxagliptin,[31] and metformin.[32]

The safety evaluations were similar between both FCDPs and the ICs, with no significant changes from baseline or significant abnormal results being reported. Both FCDPs did have some AEs reported during the study that were not reported for the ICs; however, all were mild to moderate in intensity and not related to the study drugs.

CONCLUSIONS

In the fed state in healthy subjects, dapagliflozin/saxagliptin/metformin XR FCDPs in strengths of 5 mg/2.5 mg/1000 mg and 10 mg/5 mg/1000 mg showed bioequivalence to the coadministered ICs, saxagliptin and dapagliflozin/metformin hydrochloride XR FCDP.[8,19] In both FCDPs, the C_{max} for dapagliflozin was lower in the fed versus the fasted state; however, this finding is unlikely to have a clinically relevant impact on efficacy. Similarly, the impact of food on both saxagliptin and metformin is not considered clinically meaningful. Drug exposure

was higher in female subjects compared with male subjects, potentially due to their lower body weight. Single doses of all study drugs were well tolerated with no safety concerns. These data support the use of a dapagliflozin/saxagliptin/metformin XR FCDP in patients with T2DM.

CONFLICTS OF INTEREST

Drs. Tang, Engman, and Boulton are employees of AstraZeneca. Dr. Dayton and Ms. Zhu are employees of Covance Laboratories Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

The sponsor was involved in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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All authors contributed to the interpretation of the data and provided critical revisions to the manuscript. All authors read and approved the final version.

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