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APPLICATION NUMBER:

209091Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY MEMO

NDA	209-091 Serial 000
Submission Date	April 5, 2016
Brand Name	QTERN
Generic Names	Saxagliptin and dapagliflozin
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	AstraZeneca
Formulation; Strength	Fixed dose combination immediate release oral tablet; 5 mg saxagliptin/10 mg dapagliflozin
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

This memo serves the purpose of referring the Clinical Pharmacology review of NDA 209-091 Serial 000 to that of NDA [REDACTED] (b)(4) as appeared in DARRTS dated August 24, 2015 with the Reference ID number of 3810575 for the Office of Clinical Pharmacology (OCP) to assess and recommend the clinical pharmacology data cross-referenced under the NDA 209-091.

Executive Summary

The sponsor submitted NDA 209-091 for QTERN (saxagliptin/dapagliflozin) fixed dose combination (FDC) tablets, to support the following proposed indication:

- QTERN (saxagliptin and dapagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) [REDACTED] (b)(4)

For difficult to control patients with T2DM, who have not met treatment goals with metformin and the maximum recommended dose of 10 mg dapagliflozin, there are clinical trial data to support the option of adding saxagliptin to the treatment regimen.

The clinical pharmacology information for NDA 209-091 is the same as that reviewed under NDA [REDACTED] (b)(4). This reviewer reviewed portions of NDA 209-901 that was previously submitted to NDA [REDACTED] (b)(4).

The sponsor provided additional safety data for the 24-week short term treatment periods of Studies CV181168 and MB102129 in the 4-month safety update (4-MSU, submitted April 15, 2015 Sequence No. 0003). NDA [REDACTED] (b)(4) received a complete response letter on October 15, 2015.

Recommendation for NDA [REDACTED] (b)(4)1

The OCP/Division of Clinical Pharmacology 2 (DCP2) has reviewed NDA [REDACTED] (b)(4)'s Clinical Pharmacology data submitted [REDACTED] (b)(4). The data is acceptable to support approval provided

¹ See this reviewer's Clinical Pharmacology review in DARRTS dated August 24, 2015 with Reference ID number 3810575.

that a mutual agreement regarding the label language can be reached between the sponsor and the Food and Drug Administration.

Recommendation for NDA 209-091

OCP/DCP2 recommends approval of NDA 209-091 provided that a mutual agreement regarding the label language can be reached between the sponsor and the Food and Drug Administration.

Notes on Labeling Recommendation

This note documents the rationale for the recommendation to discontinue QTERN when the eGFR value persistently falls between 45 mL/min/1.73 m² and 60 mL/min/1.73 m² in the label.

The dapagliflozin (FARXIGA) label states that use of dapagliflozin is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m². Thus, the 60 mL/min/1.73 m² recommendation in the QTERN label originates from the dapagliflozin label.

The saxagliptin (ONGLYZA) label recommends that the dosage for patients with moderate or severe renal impairment, or end-stage renal disease (CrCl ≤ 50 mL/min) is 2.5 mg once daily regardless of meals. QTERN does not have the 2.5 mg saxagliptin strength of FDC. The recommended dose of saxagliptin is 2.5 or 5 mg once daily taken regardless of meals (ONGLYZA label). The saxagliptin label uses creatinine clearance (CrCl) to characterize renal function, whereas QTERN label uses eGFR instead. Thus, this makes it difficult to directly relate the exposure of saxagliptin at CrCl ≤ 50 mL/min to that at eGFR 45 mL/min/1.73 m².

The reanalysis of the original NDA pharmacokinetic data of saxagliptin tablets through current eGFR based classification criteria² and further subgrouping of moderate renal impairment³ showed that the molar ratio of saxagliptin in participants of eGFR 45 – 59 mL/min/1.73 m² is similar to those of healthy participants. However, the molar ratio of saxagliptin in participants of eGFR 30 – 45 mL/min/1.73 m² is 2 fold higher than that of healthy participants. This reanalysis of saxagliptin pharmacokinetic data was necessary because of the efforts to align the saxagliptin and metformin FDC tablets' labels with the changes to the metformin safety label changes for the use of metformin in renal impairment subgroups.

Combining the restrictions of saxagliptin and dapagliflozin use in renal impairment, OCP/DCP2 recommends discontinuing QTERN when the eGFR value persistently falls between 45 mL/min/1.73 m² and 60 mL/min/1.73 m² (b) (4)

Again, the FDC combinations containing 2.5 mg saxagliptin component are not available.

² Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling, Issued March 2010

³ Clinical Pharmacology Memo for NDA 200-678 for KOMBIGLYZE XR in DARRTS, Reference ID:4043391

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/s/

SZE W LAU
01/24/2017

MANOJ KHURANA
01/30/2017

CLINICAL PHARMACOLOGY REVIEW

NDA	(b) (4)
Submission Date	November 17, 2015
Brand Name	QTERN
Generic Names	Saxagliptin and dapagliflozin
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader (Acting)	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	AstraZeneca
Formulation; Strength	Fixed dose combination immediate release oral tablet; 5 mg saxagliptin/10 mg dapagliflozin
Relevant IND	118,840
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Purpose

This document reviews the Clinical Pharmacology related questions for the End of Review Meeting for immediate release (IR) 5 mg saxagliptin (SAXA) and 10 mg dapagliflozin (DAPA) (5 mg SAXA/10 mg DAPA) fixed dose combination (FDC) tablet with the sponsor.

Background

The sponsor received a Complete Response letter for NDA (b) (4) from the Division of Metabolism and Endocrinology Products on October 15, 2015 and the letter contains the following salient points:

(b) (4)

The currently approved dapagliflozin label recommends starting dapagliflozin at 5 mg with an increase to 10 mg only for those patients who can tolerate dapagliflozin 5 mg and require additional glucose lowering. Initiating dapagliflozin at 5 mg in the general population of patients with type 2 diabetes mellitus, naïve to dapagliflozin, was determined to be an essential condition of use for dapagliflozin

containing products based on review of safety data in NDA 202293 and this condition of use would also apply to your fixed combination drug product. (b) (4)

Path Forward

(b) (4) you will need to submit additional clinical trial data to inform the combination use of saxagliptin and dapagliflozin.

(b) (4)

(b) (4) you will need to provide clinical data (b) (4)

The sponsor requested the End of Review Meeting through this current submission.

Findings

Integrated safety analysis plan (see Section 7.1)

Question 1: Does the Agency agree with the proposed [REDACTED] (b) (4) in the Safety Update package?

Question 2: Does the Agency agree with the proposed plans for the format and content to be included in the Safety Update and Module 2.7.4 Summary of Clinical Safety Addendum and Module 2.5 Clinical Overview?

Question 3: Does the Agency agree [REDACTED] (b) (4) [REDACTED] ?

Prescribing information (see Section 7.2)

Question 4: Does the Agency agree that 5 mg saxagliptin/10 mg dapagliflozin FDC can be approved [REDACTED] (b) (4)? If yes:

- Does the Agency agree [REDACTED] (b) (4) [REDACTED]
- Does the Agency agree that approval based on the second scenario (restricted use in patients who can tolerate dapagliflozin 10 mg) would be fully supported by the current NDA package, planned updated LT safety analyses and individual study ST data from Study CV181168?

[REDACTED] (b) (4)

Clinical Pharmacology Response:

Clinical pharmacology defers Questions 1 – 4 and 6 – 8 to Clinical to answer.

Question 5. [REDACTED] (b) (4)

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/s/

SZE W LAU
12/10/2015

MANOJ KHURANA
12/15/2015

CLINICAL PHARMACOLOGY REVIEW

NDA	(b) (4)
Submission Dates	(b) (4) August 11, 2015
Brand Name	QTERN
Generic Names	Saxagliptin and dapagliflozin
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader (Acting)	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	AstraZeneca
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1 Executive Summary

The sponsor is seeking approval for immediate release (IR) 5 mg saxagliptin (SAXA) and 10 mg dapagliflozin (DAPA) (5 mg SAXA/10 mg DAPA) fixed dose combination (FDC) tablet as an adjunct to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Saxagliptin (ONGLYZA; 5 and 2.5 mg tablets) has an approved indication to improve glycemic control in adults with T2DM (NDA 22-350, approval on July 31, 2009). Dapagliflozin propanediol (FARXIGA; 5 and 10 mg tablets) also has an approved indication to improve glycemic control in adults with T2DM (NDA 20-702, approval on January 8, 2014).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA (b)(4)'s Clinical Pharmacology data submitted (b)(4). The data is acceptable to support approval provided that a mutual agreement regarding the label language can be reached between the sponsor and the Food and Drug Administration.

1.2 Post Marketing Requirement

None.

1.3 Summary of Important Clinical Pharmacology Findings

The sponsor submitted the results of 2 clinical pharmacology studies (CV181191 and CV181341), a pivotal efficacy study (CV181169), and 2 clinical safety studies (CV181169 and D1690C00010) to support NDA (b)(4). Study CV181191 assesses the mutual interaction upon oral administration between a 5 mg SAXA tablet and a 10 mg DAPA tablet. Study CV181341 assesses the bioequivalence between coadministration of 5 mg SAXA tablet plus 10 mg DAPA tablet and 5 mg SAXA/10 mg DAPA FDC tablet (b)(4).

(b)(4) Study CV181341 also has 2 additional arms to assess the food effect on the 5 mg SAXA/10 mg DAPA FDC tablet (b)(4).

(b)(4) See Biopharmaceutics reviewer's review for Study CV181341. Also, the sponsor only seeks approval for the 5 mg SAXA/10 mg DAPA FDC (b)(4).

(b)(4)
The 5 mg SAXA/10 mg DAPA FDC tablets used in the pivotal bioequivalence study were the same as the to-be-marketed 5 mg SAXA/10 mg DAPA FDC tablets.

According to the results of Study CV181191, SAXA and DAPA do not significantly interact with each other upon coadministration of 5 mg SAXA and 10 mg DAPA tablets.

(b)(4)

S.W. Johnny Lau, R.Ph., Ph.D.
OCP/DCP2

FT signed by Manoj Khurana, Ph.D., Acting Team Leader, _____ 8/ /15

2 Question-Based Review

2.1 Background

The sponsor developed the following strengths of FDC immediate release tablets:

- 5 mg SAXA/10 mg DAPA

(b) (4)

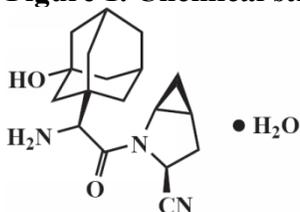
The sponsor submitted this 505(b)(1) new drug application to seek marketing approval only for the 5 mg SAXA/10 mg DAPA FDC oral tablet as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

2.2 General Attributes

2.2.1 What are SAXA and DAPA's key physicochemical properties?

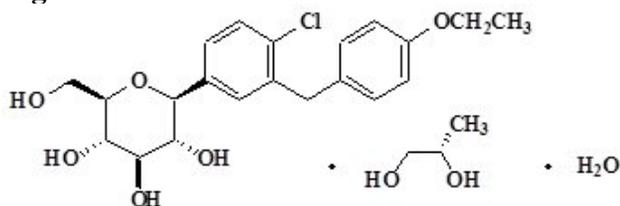
SAXA has a molecular weight of 333.43, empirical formula of $C_{18}H_{25}N_3O_2 \cdot H_2O$. See Figure 1 for the chemical structure of SAXA. SAXA is sparingly soluble in water with an aqueous solubility of 17.6 mg/mL at $24^\circ C \pm 3^\circ C$. SAXA has a pK_a of 7.3. SAXA's apparent octanol/water distribution coefficient ($D_{o/w}$) is 0.015 at pH 1.2, 0.04 at pH 4.5, and 0.607 at pH 7.

Figure 1. Chemical structure of SAXA.



DAPA has a molecular weight of 502.98, empirical formula of $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$. See Figure 2 for the chemical structure of DAPA. The solubility of DAPA in water at $24^\circ C \pm 3^\circ C$ is 1.6 mg/mL. DAPA's octanol/water partition coefficient is 2.45 at pH 7.4.

Figure 2. Chemical structure of DAPA.



2.2.2 What is the formulation for the to-be-marketed SAXA/DAPA FDC oral tablet?

Table 1 below details the formulation of the to-be-marketed 5 mg SAXA/10 mg DAPA FDC oral tablets.

Table 1. Composition of the to-be-marketed 5 mg SAXA/10 mg DAPA Film-Coated Tablet.

Component	Quality Standard	Function	Quantity per Tablet	
			(%w/w)	(mg)
(b) (4)				

Source: Sponsor's Table 3.2.P.1-6

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2.2.3 How does SAXA/DAPA FDC tablet work for the proposed indications?

Both drugs lower blood glucose concentrations in the body through the following mechanisms:

- Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the (dipeptidyl peptidase-4) DPP4 enzyme within minutes. SAXA is a DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with T2DM.
- Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. DAPA is an inhibitor of SGLT2. By inhibiting SGLT2, DAPA reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

2.2.4 What are the sponsor's proposed indication and dosing regimen for SAXA/DAPA FDC tablet?

The 5 mg SAXA/10 mg DAPA FDC tablet's proposed indication is an adjunct to diet and exercise to improve glycemic control in adults with T2DM (b) (4)

The 5 mg SAXA/10 mg DAPA FDC tablet's proposed dosing regimen is:

- a tablet taken once daily in the morning with or without food, but:
 - Do not initiate the tablet if eGFR is $< 60 \text{ mL/min/1.73 m}^2$.
 - Discontinue the tablet if eGFR falls persistently $< 60 \text{ mL/min/1.73 m}^2$.
 - Do not coadminister the tablet with strong cytochrome P450 3A4/5 inhibitors.

2.3 General Clinical Pharmacology

2.3.1 What are SAXA and DAPA's clinical pharmacokinetic (PK) characteristics?

Besides SAXA and DAPA's product labels, the following publications detail SAXA and DAPA's clinical PK and interactions:

- Scheen A.J. Dipeptidylpeptidase-4 Inhibitors (Gliptins) Focus on Drug-Drug Interactions. *Clin Pharmacokinet* 2010;49: 573-88.
- Scheen A.J. Drug-Drug Interactions with Sodium-Glucose Cotransporters Type 2 (SGLT2) Inhibitors, New Oral Glucose-Lowering Agents for the Management of Type 2 Diabetes Mellitus. *Clin Pharmacokinet* 2014;53:295-304.
- Amin M and Suksomboon N. Pharmacotherapy of Type 2 Diabetes Mellitus: An Update on Drug-Drug Interactions. *Drug Saf* 2014;37:903-19.

2.3.2 How is the proposed daily SAXA/DAPA FDC tablet dosing regimen determined for patients with T2DM?

The proposed dosing regimen of SAXA/DAPA FDC tablet follows the dosing recommendations of individual SAXA and DAPA tablets. The recommended starting dose of SAXA is 2.5 mg or 5 mg once daily taken regardless of meals (*see saxagliptin product label*). The recommended starting dose of DAPA is 5 mg once daily taken in the morning with or without food and can be increased to 10 mg once daily in patients who require additional glycemic control (*see dapagliflozin product label*).

2.3.3 What is the efficacy response of coadministration of SAXA and DAPA tablets?

The sponsor conducted Study CV181169 to show the efficacy response of the coadministered 5 mg SAXA tablet and 10 mg DAPA tablet. This was a Phase 3, double-blind, randomized, placebo-controlled

study in 534 subjects with T2DM and with a screening HbA1c > 8% and ≤ 12%, who did get adequate glycemic control on metformin monotherapy. This study compared the primary efficacy endpoint as the mean change from baseline in HbA1c achieved with the following treatments after 24 weeks of double-blind treatment:

- 5 mg SAXA + 10 mg DAPA + metformin XR
- 5 mg SAXA + metformin
- 10 mg DAPA + metformin

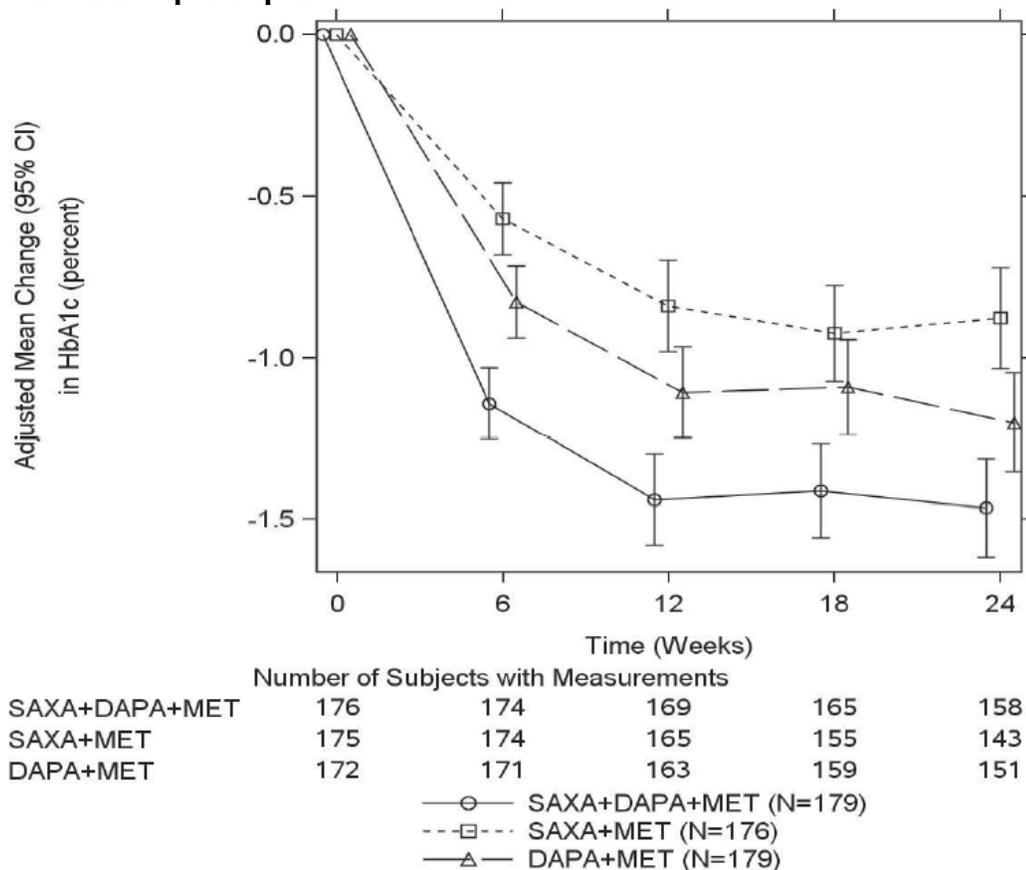
The sponsor claimed that the 5 mg SAXA + 10 mg DAPA + metformin treatment group showed superiority against the other treatment groups, 5 mg SAXA + metformin, and 10 mg DAPA + metformin, respectively (See Table 2 and Figure 3 below).

Table 2. Study CV181169's efficacy endpoint at Week 24.

Endpoint	Comparison	Saxagliptin + Dapagliflozin + Metformin XR	Saxagliptin + Metformin XR	Dapagliflozin + Metformin XR
A1c (%) Adjusted Mean Change from Baseline ^a (95% CI)	Mean Change from Baseline	-1.47% (-1.62, -1.31)	-0.88% (-1.03, -0.72)	-1.20% (-1.35, -1.04)
	Saxa/Dapa + Met XR	-0.59% (-0.81, -0.37)		
	vs. Saxa + Met XR	p<0.0001		
	Saxa/Dapa + Met XR	-0.27% (-0.48, -0.05)		
	vs. Dapa + Met XR	p = 0.0166		

Source: Study CV181169's report Table -3.

Figure 3. Longitudinal plot of change from baseline in HbA1c - 24-Week double blind period – randomized participants



Source: Study CV181169's report Figure 7.2-1.

For detailed discussion of Study CV181169's results and acceptability of the sponsor's claims on efficacy, see Dr. Suchitra Balakrishnan's medical review and Dr. Anna Kettermann's statistical review in DARRTS.

2.4 Intrinsic Factors

2.4.1 What intrinsic factors may affect the use of SAXA/DAPA FDC tablet?

See the individual SAXA and DAPA product labels for further information.

2.5 Extrinsic Factors

2.5.1 How does food affect the bioavailability (BA) of SAXA and DAPA from the FDC tablet?

Study CV181341 examined the effect of food on the BA of SAXA and DAPA from the FDC tablet. See Biopharmaceutics reviewer's (Dr. Peng Duan) review in DARRTS.

2.5.2 What is the potential for mutual interactions between SAXA and DAPA?

The sponsor conducted the following 2 studies to assess the interaction potential between SAXA and DAPA:

- Study 930059456
- Study CV181191

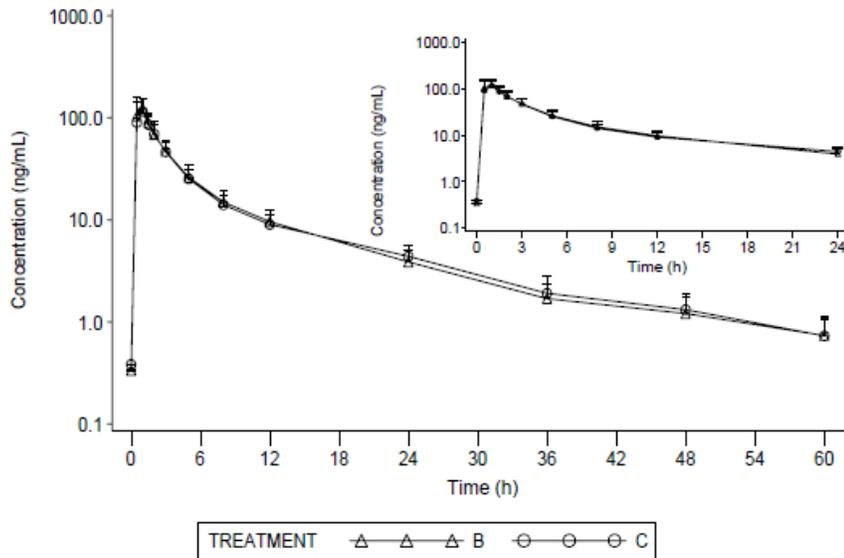
Study 930059456 is an in vitro study to assess the potential of SAXA and 5-OH SAXA (major active metabolite) to inhibit UGT1A9 to glucuronidate DAPA. The IC₅₀ values for SAXA and 5-OH SAXA were ≥ 50 μM, which was the highest concentration tested. In the same test systems, the positive control inhibitor, niflumic acid, inhibited DAPA and propofol glucuronidation with IC₅₀ values of 0.2 μM and 0.42 μM, respectively. These data suggest that SAXA and 5-OH SAXA have little or no potential to inhibit UGT1A9 and the metabolism of DAPA to its 3-O-glucuronide. See Dr. Fred Alavi's pharmacology/toxicology review in DARRTS dated June 15, 2015.

Study CV181191 was a single-dose, 3-period, 3-treatment, crossover study to assess the mutual interaction of SAXA and DAPA in 42 randomized healthy volunteers (29 men, 13 women, body mass index of 19.5 – 30.1 kg/m², and aged 19 – 43 years). The 3 treatments are the following with 6 days of washout period between treatments:

- 5 mg SAXA
- 10 mg DAPA
- 5 mg SAXA coadministered with 10 mg DAPA

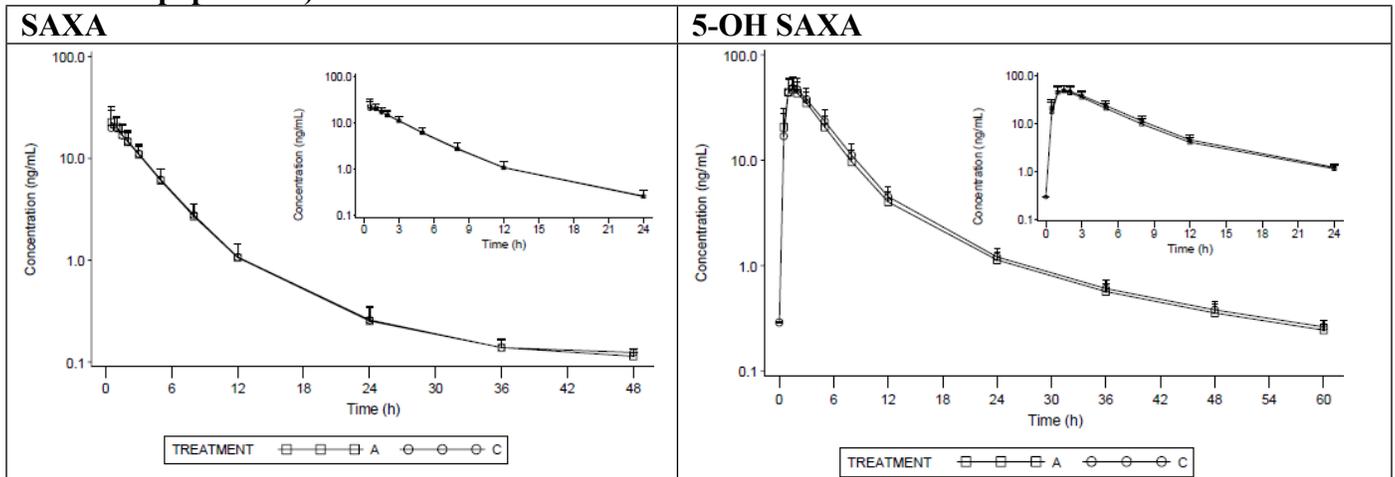
Serial blood samples were collected predose and 60 hours postdose to determine SAXA, 5-OH SAXA, and DAPA via validated liquid chromatography tandem mass spectrometry (LC/MS/MS) bioanalytical assays.

Figure 4. Mean (+SD) DAPA plasma concentration versus time profile (PK evaluable population)



Treatment B = 10 mg DAPA
 Treatment C = 5 mg SAXA + 10 mg DAPA
 Source: Study CV181191's report Figure 11.1

Figure 5. Mean (+SD) SAXA and 5-OH SAXA plasma concentration versus time profile (PK evaluable population).



Source: Study CV181191's report Figures 11.2 (SAXA) and 1.31 (5-OH SAXA)

Table 3. Effect of concomitant administration of SAXA on DAPA PK.

Analyte	Treatment and Comparison	C_{max}	AUC (0-T)	AUC (INF)
		(ng/mL)	(ng h/mL)	(ng h/mL)
		Adjusted GM [n]	Adjusted GM [n]	Adjusted GM [n]
Dapagliflozin	B	133 [41]	529 [41]	547 [41]
	C	125 [42]	523 [42]	539 [42]
Ratio of Adjusted GM (90% CI)				
C vs B		0.943 (0.867, 1.026)	0.990 (0.966, 1.014)	0.984 (0.961, 1.008)

Treatment B = 10 mg DAPA; Treatment C = 5 mg SAXA + 10 mg DAPA
 Source: Section 2.7.2 Table 2.

The ratios of adjusted geometric mean (GM) for DAPA C_{max} , $AUC_{(0-T)}$, and $AUC_{(INF)}$ indicated a decrease of 6, 1, and 2%, respectively, with concomitant administration of SAXA (Table 3). The 90% CI of ratios of adjusted GM for DAPA C_{max} , $AUC_{(0-T)}$, and $AUC_{(INF)}$ with concomitant administration of SAXA contained 1 and were all within the 0.8 – 1.25 bioequivalent goalpost (Table 3).

Table 4. Effect of concomitant administration of DAPA on SAXA and 5-OH SAXA PK.

Analyte	Treatment and Comparison	C _{max} (ng/mL) Adjusted GM [n]	AUC (0-T) (ng h/mL) Adjusted GM [n]	AUC (INF) (ng h/mL) Adjusted GM [n]
Saxagliptin	A	23.6 [42]	87.8 [42]	89.0 [42]
	C	21.9 [42]	87.0 [42]	88.2 [42]
	Ratio of Adjusted GM (90% CI)			
	C vs A	0.927 (0.883, 0.972)	0.991 (0.960, 1.022)	0.991 (0.961, 1.022)
5-OH Saxagliptin	A	47.0 [42]	267 [42]	273 [42]
	C	49.6 [42]	289 [42]	296 [42]
	Ratio of Adjusted GM (90% CI)			
	C vs A	1.055 (1.004, 1.109)	1.085 (1.058, 1.113)	1.085 (1.058, 1.113)

Treatment A = 5 mg SAXA; Treatment C = 5 mg SAXA + 10 mg DAPA
Source: Section 2.7.2 Table 3.

The ratios of adjusted GM for SAXA C_{max}, AUC_(0-T), and AUC_(INF) indicated a decrease of 7, 1, and 1%, respectively, with concomitant administration of DAPA (Table 4). The 90% CI of ratios of adjusted GM for SAXA C_{max}, AUC_(0-T), and AUC_(INF) with concomitant administration of DAPA were, however, all within the 0.8 – 1.25 bioequivalent goalpost (Table 4) and contained 1. The ratios of adjusted GM for 5-OH SAXA C_{max}, AUC_(0-T), and AUC_(INF) indicated an increase of 6, 9, and 9%, respectively, with concomitant administration of DAPA (Table 4). The 90% CI of ratios of adjusted GM for 5-OH SAXA C_{max}, AUC_(0-T), and AUC_(INF) with concomitant administration of DAPA were, however, all within the 0.8 – 1.25 bioequivalent goalpost (Table 4) and contained 1.

This reviewer’s statistical analyses results for DAPA and SAXA are consistent with the sponsor’s analyses. See Attachment.

According to the above analyses, SAXA and DAPA do not significantly interact with each other upon coadministration of 5 mg SAXA and 10 mg DAPA.

2.6 General Biopharmaceutics

2.6.1 Are the clinically tested SAXA oral tablets and DAPA oral tablets identical to the marketed commercial SAXA oral tablets and DAPA oral tablets?

(b) (4)

The bioequivalence study (CV181341) used commercial SAXA tablets and DAPA tablets (see Project Manager, A. Adeolu’s memo in DARRTS dated January 30, 2015).

2.6.2 Are the clinically tested SAXA/DAPA FDC tablets identical to the to-be-marketed SAXA/DAPA FDC tablets?

Except for (b) (4) the (b) (4) 5 mg SAXA/10 mg DAPA FDC tablets used in the pivotal bioequivalence study were the same as the to-be-marketed FDC tablets (Section 3.2.P.2.2 Page 18/20).

2.6.3 What is the relative BA of the SAXA/DAPA FDC oral tablets to the coadministration of corresponding individual innovator SAXA oral tablets and DAPA oral tablets?

Study CV181341 examined the relative bioavailability of SAXA/DAPA FDC oral tablets to individual innovator SAXA oral tablets and DAPA oral tablets. See Dr. Peng Duan’s Biopharmaceutics review in DARRTS.

2.7 Bioanalytical

Are the bioanalytical methods properly validated for Study CV181191 in NDA (b)(4)?

Table 5 below summarizes the bioanalytical method validation for saxagliptin, 5-OH saxagliptin, and dapagliflozin for Study CV181191.

Table 5. Validation of LC/MS/MS bioanalytical assays for saxagliptin, 5-OH saxagliptin, and dapagliflozin for Study CV181191.

	Saxagliptin	5-OH saxagliptin	Dapagliflozin
Matrix	plasma	plasma	plasma
Sample volume, µL	100	100	50
LLOQ, ng/mL	0.1	0.2	0.2
Linear range, ng/mL	0.1 – 50	0.2 – 100	0.2 – 100
Assay Precision (% CV)			
Inter-	≤ 2.8	≤ 4.4	≤ 4.9
Intra-	≤ 9.2	≤ 5.2	≤ 3.8
Accuracy (% deviation)	± 4.3	± 4.2	± 2.0

These are LC/MS/MS bioanalytical assays. Ethylenediaminetetra acetic acid was the anticoagulant for the blood samples. LLOQ = lower limit of quantitation Source: This reviewer’s modified version of the sponsor’s submission, Section 2.7.1, Table 8.

Stability data were established for saxagliptin and 5-OH saxagliptin as the following:

- benchtop stability in human plasma for at least 24 hours for saxagliptin and at least 42 hours for 5-OH saxagliptin
- 6 freeze thaw cycles and autosampler stability for at least 31 hours at room temperature
- long term stability at -20°C for 401 days

Stability data were established for dapagliflozin as the following:

- bench-top stability of dapagliflozin in human plasma for at least 24 hours
- 5 freeze-thaw cycles at -20°C and -70°C post-preparative extract stability for at least 72 hours at room temperature and 141 hours at 2 to 8°C
- long term stability at -20°C and -70°C for 337 days

All validations for the LC/MS/MS bioanalytical methods for Study CV181191 appear acceptable with reasonable precision and accuracy. For the review of bioanalytical methods validation of Study CV181341, see Dr. Peng Duan’s Biopharmaceutics review in DARRTS.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Attachment

Reviewer's Analysis:

Statistical Comparison of Dapagliflozin PK Parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
A	B	AUC(0-inf)	ng.hr/mL	98.4	96.14 - 100.71
		AUC(0-t)	ng.hr/mL	98.89	96.57 - 101.27
		Cmax	ng/mL	94.98	87.35 - 103.28

A = Saxagliptin + Dapagliflozin (B in the Study Report)
 B = Dapagliflozin Alone (C in the Study Report)

Source: Reviewer's analysis

Statistical Comparison of Saxagliptin PK Parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
A	B	AUC(0-inf)	ng.hr/mL	99.13	96.14 - 102.22
		AUC(0-t)	ng.hr/mL	99.1	96.04 - 102.24
		Cmax	ng/mL	92.65	88.27 - 97.25

A = Saxagliptin Alone (C in the Study Report)
 B = Saxagliptin + Dapagliflozin (A in the Study Report)

Source: Reviewer's analysis

These results were consistent with the sponsor's analysis except some minor differences in the GMR and 90% CI estimates, which did not alter the interpretation of the results. This reviewer used the SAS PROC GLM procedure to calculate the GMR and 90% CI, whereas the sponsor used the SAS PROC MIXED procedure.

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/s/

SZE W LAU
08/24/2015

MANOJ KHURANA
08/24/2015