ORIGINAL ARTICLE

Bioequivalence of saxagliptin/dapagliflozin fixed-dose combination tablets compared with coadministration of the individual tablets to healthy subjects

Blisse Vakkalagadda[1], Marion L. Vetter[1], Jignasa Rana[1], Charles H. Smith[2], Jian Huang[2], Jennifer Karkas[1], David W. Boulton[3] & Frank LaCreta[1]

[1]Bristol-Myers Squibb, Princeton, New Jersey
[2]PPD, Wilmington, North Carolina
[3]AstraZeneca, Gaithersburg, Maryland

Abstract

Saxagliptin and dapagliflozin are individually indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The bioequivalence of saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg fixed-dose combination (FDC) tablets compared with coadministration of the individual tablets and the food effect on both strengths of saxagliptin/dapagliflozin FDCs were evaluated in this open-label, randomized, single-dose crossover study. Healthy subjects were randomized to saxagliptin 2.5 mg + dapagliflozin 5 mg fasted, 2.5/5 mg FDC fasted, 2.5/5 mg FDC fed (Cohort 1) or saxagliptin 5 mg + dapagliflozin 10 mg fasted, 5/10 mg FDC fasted, 5/10 mg FDC fed (Cohort 2). Serial blood samples for pharmacokinetics of saxagliptin and dapagliflozin were obtained predose and up to 60 h postdose. Bioequivalence of FDC tablets versus individual components was concluded if the 90% CIs for FDC to individual component geometric mean ratios of C_{max}, AUC_{0-T}, and AUC_{inf} of both analytes were between 0.80 and 1.25. Seventy-two subjects were randomized; 71 (98.6%) completed the study. Saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg FDC tablets were bioequivalent to the individual tablets administered concomitantly. Food had no clinically meaningful effect on saxagliptin or dapagliflozin overall systemic exposure. Saxagliptin/dapagliflozin FDC tablets were bioequivalent to coadministration of the individual components in healthy subjects under fasted conditions and food had no clinically meaningful effect on bioavailability.

Abbreviations

AE, adverse event; AUC_{0-T}, AUC from time zero to the time of the last quantifiable concentration; AUC, area under the plasma concentration-time curve; AUC_{inf}, AUC from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; DAPA, dapagliflozin; ECG, electrocardiogram; FDC, fixed-dose combination; GM, geometric least squares mean; LLOQ, lower limit of quantitation; PK, pharmacokinetics; SAXA, saxagliptin; $t_{1/2}$, terminal plasma half-life; T2DM, type 2 diabetes mellitus; t_{max}, time to maximum plasma concentration; ULN, upper limit of normal.

Introduction

The treatment of type 2 diabetes mellitus (T2DM) often requires combining two or more antidiabetes medications (American Diabetes Association, 2015). Combination therapies are effective because they target different underlying pathophysiologic aspects of the disease to achieve additive, synergistic, or complementary glucose-lowering effects (Bailey and Day 2009; Merovci et al. 2014). Saxagliptin (Onglyza®; AstraZeneca; Wilmington, DE), a selec-

tive and competitive dipeptidyl peptidase-4 (DPP-4) inhibitor, prevents inactivation of glucagon-like peptide-1 and glucose-dependent insulintropic polypeptide, to reduce postprandial and fasting glucose in patients with T2DM (Onglyza®, 2014). Saxagliptin is rapidly absorbed, with maximum plasma concentrations (C_{max}) achieved at 2 h after a single oral 5 mg dose in healthy subjects (Onglyza®, 2014). The C_{max} and overall systemic exposure, that is, area under the plasma concentration-time curve (AUC) for saxagliptin 5 mg are 24 ng/mL and 78 ng×h/mL, respectively (Onglyza®, 2014). Saxagliptin is primarily metabolized by cytochrome P450 3A4 and 3A5 to 5-hydroxy saxagliptin, which is half as potent as saxagliptin in inhibiting DPP-4 (Su et al. 2012). For 5-hydroxy saxagliptin, following ingestion of saxagliptin 5 mg, the C_{max} of 47 ng/mL was achieved at 4 h and the AUC was 214 ng×h/mL (Onglyza®, 2014). Dapagliflozin (Forxiga® [EU], AstraZeneca AB, Södertälje, Sweden; or Farxiga® [US]; AstraZeneca, Wilmington, DE) is a competitive inhibitor of human sodium-glucose cotransporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption in the kidney (Forxiga®, 2012; Farxiga®, 2015). The mechanism of action of dapagliflozin results in the direct and insulin-independent elimination of glucose by the kidney into the urine (Farxiga®, 2015). Dapagliflozin is rapidly absorbed, with C_{max} achieved at 1 h after a single oral 10 mg dose (Kasichayanula et al. 2014). The C_{max} and AUC extrapolated from time 0 to infinity (AUC_{inf}) for dapagliflozin 10 mg are 158 ng/mL and 585 ng×h/mL, respectively (Kasichayanula et al. 2014). Dapagliflozin is metabolized by UDP glucuronolsyltransferase 1A9 to dapagliflozin 3-O-glucuronide, which is an inactive metabolite (Obermeier et al. 2010). Recently, dual add-on therapy with saxagliptin plus dapagliflozin has demonstrated efficacy in reducing glycated hemoglobin (i.e., HbA1c) to a greater extent than the addition of either drug alone in combination with metformin in patients with T2DM poorly controlled with metformin monotherapy (Rosenstock et al. 2015). Both medications are individually indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (Onglyza®, 2014; Farxiga®, 2015).

In the past, combination treatments were often added sequentially and taken as separate tablets (Bailey and Day 2009). However, fixed-dose combination (FDC) tablets are now becoming increasingly common in clinical practice for the treatment of T2DM (Bailey and Day 2009). One potential advantage of an FDC treatment versus administration of separate tablets is improved adherence, which has been associated with improved glycemic control and less medication waste (Pan et al. 2008; Bailey and Day 2009). To support regulatory approval for commercialization of an FDC tablet, the bioequivalence of FDC tablets and individual tablets must be demonstrated, especially if the pivotal safety and efficacy studies were conducted using the individual tablets (Bailey and Day 2009).

This study assessed the bioequivalence of saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg FDC tablets compared with coadministration of the respective individual tablets. The effects of food on the bioavailability and safety of saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg were also evaluated to ensure the FDC tablets performed similarly to the individual components, both of which can be administered without regard to timing of meals relative to dosing (Onglyza®, 2014; Farxiga®, 2015).

Materials and Methods

Subjects

Healthy male and female subjects (18–50 years old and a body mass index of 18.5–30 kg/m^2) with no clinically significant abnormalities noted in their medical history, physical examination findings, 12-lead electrocardiogram (ECG) measurements, and clinical laboratory test results were eligible for study inclusion. Eligible women of childbearing potential were not pregnant or breastfeeding during the study period and were using an acceptable method of contraception.

This study was conducted at a single site (PPD Development, Austin, TX) from February to May 2014. The study protocol was approved by an institutional review board before study initiation. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Before the beginning of the study, subjects provided written informed consent.

Treatment and assessments

There were two cohorts in this 3-period crossover study (Table 1). One received low doses of both products (2.5 mg saxagliptin + 5 mg dapagliflozin), and the other received higher doses (5 mg saxagliptin + 10 mg dapagliflozin). A single dose of the assigned study drug was administered on day 1 of each period under fasted or fed (high fat, high calorie) conditions. There was a 6-day washout between doses, which is >5 times the half-life ($t_{1/2}$) for both drugs, meaning that sufficient clearance would have occurred so that little or no drug would be detectable at the beginning of the next period. Following period 3 for each cohort, subjects were confined for an additional 12 h after the last pharmacokinetic (PK) sample was collected to allow for fasted safety assessments.

Table 1. Study design.

	Period 1[2] (Days 1 to 3)		Period 2[2] (Days 1 to 3)		Period 3[2,3] (Days 1 to 3)	
	Cohort 1 (*N* = 36)					
	Treatment A		Treatment B		Treatment C	
	Treatment B	Washout	Treatment A	Washout	Treatment C	
	Treatment C	(6 days)	Treatment B	(6 days)	Treatment A	
	Treatment B		Treatment C		Treatment A	
	Treatment C		Treatment A		Treatment B	
Screening	Treatment A		Treatment C		Treatment B	
Enrollment	Cohort 2 (*N* = 36)					Discharge
Randomization[1]	Treatment D		Treatment E		Treatment F	
(Days −21 to −1)	Treatment E	Washout	Treatment D	Washout	Treatment F	
	Treatment F	(6 days)	Treatment E	(6 days)	Treatment D	
	Treatment D		Treatment F		Treatment E	
	Treatment E		Treatment F		Treatment D	
	Treatment F		Treatment D		Treatment E	

Treatment A, 2.5 mg SAXA + 5 mg DAPA tablets under fasted conditions; Treatment B, 2.5 mg SAXA/5 mg DAPA FDC tablet under fasted conditions; Treatment C, 2.5 mg SAXA/5 mg DAPA FDC tablet under fed conditions; Treatment D, 5 mg SAXA + 10 mg DAPA tablets under fasted conditions; Treatment E, 5 mg SAXA/10 mg DAPA FDC tablet under fasted conditions; Treatment F, 5 mg SAXA/10 mg DAPA FDC tablet under fed conditions; DAPA, dapagliflozin; FDC, fixed-dose combination; SAXA, saxagliptin.

[1]On day −1 subjects were admitted to the clinical facility, assigned to Cohort 1 or 2, and randomly assigned to a treatment sequence.

[2]A single dose of study drug was administered on day 1 of each period under fasted (10 h and subjects were not permitted to eat until 4 h after dosing) or fed (high-fat) conditions.

[3]Fasted safety assessments were conducted following period 3 for each cohort and required that subjects remain in the clinical facility for 12 h after their last pharmacokinetic assessment.

Subjects were confined to the clinic for the duration of treatment, which was 16 days. On dosing days, for the fasted bioequivalence assessment, subjects were required to fast from 10 h before administration of study drug until 4 h after dosing. Subjects receiving study drug under fed conditions were provided a high-fat breakfast consisting of ~ 917 kcal (~58.5% of calories from fat, ~26.2% of calories from carbohydrates, and ~15.4% of calories from protein) after fasting for 10 h. Breakfast started within 30 min of scheduled dosing, and dosing occurred within approximately 5 min of completion of the meal. At the time of dosing, 240 mL of water was provided to the subject along with his or her dose of study drug.

Subjects were closely monitored for adverse events (AEs) and serious AEs throughout the study. Clinical laboratory tests, vital sign measurements, physical examinations, and 12-lead ECG measurements were performed at selected times throughout the study. Serial blood samples were collected for up to 60 h after study drug administration for plasma PK analysis.

Blood samples were collected in 3-mL tubes containing K_2EDTA as the anticoagulant. Immediately after collection, each blood sample was mixed with the anticoagulant and placed in a cryoblock or in chipped wet ice equivalent to the approximate height of the blood in the tube. Within 2 h of collection, each blood sample was centrifuged under refrigeration (2–8°C) at approximately 1000 g for 15 min to separate the plasma. Plasma samples were stored immediately at or below −20°C to ensure stability of the samples until they were shipped on dry ice to the bioanalytical laboratory. Plasma samples were analyzed for saxagliptin, 5-hydroxy saxagliptin, and dapagliflozin by validated liquid chromatography tandem mass spectrometry assays. Precision and accuracy were evaluated by replicate analyses of human plasma quality control (QC) samples prepared at five concentrations spanning the calibration range. Precision was measured as the percent coefficient of variation (%CV) of the set of values for each QC sample. Accuracy was expressed as the percent difference of the mean value for each QC sample from the theoretical concentration. The between-run %CV was ≤7.52%, ≤5.82%, and ≤7.17%, and the within-run %CV was ≤20.7%, ≤15.0%, and ≤24.7% for saxagliptin, 5-hydroxy saxagliptin, and dapagliflozin, respectively. The accuracy was ±1.84%, ±2.32%, and ±2.21% for saxagliptin, 5-hydroxy saxagliptin, and dapagliflozin, respectively. The PK parameters of both saxagliptin and dapagliflozin were calculated from plasma concentration-time data using non-compartmental analysis.

Compliance with design and statistical analyses

This was an open-label, randomized, single-dose, 3-treatment, 3-period crossover study in fasted and fed healthy

subjects. For each cohort, if there was no difference between the bioavailability of dapagliflozin and saxagliptin after administration of the FDC tablets and the respective strength coadministered tablets, a sample size of 30 subjects would provide 94% and 97% power, respectively, to conclude bioequivalence for dapagliflozin and saxagliptin C_{max}, AUC from time 0 to the time of the last quantifiable concentration (AUC_{0-T}), and AUC_{inf}. If there was a 5% difference, a sample size of 30 subjects would provide 86% power to conclude bioequivalence for dapagliflozin and >97% power to conclude bioequivalence for saxagliptin for each PK parameter (C_{max}, AUC_{0-T}, and AUC_{inf}). Overall, if there was no difference in bioavailability between the FDC tablets and the respective strength coadministered tablets within each cohort, 30 subjects per cohort would provide 91% power to conclude bioequivalence with respect to C_{max}, AUC_{0-T}, and AUC_{inf} of both dapagliflozin and saxagliptin. The overall power would be 83% if there was a 5% difference in bioavailability. To allow for dropouts, 72 subjects (36 subjects per cohort) were planned to be randomly assigned to a treatment sequence. Subjects were assigned to 1 of the 2 cohorts and then randomly assigned to 1 of 6 treatment sequences, according to a computer-generated randomization scheme.

Descriptive statistics were calculated for plasma concentration-time data, PK parameters, and safety variables. To demonstrate bioequivalence of the saxagliptin/dapagliflozin FDC tablets with coadministration of the individual saxagliptin and dapagliflozin tablets, point estimates and 90% CIs for the geometric least squares means for C_{max}, AUC_{0-T}, and AUC_{inf} of saxagliptin and dapagliflozin were constructed for FDC tablets relative to the respective strengths of saxagliptin and dapagliflozin administered together as individual components. To estimate the food effect on the FDC tablets, point estimates and 90% CIs for the geometric least squares means for C_{max}, AUC_{0-T}, and AUC_{inf} of saxagliptin and dapagliflozin were constructed for the FDC tablets in the fed state relative to the respective strengths of the FDC tablets in the fasted state. A linear mixed-effects model with treatment and period as fixed effects and measurement within each subject as repeated measures was fitted to the natural log-transformed PK parameters for use in estimation of effects and construction of CIs. Bioequivalence of FDC tablets versus individual components was concluded if the 90% CIs for test-to-reference ratios of the geometric means were between 0.80 and 1.25. This study was conducted in compliance with the study protocol. There were no significant deviations from the proposed study and the statistical analysis plan was prespecified prior to the start of analysis.

Results

Subject disposition and demographics

A total of 199 subjects were enrolled in the study, and 36 subjects were assigned to each of the two cohorts and randomly assigned to a treatment sequence within their cohort. Subjects enrolled but not randomly assigned to treatment were determined to no longer meet study criteria or did not enter the treatment period owing to other reasons (e.g., screening was not completed, back-up subject not used or extra subject screened, subject did not show up for check-in, or subject changed his or her mind). Data from 72 subjects were included in the safety and PK analyses.

Seventy-one subjects (98.6%) received all three treatments in their assigned cohort and completed the study. All subjects in Cohort 1 completed the study. One subject (1.4%) in Cohort 2 did not complete the study because of noncompliance. Baseline demographics were generally similar across both cohorts (Table 2). However, there were more white subjects in Cohort 1 than in Cohort 2 (75% vs. 47%) and fewer black subjects (22% vs. 50%).

Pharmacokinetic results

Plasma dapagliflozin and saxagliptin concentrations decreased in a multiexponential way (Figs. 1 and 2, respectively). In the fasted state, the dapagliflozin profiles were similar between the administration of individual components separately or as an FDC. The dapagliflozin plasma concentration-time profiles showed lower peak concentrations under fed conditions compared with dosing under fasted conditions, but the overall exposure (AUC parameters) was not markedly affected by food. In the fasted and fed state, the saxagliptin profiles were similar between the administrations of components separately or as an FDC.

The median time to maximum plasma concentration (t_{max}) of dapagliflozin was observed at 1 h for the FDC or individual components under fasted conditions and at 3 h for the FDC under fed conditions (Table 3). A similar delay in t_{max} under fed conditions was shown in Cohort 2. The mean dapagliflozin $t_{1/2}$ was approximately 13 h across all treatments in Cohort 1 and approximately 15–16 h across all treatments in Cohort 2. The median t_{max} of plasma saxagliptin was observed between 0.6 and 1.5 h for Cohorts 1 and 2 (Table 4). The mean saxagliptin $t_{1/2}$ was approximately 5.4 to 7.3 h across all treatments for both cohorts. Food had no clinically meaningful effect on the saxagliptin or dapagliflozin overall drug exposure (AUC parameters). However, the C_{max} of dapagliflozin

Table 2. Baseline demographic characteristics.

Characteristic	Cohort 1[1] (*n* = 36)	Cohort 2[2] (*n* = 36)	All Subjects (*N* = 72)
Age, year			
Mean (SD)	34.8 (7.82)	33.3 (7.86)	34.0 (7.82)
Range	20–49	20–48	20–49
Sex, *n* (%)			
Male	21 (58.3)	21 (58.3)	42 (58.3)
Female	15 (41.7)	15 (41.7)	30 (41.7)
Race, *n* (%)			
White	27 (75.0)	17 (47.2)	44 (61.1)
Black	8 (22.2)	18 (50.0)	26 (36.1)
Asian	1 (2.8)	1 (2.8)	2 (2.8)
Ethnicity, *n* (%)			
Hispanic/Latino	11 (30.6)	9 (25.0)	20 (27.8)
Not Hispanic/Latino	25 (69.4)	27 (75.0)	52 (72.2)
Height, cm			
Mean (SD)	170.83 (10.825)	169.91 (11.145)	170.37 (10.918)
Range	150.0–203.1	145.5–199.0	145.5–203.1
Weight, kg			
Mean (SD)	73.29 (11.954)	75.99 (12.876)	74.64 (12.410)
Range	51.9–92.7	49.3–100.2	49.3–100.2
Body mass index, kg/m^2			
Mean (SD)	25.04 (2.766)	26.22 (2.983)	25.63 (2.918)
Range	20.5–29.7	19.7–29.8	19.7–29.8

dapagliflozin; FDC, fixed-dose combination; SAXA, saxagliptin; Treatment A: 2.5 mg SAXA + 5 mg DAPA tablets under fasted conditions; Treatment B: 2.5/5 mg FDC SAXA/DAPA tablet under fasted conditions; Treatment C: 2.5/5 mg SAXA/DAPA FDC tablet under fed conditions; Treatment D: 5 mg SAXA + 10 mg DAPA tablets under fasted conditions; Treatment E: 5/10 mg SAXA/DAPA FDC tablet under fasted conditions; Treatment F: 5/10 mg SAXA/DAPA FDC tablet under fed conditions.
[1]Treatments A, B, and C.
[2]Treatments D, E, and F.

was reduced by ~35% to 50% under fed conditions compared with fasted conditions in Cohorts 1 and 2 for the FDC tablet. The C_{max} of saxagliptin was unaffected by food. Saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg FDC tablets were bioequivalent to the individual component tablets administered concomitantly in the fasted state (Table 5).

Safety results

Although not powered to detect differences in AEs between saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg FDC tablets compared with coadministration of the respective individual tablets, the incidence of AEs was tabulated and reviewed for potential signals and clinical importance. The 2.5 mg saxagliptin + 5 mg dapagliflozin tablets (fasted), the 5 mg saxagliptin + 10 mg dapagliflozin tablets (fasted), a 2.5 mg saxagliptin/5 mg dapagliflozin FDC tablet (fed and fasted), and a 5 mg saxagliptin/10 mg dapagliflozin FDC tablet (fed and fasted) were generally safe and well tolerated by the healthy subjects in this study. There were no deaths or serious AEs reported during this study. None of the subjects discontinued from the study because of AEs. In Cohort 1, 13 subjects (36.1%) reported ≥1 AE. The most frequent AEs overall in Cohort 1 were headache and nausea (Table 6). Three subjects (8.3%) reported AEs with 2.5 mg saxagliptin + 5 mg dapagliflozin tablets under fasted conditions, four subjects (11.1%) reported AEs with a 2.5 mg saxagliptin/5 mg dapagliflozin FDC tablet under fasted conditions, and eight subjects (22.2%) reported AEs with a 2.5 mg saxagliptin/5 mg dapagliflozin FDC tablet under fed conditions. In Cohort 2, 9 subjects (25.0%) reported ≥1 AE during the study. The most frequent AE overall in Cohort 2 was nausea (Table 7). Six subjects (17.1%) reported AEs with either 5 mg saxagliptin + 10 mg dapagliflozin tablets or a 5 mg saxagliptin/10 mg dapagliflozin FDC tablet under fasted conditions. Five subjects (13.9%) reported AEs with a 5 mg saxagliptin/10 mg dapagliflozin FDC tablet under fed conditions.

Standard hematology, serum chemistry, and urinalysis results generally were similar at screening and posttreatment across the treatment groups. There were no AEs reported based on clinical laboratory abnormalities. Additionally, no subjects met aminotransferase or total bilirubin criteria for potential drug-induced liver injury,
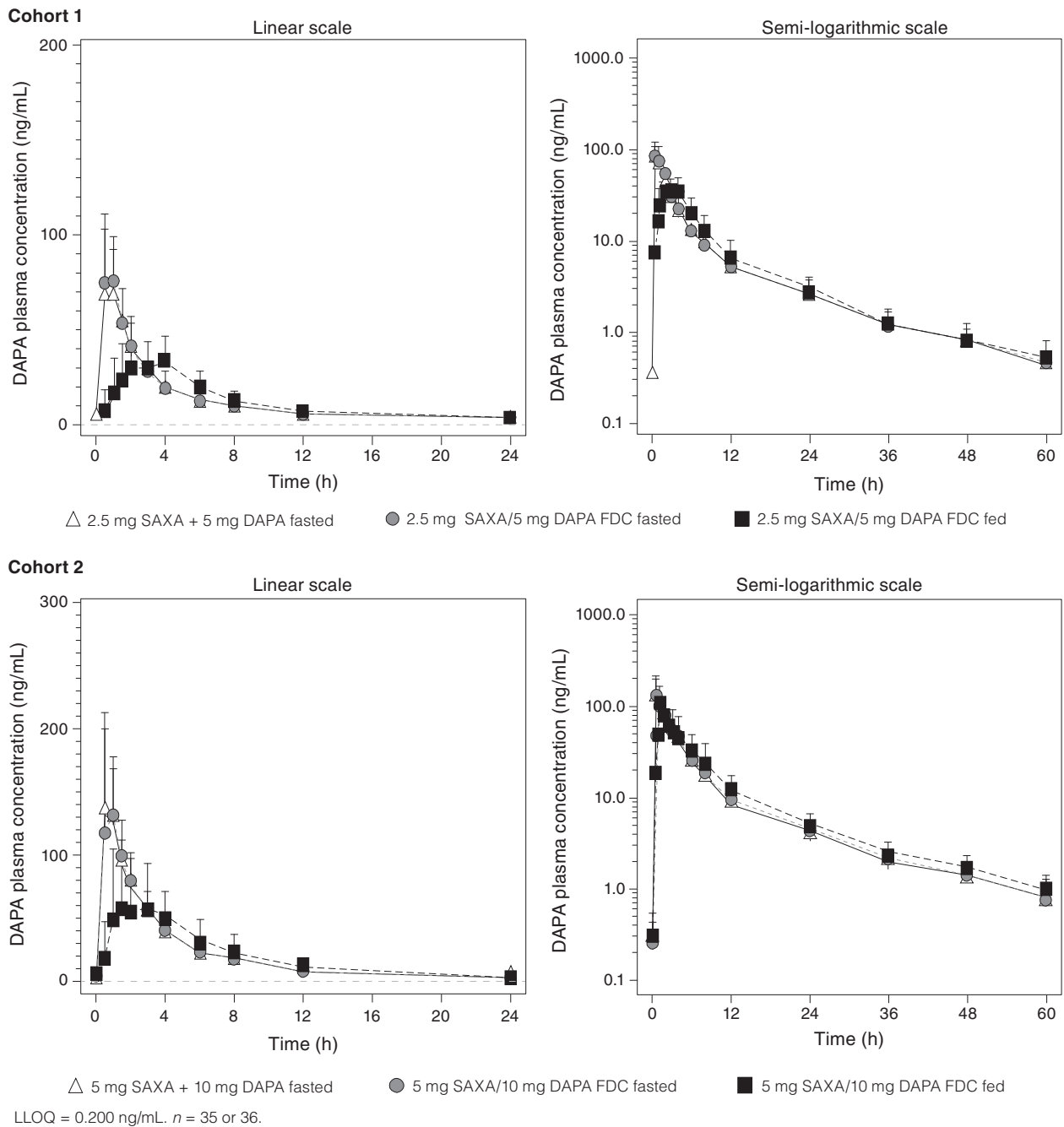
Cohort 1

△ 2.5 mg SAXA + 5 mg DAPA fasted   ● 2.5 mg SAXA/5 mg DAPA FDC fasted   ■ 2.5 mg SAXA/5 mg DAPA FDC fed

Cohort 2

△ 5 mg SAXA + 10 mg DAPA fasted   ● 5 mg SAXA/10 mg DAPA FDC fasted   ■ 5 mg SAXA/10 mg DAPA FDC fed

LLOQ = 0.200 ng/mL. *n* = 35 or 36.

Figure 1. Mean (+SD) dapagliflozin plasma concentration versus time profile for Cohort 1 and Cohort 2. DAPA, dapagliflozin; FDC, fixed-dose combination; LLOQ, lower limit of quantitation; SAXA, saxagliptin.

defined as an aminotransaminase elevation >3 times the upper limit of normal (ULN) and total bilirubin >2 times the ULN without initial findings of cholestasis (elevated serum alkaline phosphatase) and no other immediately apparent possible causes of aminotransaminase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drugs known to be hepatotoxic. Overall, the mean values of ECG measurements at screening, period 1 day −1, and the end of study visit were similar. Overall, the mean vital sign measurements at screening, period 1 day −1, predose on day 1 of each period, and the end of study visit were similar.
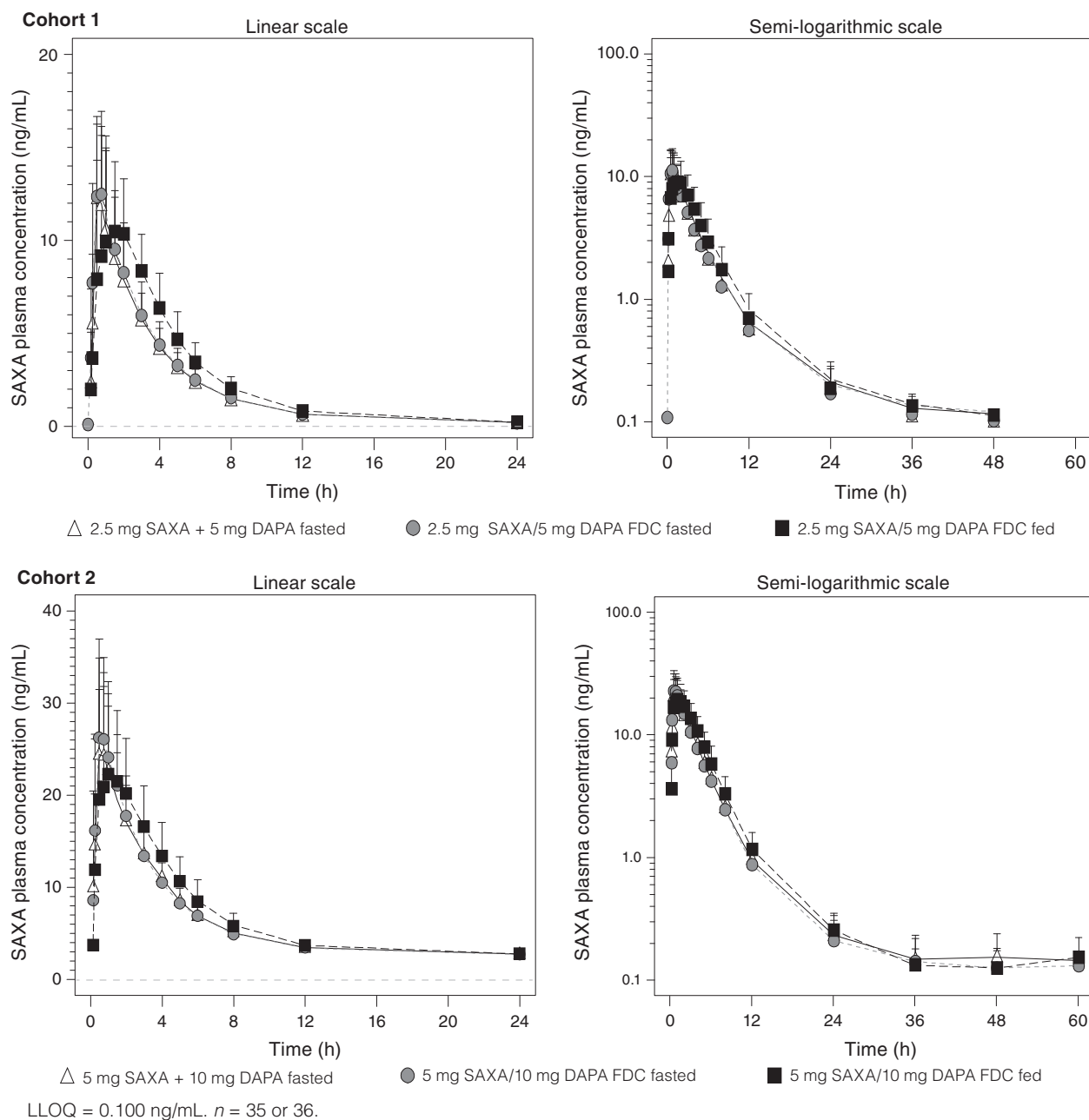
Figure 2. Mean (+SD) saxagliptin plasma concentration versus time profile for Cohort 1 and Cohort 2. DAPA, dapagliflozin; FDC, fixed-dose combination; LLOQ, lower limit of quantitation; SAXA, saxagliptin.

Discussion

Findings from the present study demonstrate the bioequivalence of both strengths of saxagliptin/dapagliflozin FDC tablets with coadministration of the respective individual components in healthy subjects under fasted conditions. Coadministration of saxagliptin and dapagliflozin, either as individual components separately or as an FDC

tablet, yielded a PK profile similar to that observed when saxagliptin and dapagliflozin are administered alone as monotherapy (Kasichayanula et al. 2014; Onglyza®, 2014). At the usual prescribed doses of saxagliptin (5 mg) and dapagliflozin (10 mg), time to reach C_{max} (t_{max}) for both saxagliptin and dapagliflozin was shorter (≤1 h) in the present study compared with when they are used alone as monotherapy (1–2 h), whereas AUC and C_{max}

Table 3. Dapagliflozin pharmacokinetic parameters

Pharmacokinetic parameters	Cohort 1			Cohort 2		
	SAXA 2.5 mg + DAPA 5 mg fasted (Treatment A) (n = 36)	SAXA 2.5-mg/DAPA 5-mg FDC fasted (Treatment B) (n = 36)	SAXA 2.5-mg/DAPA 5-mg FDC fed (Treatment C) (n = 36)	SAXA 5 mg + DAPA 10 mg fasted (Treatment D) (n = 35)	SAXA 5-mg/DAPA 10-mg FDC fasted (Treatment E) (n = 35)	SAXA 5-mg/DAPA 10-mg FDC fed (Treatment F) (n = 36)
C_{max}, ng/mL, GM (CV%)	78.5 (30)	85.6 (31)	45.1 (29)	150 (38)	141 (40)	91.3 (43)
t_{max}, h						
Median	1.00	1.00	3.00	0.550	1.00	2.50
Minimum–maximum	0.50–3.00	0.50–2.00	1.00–4.15	0.50–4.00	0.50–3.00	0.50–8.08
$AUC_{0–T}$, ng·h/mL, GM (CV%)	313 (25)	314 (28)	293 (25)	580 (23)	601 (21)	557 (21)
AUC_{inf}, ng·h/mL, GM (CV%)	321 (25)	323 (28)	303 (25)	598 (23)	620 (21)	582 (21)
$t_{½}$, h						
Mean (SD)	12.8 (2.80)	13.1 (5.19)	13.3 (4.56)	15.0 (4.72)	15.6 (5.54)	16.4 (5.53)

$AUC_{0–T}$, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf}, area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation; DAPA, dapagliflozin; GM, geometric mean; SAXA, saxagliptin; $t_{½}$, half-life; t_{max}, time to maximum plasma concentration.

Table 4. Saxagliptin pharmacokinetic parameters.

Pharmacokinetic parameters	Cohort 1			Cohort 2		
	SAXA 2.5 mg + DAPA 5 mg fasted (Treatment A) (n = 36)	SAXA 2.5-mg/DAPA 5-mg FDC fasted (Treatment B) (n = 36)	SAXA 2.5-mg/DAPA 5-mg FDC fed (Treatment C) (n = 36)	SAXA 5 mg + DAPA 10 mg fasted (Treatment D) (n = 35)	SAXA 5-mg/DAPA 10-mg FDC fasted (Treatment E) (n = 35)	SAXA 5-mg/DAPA 10-mg FDC fed (Treatment F) (n = 36)
C_{max}, ng/mL, GM (CV%)	12.8 (32)	13.4 (27)	12.6 (31)	26.1 (38)	27.6 (32)	25.6 (36)
t_{max}, h						
Median	0.750	0.658	1.50	0.750	0.600	1.00
Minimum–maximum	0.50–5.00	0.25–2.00	0.50–4.00	0.25–3.00	0.25–1.50	0.50–4.00
$AUC_{0–T}$, ng·h/mL, GM (CV%)	47.8 (20)	49.7 (22)	58.4 (19)	95.6 (23)	96.4 (23)	111 (20)
AUC_{inf}, ng·h/mL, GM (CV%)	49.1 (19)	51.1 (22)	59.7 (19)	97.2 (23)	97.5 (23)	113 (20)
$t_{½}$, h						
Mean (SD)	5.60 (2.17)	6.00 (2.47)	5.98 (1.86)	7.20 (4.66)	5.37 (2.94)	7.28 (4.31)

$AUC_{0–T}$, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf}, area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation; DAPA, dapagliflozin; GM, geometric mean; SAXA, saxagliptin; $t_{½}$, half-life; t_{max}, time to maximum plasma concentration.

for both drugs were similar to that observed when saxagliptin or dapagliflozin are used alone as monotherapy (Kasichayanula et al. 2014; Onglyza®, 2014). Additionally, food had no clinically meaningful effect on the overall bioavailability of either component. Although administration of the FDC tablet in the fed versus the fasted state reduced the peak systemic exposure of dapagliflozin by up to ~50%, this effect is not considered clinically meaningful (Kasichayanula et al. 2011). In addition, there was no meaningful effect on the overall systemic exposure of dapagliflozin (AUC parameters) (Kasichayanula et al. 2011). Administration in the fed state had no meaningful effect on the peak or overall systemic exposure of saxagliptin. Studies on the individual components of the FDC

Table 5. Summary of bioequivalence and food–drug interaction results for dapagliflozin and saxagliptin.

	Dapagliflozin[1]				Saxagliptin[1]			
	Cohort 1		Cohort 2		Cohort 1		Cohort 2	
	FDC SAXA 2.5/DAPA 5, fasted versus SAXA 2.5 + DAPA 5, fasted	FDC SAXA 2.5/DAPA 5, fed versus FDC SAXA 2.5/DAPA 5, fasted	FDC SAXA 5/DAPA 10, fasted versus SAXA 5 + DAPA 10, fasted	FDC SAXA 5/DAPA 10, fed versus FDC SAXA 5/DAPA 10, fasted	FDC SAXA 2.5/DAPA 5, fasted versus SAXA 2.5 + DAPA 5, fasted	FDC SAXA 2.5/DAPA 5, fed versus FDC SAXA 2.5/DAPA 5, fasted	FDC SAXA 5/DAPA 10, fasted versus SAXA 5 + DAPA 10, fasted	FDC SAXA 5/DAPA 10, fed versus FDC SAXA 5/DAPA 10, fasted
C_{max}, ng/mL	1.093 (1.013–1.178)	0.526 (0.478–0.579)	0.946 (0.878–1.019)	0.648 (0.565–0.743)	1.047 (0.967–1.133)	0.939 (0.859–1.027)	1.059 (0.993–1.129)	0.925 (0.837–1.022)
AUC_{0-T}, ng·h/mL	1.006 (0.982–1.030)	0.933 (0.906–0.960)	1.036 (1.010–1.062)	0.931 (0.908–0.955)	1.040 (1.006–1.075)	1.175 (1.130–1.223)	1.007 (0.973–1.042)	1.155 (1.117–1.194)
AUC_{inf}, ng·h/mL	1.007 (0.984–1.030)	0.937 (0.911–0.964)	1.035 (1.008–1.063)	0.943 (0.919–0.968)	1.040 (1.007–1.074)	1.169 (1.125–1.214)	1.003 (0.969–1.038)	1.155 (1.118–1.194)

AUC_{0-T}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf}, area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{max}, maximum observed plasma concentration; DAPA, dapagliflozin; FDC, fixed-dose combination; SAXA, saxagliptin.
[1]Data are adjusted geometric mean ratios (90% CI). Study medication doses are milligrams.

tablet under the fed and fasted state have concluded that there are no clinically meaningful interactions for either drug despite modest effects on PK parameters (Patel et al. 2010; Kasichayanula et al. 2011). The mechanism of action of dapagliflozin was unlikely to be affected by the PK changes and was more directly related to its overall systemic exposure (i.e., AUC), which was unaffected (Kasichayanula et al. 2011). The conditions under which saxagliptin was being tested—high fat and double the recommended starting dose—would have the greatest possible effect on PK parameters but likely not have substantial clinical implications (Patel et al. 2010). Although there were more white and fewer black subjects in Cohort 1 than Cohort 2, racial differences in the systemic exposure of either dapagliflozin or saxagliptin are not expected based on the results observed in population PK analyses (Zhang et al. 2010; Kasichayanula et al. 2014). In the present analysis, administration of saxagliptin and dapagliflozin as individual tablets and as an FDC tablet were well tolerated. There were no deaths or serious AEs during the study. No subjects discontinued from the study owing to AEs.

Bioequivalence is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" (Biopharmaceutics Coordinating Committee, 2002). Before FDCs can be approved, it is important to demonstrate therapeutic equivalence to the individual components administered separately or to conduct a bioequivalence study comparing the FDC to the coadministration of the respective individual medications as a surrogate to show therapeutic equivalence to the coadministration of the individual medications (Mitra and Wu 2012). Generally, bioequivalence guidelines for FDCs recommend assessing AUC_{0-T}, AUC_{0-inf}, and C_{max} PK parameters (Mitra and Wu 2012). The 90% CI for the ratio of an FDC and individual components for these PK parameters should be between 0.8% and 1.25%, which is considered the acceptable interval (Mitra and Wu 2012). It also is important to evaluate the effect food has on the PK of a drug, because food has the potential to affect the absorption or bioavailability of medications, and the interaction between food and an FDC may be different than that of the individual components (Singh 1999).

This study evaluated the performance of saxagliptin and dapagliflozin as an FDC, which is important because FDC medications reduce pill burden and improve medication adherence (Wertheimer and Morrison 2002; Pan et al. 2008). In general, the more complicated a medication regimen is, the lower the patient adherence (Wertheimer and Morrison

Table 6. Adverse events for Cohort 1.

Adverse event, n (%)	SAXA 2.5 mg + DAPA 5 mg fasted (Treatment A) (n = 36)	SAXA 2.5 mg/DAPA 5 mg FDC fasted (Treatment B) (n = 36)	SAXA 2.5 mg/DAPA 5 mg FDC fed (Treatment C) (n = 36)	Total (N = 36)
Total subjects with an AE	3 (8.3)	4 (11.1)	8 (22.2)	13 (36.1)
Nausea	0	1 (2.8)	1 (2.8)	2 (5.6)
Infrequent bowel movements	0	1 (2.8)	0	1 (2.8)
Influenza-like illness	0	0	1 (2.8)	1 (2.8)
Vulvovaginal mycotic infection	0	0	1 (2.8)	1 (2.8)
Arthropod bite	0	0	1 (2.8)	1 (2.8)
Contusion	0	1 (2.8)	0	1 (2.8)
Laceration	0	0	1 (2.8)	1 (2.8)
Muscle tightness	0	0	1 (2.8)	1 (2.8)
Lipoma	0	0	1 (2.8)	1 (2.8)
Headache	0	1 (2.8)	2 (5.6)	3 (8.3)
Paresthesia	1 (2.8)	0	0	1 (2.8)
Dizziness	0	0	1 (2.8)	1 (2.8)
Presyncope	0	0	1 (2.8)	1 (2.8)
Irritability	1 (2.8)	0	0	1 (2.8)
Vaginal discharge	0	0	1 (2.8)	1 (2.8)
Allergic rhinitis	1 (2.8)	0	0	1 (2.8)

AE, adverse event; DAPA, dapagliflozin; FDC, fixed-dose combination; SAXA, saxagliptin.

Table 7. Adverse events for Cohort 2.

Adverse event, n (%)	SAXA 5 mg + DAPA 10 mg fasted (Treatment D) (n = 35)	SAXA 5 mg/DAPA 10 mg FDC fasted (Treatment E) (n = 35)	SAXA 5 mg/DAPA 10 mg FDC fed (Treatment F) (n = 36)	Total (N = 36)
Total subjects with an AE	6 (17.1)	6 (17.1)	5 (13.9)	9 (25.0)
Palpitations	0	1 (2.9)	0	1 (2.8)
Nausea	3 (8.6)	1 (2.9)	0	4 (11.1)
Vomiting	2 (5.7)	0	0	2 (5.6)
Abdominal pain	1 (2.9)	0	0	1 (2.8)
Diarrhea	0	1 (2.9)	0	1 (2.8)
Oral paresthesia	1 (2.9)	0	0	1 (2.8)
Vessel puncture site bruise	0	1 (2.9)	1 (2.8)	2 (5.6)
Influenza-like illness	0	0	1 (2.8)	1 (2.8)
Axillary mass	0	1 (2.9)	0	1 (2.8)
Back pain	1 (2.9)	0	0	1 (2.8)
Pain in extremity	0	1 (2.9)	0	1 (2.8)
Headache	0	1 (2.9)	1 (2.8)	1 (2.8)
Paresthesia	0	0	1 (2.8)	1 (2.8)
Decreased micturition frequency	1 (2.9)	0	0	1 (2.8)
Micturition urgency	0	1 (2.9)	0	1 (2.8)
Vaginal discharge	0	1 (2.9)	0	1 (2.8)
Vulvovaginal discomfort	1 (2.9)	0	0	1 (2.8)
Nasal congestion	0	1 (2.9)	0	1 (2.8)
Papule	0	1 (2.9)	1 (2.8)	2 (5.6)
Erythema	1 (2.9)	0	0	1 (2.8)
Pruritus	0	1 (2.9)	0	1 (2.8)
Generalized pruritus	0	0	1 (2.8)	1 (2.8)
Skin irritation	0	1 (2.9)	0	1 (2.8)

AE, adverse event; DAPA, dapagliflozin; FDC, fixed-dose combination; SAXA, saxagliptin.

2002). A retrospective database analysis of medication adherence among patients in a managed care organization demonstrated lower medication adherence rates in patients who switched from a single pill regimen to two separate pills compared with patients who switched to an FDC of the same medications (54% vs. 77%; $P < 0.001$) (Melikian et al.

2002). Similarly, increased medication adherence rates were observed among patients who, after receiving combination therapy, switched to FDC therapy (71% vs. 87%; $P < 0.001$) (Melikian et al. 2002). In addition to improved adherence, FDC tablets are cost-effective options for patients and payers and have been associated with reductions in healthcare service utilization (Cheong et al. 2008; Hutchins et al. 2011; Akazawa and Fukuoka 2013).

Findings from the present study showed that saxagliptin/dapagliflozin FDC tablets were bioequivalent to coadministration of the respective strength individual components in healthy subjects under fasted conditions. Additionally, food had no clinically meaningful effect on the overall systemic exposure of saxagliptin or dapagliflozin, and all treatments were well tolerated. These results support the value proposition of an FDC-containing saxagliptin and dapagliflozin.

Acknowledgements

Disclosures

Blisse Vakkalagadda, Marion L. Vetter, Jignasa Rana, Jennifer Karkas, and Frank LaCreta are stock holders and/or employees of Bristol-Myers Squibb and David W. Boulton is a stock holder and employee of AstraZeneca. Charles H. Smith and Jian Huang are employees of PPD and have no conflicts to report.

References

Akazawa M, Fukuoka K (2013). Economic impact of switching to fixed-dose combination therapy for Japanese hypertensive patients: a retrospective cost analysis. BMC Health Serv Res 13: 124.

American Diabetes Association (2015). Standards of medical care in diabetes-2015. Diabetes Care 38(Suppl 1): S88–S89.

Bailey CJ, Day C (2009). Fixed-dose single tablet antidiabetic combinations. Diabetes Obes Metab 11: 527–533.

Biopharmaceutics Coordinating Committee, US Center for Drug Evaluation and Research (2003). Guidance for industry bioavailability and bioequivalence studies for orally administered drug products — general considerations. US Department of Health and Human Services, US Food and Drug Administration. Available at http://www.fda.gov/downloads/Drugs/Guidances/ucm154838 (accessed 1 Dec 2015).

Cheong C, Barner JC, Lawson KA, Johnsrud MT (2008). Patient adherence and reimbursement amount for antidiabetic fixed-dose combination products compared with dual therapy among Texas Medicaid recipients. Clin Ther 30: 1893–1907.

Farxiga® (dapagliflozin) (2015). Full prescribing information. AstraZeneca, Wilmington, DE.

Forxiga® (dapagliflozin) (2012). Full prescribing information. AstraZeneca, United Kingdom.

Hutchins V, Zhang B, Fleurence RL, Krishnarajah G, Graham J (2011). A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. Curr Med Res Opin 27: 1157–1168.

Kasichayanula S, Liu X, Zhang W, Pfister M, Reele SB, Aubry AF, et al. (2011). Effect of a high-fat meal on the pharmacokinetics of dapagliflozin, a selective SGLT2 inhibitor, in healthy subjects. Diabetes Obes Metab 13: 770–773.

Kasichayanula S, Liu X, Lacreta F, Griffen SC, Boulton DW (2014). Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a selective inhibitor of sodium-glucose cotransporter type 2. Clin Pharmacokinet 53: 17–27.

Melikian C, White TJ, Vanderplas A, Dezii CM, Chang E (2002). Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. Clin Ther 24: 460–467.

Merovci A, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, et al. (2014). Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 124: 509–514.

Mitra A, Wu Y (2012). Challenges and opportunities in achieving bioequivalence for fixed-dose combination products. AAPS J 14: 646–655.

Obermeier M, Yao M, Khanna A, Koplowitz B, Zhu M, Li W, et al. (2010). In vitro characterization and pharmacokinetics of dapagliflozin (BMS-512148), a potent sodium-glucose cotransporter type II inhibitor, in animals and humans. Drug Metab Dispos 38: 405–414.

Onglyza® (saxagliptin) (2014). Full prescribing information. AstraZeneca, Wilmington, DE.

Pan F, Chernew ME, Fendrick AM (2008). Impact of fixed-dose combination drugs on adherence to prescription medications. J Gen Intern Med 23: 611–614.

Patel CG, Zhang J, Li L, Gooding L, Croop R, Li T, et al. (2010). Effect of a high-fat meal on the pharmacokinetics of saxagliptin in healthy subjects. J Clin Pharmacol 50: 1211–1216.

Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B, et al. (2015). Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition

versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care 38: 376–383.

Singh BN (1999). Effects of food on clinical pharmacokinetics. Clin Pharmacokinet 37: 213–255.

Su H, Boulton DW, Barros A Jr, Wang L, Cao K, Bonacorsi SJ Jr, et al. (2012). Characterization of the in vitro and in vivo metabolism and disposition and cytochrome P450 inhibition/induction profile of saxagliptin in human. Drug Metab Dispos 40: 1345–1356.

Wertheimer AI, Morrison A (2002). Combination drugs: innovation in pharmacotherapy. P&T 27: 44–49.

Zhang L, Boulton D, Pfister M (2010). Exposure modeling of saxagliptin and 5-hydroxy saxagliptin in healthy subjects and in patients with type 2 diabetes to support saxagliptin dosing recommendations. Presented at: 70th Scientific Sessions of the American Diabetes Association, June 25–29, 2010; Orlando, Florida.