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APPLICATION NUMBER:

210913Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	210874
Submission Date	07/02/2018
Brand Name	QTERNMET XR
Generic Name	Dapagliflozin, Saxagliptin and Metformin Hydrochloride
Reviewer	Mohammad Absar, Ph.D.
Team Leader (Acting)	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Division of Metabolic and Endocrine Products
Applicant	AstraZeneca
Formulation; Strength	Extended release oral tablet; four strengths- Dapagliflozin/Saxagliptin/Metformin HCL 10/5/1000 mg Dapagliflozin/Saxagliptin/Metformin HCL 5/5/1000 mg Dapagliflozin/Saxagliptin/Metformin HCL 2.5/2.5/1000 mg Dapagliflozin/Saxagliptin/Metformin HCL 5/2.5/1000 mg
Dosage Regimen (proposed)	For patients not currently taking dapagliflozin, the recommended starting total daily dose of QTERNMET XR is dapagliflozin/saxagliptin/Metformin HCl 5/5/1000 or 2000 mg taken orally, once daily in the morning with food
Relevant IND/NDA	IND 131385
Indication	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM (b) (4) [redacted]

Table of Contents

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

AstraZeneca (Applicant) has submitted NDA 210874 under the 505(b)(1) pathway seeking marketing approval for dapagliflozin/saxagliptin/metformin hydrochloride (HCL) (Dapa/Saxa/Met) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (b) (4) The drug product is an extended release oral tablet with four strengths: Dapa/Saxa/Met 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg. The proposed starting total daily dose for patients not currently taking dapagliflozin is Dapa/Saxa/Met 5/5/1000 or 2000 mg taken orally, once daily in the morning with food.

The clinical pharmacology program included a single Phase 1 comparative pharmacokinetic (PK)/food effect study (D168AC00001) in which the systemic exposure of dapagliflozin, saxagliptin and metformin following administration of single oral dose of the triple combination product – Dapa/Saxa/Met 5/2.5/1000 mg – were compared with that from administration of single oral dose of saxagliptin 2.5 mg (ONGLYZA) + dapagliflozin/metformin HCL 5/1000 mg (XIGDUO XR) in healthy subjects under fed condition (Cohort

1). Similar comparison was also performed following single oral dose administration of triple combination product – Dapa/Saxa/Met 10/5/1000 mg with that following single oral administration of Saxagliptin 5 mg (ONGLYZA) + dapagliflozin/metformin HCl 10/1000 mg (XIGDUO XR) in healthy subjects (Cohort 2).

In addition, the effect of food on the triple combination product was evaluated in each cohort. This study was conducted to bridge the data generated in the two pivotal Phase 3 studies in T2DM patients (Studies D1683C00005 and CV181169) that used monocomponents of dapagliflozin, saxagliptin and metformin HCl.[1] The Applicant requested biowaiver for the other two strengths – Dapa/Saxa/Met 2.5/2.5/1000 mg and 5/5/1000 mg. The following are the major findings from the current review –

1. Following single dose administration of Dapa/Saxa/Met 5/2.5/1000 mg in healthy subjects under fed condition, the mean peak concentration (C_{max}) and total systemic exposure (AUC_{inf}) of dapagliflozin were 42.3 ng/mL and 239.9 ng.hr/mL, respectively, of saxagliptin were 10.6 ng/mL and 51.6 ng.hr/mL, respectively, and of metformin were 1098 ng/mL and 10930 ng.hr/mL, respectively (Cohort 1, Study D168AC00001).
2. In the same study (Cohort 2), following single dose administration of Dapa/Saxa/Met 10/5/1000 mg, the C_{max} and AUC_{inf} dapagliflozin were 75.7 ng/mL and 463.6 ng.hr/mL, respectively, of saxagliptin were 20.9 ng/mL and 102.6 ng.hr/mL, respectively, and of metformin were 1057 ng/mL and 10470 ng.hr/mL, respectively.
3. The geometric mean ratio (GMR) of C_{max} and AUC_{inf} of dapagliflozin, saxagliptin and metformin were, in general, comparable between Dapa/Saxa/Met triple combination products (i.e., 5/2.5/1000 mg and 10/5/1000 mg) and their respective reference arms (i.e., single dose administration of ONGLYZA+XIGDUO XR) under fed condition.
4. There was no clinically meaningful effect of food on the systemic exposure of dapagliflozin, saxagliptin and metformin from the triple combination product. Under fed condition, the C_{max} and AUC_{inf} of saxagliptin and metformin were comparable to that under fasting condition for both strengths – Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg. While AUC_{inf} of dapagliflozin was comparable, C_{max} was reduced by approximately 38% under fed condition. This reduction in C_{max} is consistent with previous findings of dapagliflozin and is not considered clinically meaningful.[2]

1.1. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the clinical pharmacology data submitted under NDA 210874 and finds the data acceptable to support approval.

1.2. Post Marketing Requirement

None.

1.3. Summary of Important Clinical Pharmacology Findings

The clinical program for Dapa/Saxa/Met triple combination product includes two pivotal Phase 3 efficacy/safety studies (D1683C00005 and CV181169) that utilized a dual add-on strategy to evaluate the combination of dapagliflozin and saxagliptin when added to metformin in adults with T2DM who had inadequate glycemic control. Both the Phase 3 studies were conducted using monoproducts of dapagliflozin, saxagliptin and metformin HCl; refer to the Clinical Review by Dr. Frank Pucino for additional detail.

To bridge clinical data generated in the two pivotal Phase 3 studies with the proposed fixed dose triple combination product, the Applicant conducted a Phase 1 comparative pharmacokinetic (PK)/food effect

[1] Studies D1683C00005 and CV181169 were also submitted as an efficacy supplement under NDA 209091 (QTERN).
[2] Prescribing information of XIGDUO XR (dated 02/22/2019)

study (D168AC00001) in which healthy subjects received a single oral dose of Dapa/Saxa/Met 5/2.5/1000 mg under fasted and fed condition or saxagliptin 2.5 mg (ONGLYZA) + dapagliflozin/metformin HCL 5/1000 mg ((XIGDUO XR) under fed condition in a crossover fashion (Cohort 1). In Cohort 2, healthy subjects received the highest strength of the triple combination product, Dapa/Saxa/Met 10/5/1000 mg, under fasted and fed condition, or saxagliptin 5 mg (ONGLYZA) + dapagliflozin/metformin HCl 10/1000 mg (XIGDUO XR) under fed condition in a crossover fashion.

The results from this study demonstrated that the geometric mean ratio (GMR) of C_{max} of dapagliflozin following single dose administration of Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg to that of the respective reference arm (i.e., single dose administration of ONGLYZA + XIGDUO XR) under fed condition were 1.14 and 0.93, respectively, while that of AUC_{inf} were 1.03 and 0.98, respectively. The GMR of C_{max} of saxagliptin following single dose administration of Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg to that of the respective reference arm were 1.00 and 0.94, respectively, while that of AUC_{inf} were 1.00 and 1.01, respectively. The GMR of C_{max} of metformin following single dose administration of Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg to that of the reference arm were 1.05 and 0.96, respectively, while that of AUC_{inf} were 0.99 and 0.94, respectively.

The comparison in PK parameters from this study is summarized in Table 1.

Table 1: Comparison of PK parameters of dapagliflozin, saxagliptin and metformin following single dose administration in healthy subjects

	PK parameter	**GMR (90% CI) Dapa/Saxa/Met 5/2.5/1000 vs ONGLYZA 2.5 + XIGDUO XR 5/1000**	**GMR (90% CI) Dapa/Saxa/Met 10/5/1000 vs ONGLYZA 5 + XIGDUO XR 10/1000**
Dapagliflozin	C_{max}	1.14 (1.01 – 1.28)	0.93 (0.83 – 1.03)
	AUC_t	1.03 (0.94 – 1.12)	0.98 (0.90 – 1.07)
	AUC	1.03 (0.94 – 1.12)	0.98 (0.90 – 1.07)
Saxagliptin	C_{max}	1.00 (0.85 – 1.17)	0.94 (0.83 – 1.06)
	AUC_t	1.00 (0.88 – 1.15)	1.01 (0.91 – 1.11)
	AUC	1.00 (0.88 – 1.14)	1.01 (0.91 – 1.11)
Metformin	C_{max}	1.05 (0.95 – 1.17)	0.96 (0.86 – 1.07)
	AUC_t	0.99 (0.88 – 1.10)	0.96 (0.86 – 1.06)
	AUC	0.99 (0.88 – 1.12)	0.94 (0.84 – 1.06)

Source: NDA 210874, Module 2.7; Summary of Biopharmaceutic Studies

In general, PK of dapagliflozin, saxagliptin and metformin were comparable between the triple combination and ONGLYZA+XIGDUO XR. The 90% CI for GMR of C_{max}, AUC_t and AUC_{inf} of saxagliptin and metformin were within the prespecified bioequivalence margin of 0.8 – 1.25 for both strengths. The upper bound of 90% CI for GMR of C_{max} of dapagliflozin for the lower strength was 1.28, outside of the prespecified bioequivalence margin. However, the 90% CI for GMR of dapagliflozin AUC_t and AUC_{inf} both were within the margin of 0.8 – 1.25. In addition, for the highest strength product, the GMR of all three PK parameters (i.e., C_{max}, AUC_t and AUC_{inf}) for dapagliflozin were within 0.8 – 1.25. Since this deviation is for peak exposures for one of the component of the FDC, not consistently observed for both strengths, and difference being on the higher side with regards to the relative exposure to reference single components, there are no efficacy related concerns due to assurance of total exposure being comparable by the bioequivalence criteria; the observed marginally higher C_{max} from the lower strength does not appear to

pose any additional safety concern being only noted for the lower strength, as safety from the higher dose of dapagliflozin has already been assessed.

Notably, this bridging study compared the systemic exposure of dapagliflozin, saxagliptin and metformin from the triple combination product to that from single dose administration of ONGLYZA + XIGDUO XR (dapagliflozin+ metformin HCl). However, the pivotal clinical studies (D1683C00005 and CV181169) to which, the bridge is intended were conducted with monocomponents of dapagliflozin, saxagliptin and metformin, unlike combination of dapagliflozin + metformin (XIGDUO XR) as used in the bridging study. Nevertheless, no PK interaction between dapagliflozin 5 mg and metformin 500 mg or dapagliflozin 10 mg and metformin 1000 mg were observed in Studies 102092 and 102100, submitted under NDA 205649 for XIGDUO XR.[3] In addition, no clinically significant PK interaction between dapagliflozin and saxagliptin (Study CV181191)[4] or between saxagliptin and metformin (Study CV181017)[5] were observed during the clinical development program for QTERN and ONGLYZA, respectively.

The Applicant's biowaiver request for the two other strengths – Dapa/Saxa/Met 2.5/2.5/1000 mg and 5/5/1000 mg – was deemed acceptable by the Biopharmaceutics review team (refer to the Biopharmaceutics Review by Dr. Sarah Ibrahim for additional detail).

Taken together, a scientific bridge has been established between the triple combination product and the monoproducts used in the pivotal Phase 3 clinical studies. For clinical pharmacology related information in the proposed label, including tabulated presentation of the drug interaction data, the applicant relied on their previously approved products containing dapagliflozin, saxagliptin and/or metformin, and is generally consistent with the referenced products.

Under fed condition, the systemic exposure of dapagliflozin, saxagliptin and metformin were comparable to that under fasting condition. Compared to fasted condition, the GMR for C_{max} and AUC_{inf} of saxagliptin under fed condition were 0.91 and 1.10, respectively, for Dapa/Saxa/Met 5/2.5/1000 mg, and were 0.84 and 1.12, respectively, for Dapa/Saxa/Met 10/5/1000 mg. Similarly, the GMR of C_{max} and AUC_{inf} of metformin under fed condition were 0.92 and 1.15, respectively, for Dapa/Saxa/Met 5/2.5/1000 mg, and were 0.90 and 1.14, respectively, for Dapa/Saxa/Met 5/10/1000 mg. For dapagliflozin, while the GMR of AUC_{inf} under fed condition were 0.98 and 0.95 for Dapa/Saxa/Met 5/2.5/1000 mg and Dapa/Saxa/Met 10/5/1000 mg, respectively, GMR of C_{max} was 0.62 and 0.61, respectively. This ~38% reduction in C_{max} under fed condition is consistent with previous findings of dapagliflozin and is not considered clinically meaningful.[3]

Overall, Clinical Pharmacology recommends approval of NDA 210874.

2. QUESTION-BASED REVIEW

2.1. Background

Dapagliflozin and saxagliptin are currently approved in the United States both as monoproducts, and as combination of dapagliflozin/saxagliptin tablet. In addition, combination of dapagliflozin/metformin HCl and saxagliptin/metformin HCl are also approved. All these products were sponsored by AstraZeneca. Table 2 lists the currently approved products in the US that contain dapagliflozin and saxagliptin. In this application, the Applicant proposes a triple combination of dapagliflozin/saxagliptin/metformin HCl.

Table 2: List of FDA-approved products containing dapagliflozin and saxagliptin

Brand Name	NDA#	Active ingredient	Approved strength
FARXIGA	202293	Dapagliflozin	5 and 10 mg tablet
ONGLYZA	22350	Saxagliptin	2.5 and 5 mg tablet

[3] NDA 205649 for XIGDUO XR; Clinical Pharmacology Review by Dr. Suryanarayana Sista
[4] NDA 209782 for QTERN; Clinical Pharmacology Review by Dr. Johnny Lau
[5] NDA 22350 for ONGLYZA; Clinical Pharmacology Review by Dr. Jayabharathi Vaidyanathan

QTERN	209091	Dapagliflozin/saxagliptin	10/5 mg tablet
XIGDUO XR	205649	Dapagliflozin/metformin HCl	5/500, 5/1000, 10/500, 10/1000, 2.5/1000 mg XR tablet
KOMBIGLYZE	200678	Saxagliptin/metformin	5/500, 5/1000, 2.5/1000 XR tablet

2.1.1. What is the regulatory background pertinent to this application?

The applicant carried out the development program for the triple combination product under IND 131385. During a pre-IND correspondence dated 10/25/2016, the Agency deemed the proposed approach to establish bioequivalence between Dapa/Saxa/Met 10/5/1000 mg and ONGLYZA + XIGDUO XR as a reference, acceptable. In a response (dated 12/23/2016) to Applicant's follow-up question, the Agency stated that evaluating the intermediate strength Dapa/Saxa/Met 5/2.5/1000 mg instead of 2.5/2.5/1000 mg strength would be acceptable for the bioequivalence assessment.

2.1.2. What are the clinical pharmacology/clinical studies submitted in the NDA?

The clinical pharmacology studies/clinical studies are summarized below:

Table 3: Listing of clinical pharmacology/clinical studies

	Study ID	Objectives	Population	Study Design	Treatment and Device
PK study	D168AC00001	PK, BE, Food effect	HS (n=81)	R, OL, 2 parallel cohorts, 3T, 3P, CO, SD	Cohort 1: Dapa/Saxa/Met: 5/2.5/1000 mg; fed Dapa/Saxa/Met: 5/2.5/1000 mg; fasted ONGLYZA+XIGDUO XR: 2.5 mg + 5/1000 mg; fed Cohort 2: Dapa/Saxa/Met: 10/5/1000 mg; fed Dapa/Saxa/Met: 10/5/1000 mg; fasted ONGLYZA+XIGDUO XR: 5 mg + 10/1000 mg; fed
Efficacy/safety study	D1683C00005	Efficacy, safety	Patients with T2DM (n=754)	R, DB, active-controlled, PG MC, 24-week	Dapagliflozin 5 mg + saxagliptin 5 mg + metformin ≥1500 mg per day (administered as monoproducts) Saxagliptin 5 mg + metformin ≥1500 mg per day (administered as monoproducts) Dapagliflozin 5 mg + metformin ≥1500 mg per day (administered as monoproducts)
	CV181169	Efficacy, safety	Patients with T2DM (n=490)	R, DB, active-controlled, PG MC, 24-week	Dapagliflozin 10 mg + saxagliptin 5 mg + metformin XR ≥1500 mg per day (administered as monoproducts) Saxagliptin 5 mg + metformin XR ≥1500 mg per day (administered as monoproducts) Dapagliflozin 10 mg + metformin XR ≥1500 mg per day (administered as monoproducts)

Source: NDA 210874, Module 5.2; Tabular listing of all clinical studies

2.2. General Attributes

2.2.1. What are the key physicochemical properties of dapagliflozin, saxagliptin and metformin?

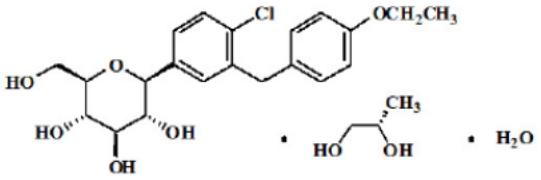
Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-*C*-*[*4-chloro-3-*[*(4ethoxyphenyl)methyl*]*phenyl*]*-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6.C_3H_8O_2.H_2O$ and the formula weight is 502.98.[2] Saxagliptin monohydrate is described chemically as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1yl)acetyl]-2-

azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is $C_{18}H_{25}N_3O_2.H_2O$ and the molecular weight is 333.43.

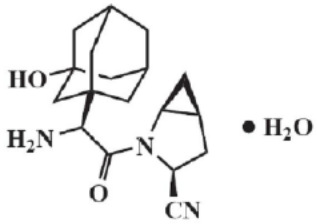
Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).[6]

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5.HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula of dapagliflozin, saxagliptin and metformin is presented in Figure 1.

Dapagliflozin



Saxagliptin



Metformin HCl

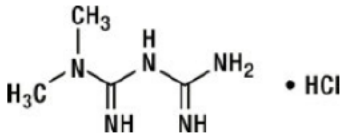


Figure 1: Chemical structure of dapagliflozin, saxagliptin and metformin HCl

2.2.2. What is the formulation for the drug product?

The proposed formulation [redacted] (b) (4)

Refer to the Product Quality Review by Dr. Christopher Galliford for additional detail on drug product formulation compositions.

[redacted] (b) (4)

Figure 2: Schematic illustration of the formulation design principle of the Dapa/Saxa/Met XR tablet
Source: NDA 210874, Module 2.7; Summary of Biopharmaceutic Studies

2.2.3. What are the proposed mechanisms of action?

The proposed drug product combines three antihyperglycemic agents with complimentary mechanisms of action – dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, saxagliptin, a dipeptidyl-peptidase-4 (DPP4) inhibitor, and metformin hydrochloride, a biguanide.

[6] Prescribing information for ONGLYZA, dated 02/27/2017

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. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.[2]

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 DPP4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Saxagliptin is a competitive 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 type 2 diabetes mellitus.[6]

Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[2]

2.2.4. What are the proposed dosages and routes of administration?

For patients not currently taking dapagliflozin, the proposed starting total daily dose is a dapagliflozin 5 mg/saxagliptin 5 mg/metformin HCl 1000 mg or 2000 mg taken orally, once daily in the morning with food.

2.3.General Clinical Pharmacology

2.3.1. What are the design features of the clinical pharmacology studies?

The Clinical Pharmacology package submitted for this NDA consisted of a single Phase 1 relative bioavailability study aimed to bridge the data generated from two pivotal Phase 3 efficacy/safety studies that was conducted using monoproducts of dapagliflozin, saxagliptin and metformin HCl instead of the to-be-marketed fixed dose triple combination product. The study was a randomized, open-label, single-dose, crossover study in 81 healthy male and female subjects performed at a single study center and conducted in two parallel cohorts. Subjects received the following treatments in a randomized fashion.

Cohort 1:

- Treatment A (reference): single dose of 2.5 mg ONGLYZA and 5/1000 mg XIGDUO XR tablet co-administered orally under fed condition
- Treatment B (test): single dose of triple fixed dose tablet consisting of 2.5 mg saxagliptin/5 mg dapagliflozin/1000 mg metformin XR under fed condition
- Treatment C (test): single dose of triple fixed dose tablet consisting of 2.5 mg saxagliptin/5 mg dapagliflozin/1000 mg metformin XR under fasted condition

Cohort 2:

- Treatment D (reference): single dose of 5 mg ONGLYZA and 10/1000 mg XIGDUO XR tablet co-administered orally under fed condition
- Treatment E (test): single dose of triple fixed dose tablet consisting of 5 mg saxagliptin/10 mg dapagliflozin/1000 mg metformin XR under fed condition
- Treatment F (test): single dose of triple fixed dose tablet consisting of 5 mg saxagliptin/10 mg dapagliflozin/1000 mg metformin XR under fasted condition

In each study cohort, every subject received a single dose of one of the treatments. Each treatment was separated by a minimum washout period of 7 to 14 days. Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60 and 72 hours post dose.

In addition, two pivotal Phase 3 studies were submitted in support of this application, in which efficacy and safety of the triple combination product were evaluated in patients with T2DM. Refer to the Clinical Review by Dr. Frank Pucino for details on the Phase 3 studies.

2.3.2. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameter and exposure response relationships?

Dapagliflozin, saxagliptin and metformin concentrations in plasma samples were measured. Concentration of the active metabolite of saxagliptin – 5-hydroxy saxagliptin – were also quantified.

2.4. What are the PK characteristics of the drug?

2.4.1. What are the PK parameters of dapagliflozin, saxagliptin and metformin in adult subjects?

Single oral doses of Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg were administered to healthy subjects under fasted and fed conditions in Study D168AC00001. The mean PK parameters are summarized in Table 4 and the plasma concentration-time profiles of dapagliflozin, saxagliptin and metformin are shown in Figure 3, Figure 4 and Figure 5, respectively. The key pharmacokinetic characteristics of the three components of triple FDC are as follows:

- In healthy subjects, C_{max} and AUC_{inf} of dapagliflozin were 42.3 ng/mL and 239.9 ng.hr/mL, respectively, for Dapa/Saxa/Met 5/2.5/1000 mg dose and were 75.7 ng/mL and 463 ng.hr/mL, respectively, for Dapa/Saxa/Met 10/5/1000 mg under fed condition.
- The C_{max} and AUC_{inf} of saxagliptin were 10.6 ng/mL and 51.6 ng.hr/mL, respectively, for Dapa/Saxa/Met 5/2.5/1000 mg dose and were 20.9 ng/mL and 102.6 ng.hr/mL, respectively, for Dapa/Saxa/met 10/5/1000 mg dose.
- The C_{max} and AUC_{inf} of metformin were 1098 ng/mL and 10930 ng.hr/mL, respectively, for Dapa/Saxa/Met 5/2.5/1000 mg and were 1057 ng/mL and 10470 ng.hr/mL, respectively, for Dapa/Saxa/Met 10/5/1000 mg dose. The pre-dose concentrations of dapagliflozin, saxagliptin and metformin between the study periods were not quantifiable, suggesting that the washout period of 7 – 14 days was adequate and pre-dose concentrations did not contribute to the PK results.

Table 4: Mean (CV%) PK parameters of dapagliflozin, saxagliptin and metformin in healthy subjects (Study D168AC00001)

	PK parameter	Dapa/Saxa/Met 5/2.5/1000 mg	Dapa/Saxa/Met 10/5/1000 mg
Dapagliflozin	C_{max} (ng/mL)	42.3 (40)	75.7 (25)
	AUC_t (ng.hr/mL)	232.5 (24)	452.4 (22)
	AUC (ng.hr/mL)	239.9 (24)	463.6 (22)
Saxagliptin	C_{max} (ng/mL)	10.6 (37)	20.9 (27)
	AUC_t (ng.hr/mL)	50.1 (36)	100.9 (27)
	AUC (ng.hr/mL)	51.6 (35)	102.6 (26)
Metformin	C_{max} (ng/mL)	1098 (27)	1057 (24)
	AUC_t (ng.hr/mL)	10780 (34)	10420 (30)
	AUC (ng.hr/mL)	10930 (34)	10470 (31)

Source: NDA 210874, Module 5.3; D168AC00001 Study report

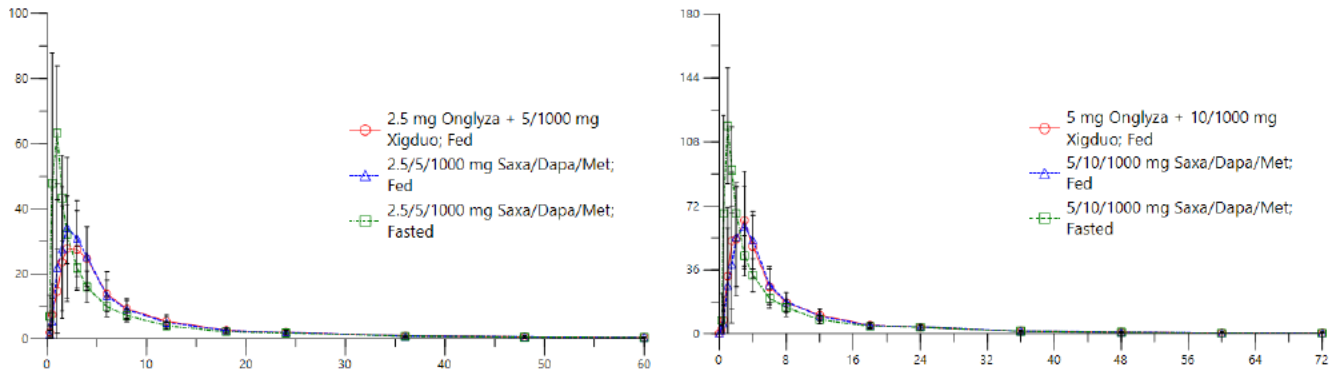


Figure 3: Plasma concentration-time profile for dapagliflozin in healthy subjects (Study D168AC00001)
Source: Reviewer analysis based on data from Study D168AC00001

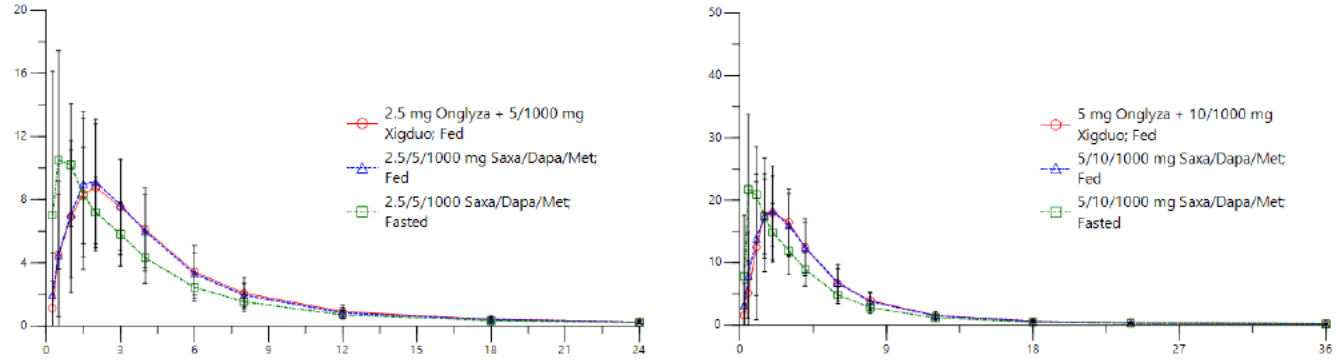


Figure 4: Plasma concentration-time profile for saxagliptin in healthy subjects (Study D168AC00001)
Source: Reviewer analysis based on data from Study D168AC00001

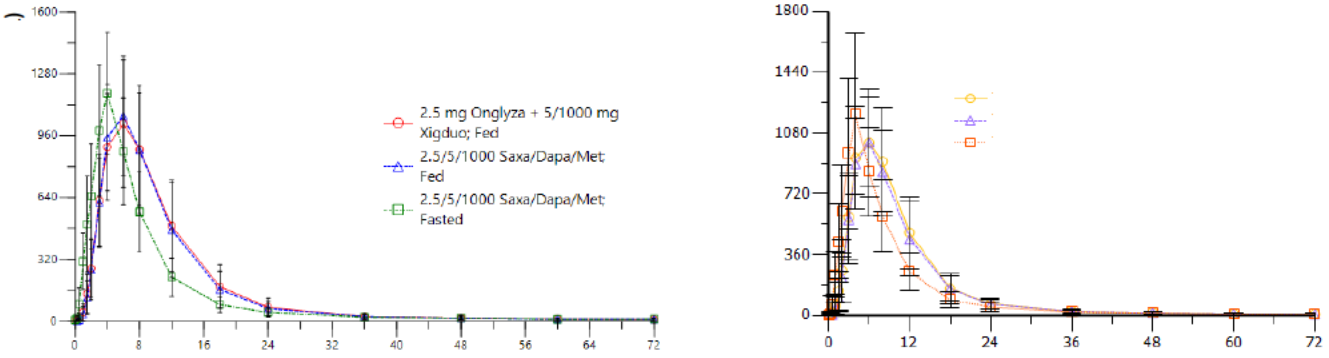


Figure 5: Plasma concentration-time profile for metformin in healthy subjects (Study D168AC00001)
Source: Reviewer analysis based on data from Study D168AC00001

PK of dapagliflozin, saxagliptin and metformin were in general comparable between the triple combination product and co-administration of ONGLYZA + XIGDUO XR. The comparison of PK parameters is summarized in Table 1. Plasma concentration of the active metabolite of saxagliptin – 5-OH saxagliptin – was also measured and was found comparable between the proposed triple combination product to

ONGLYZA + XIGDUO XR, i.e., 90% CI for the GMR of C_{max} and AUC_{inf} were within 0.8 – 1.25 for both doses.

2.4.2. What is the effect of food on the proposed drug product?

The effect of food on the proposed triple combination drug product was evaluated in healthy subjects in Study D168AC10001, in which subjects received a single oral dose of Dapa/Saxa/Met 5/2.5/1000 mg or 10/5/1000 mg under fasting and fed condition (light-fat, low-calorie meal). Since diet and exercise are part of the recommended treatment of T2DM, a standard light meal was employed rather than a high-fat meal in order to replicate the recommended clinical guidelines. This is consistent with XIGDUO XR application where a light-fat meal was utilized to assess the effect of food on dapagliflozin/metformin HCl XR product.

In general, food had no effect on PK of dapagliflozin, saxagliptin and metformin. The 90% CI for GMR of C_{max} and AUC_{inf} for saxagliptin and metformin were within 0.8 – 1.25 (Table 5); comparison of plasma concentration-time profile under fasted and fed condition for dapagliflozin, saxagliptin and metformin are outlined in Figure 3, Figure 4 and Figure 5, respectively. For dapagliflozin, while the 90% CI for GMR of AUC_{inf} under fed condition were 0.98 and 0.95 for Dapa/Saxa/Met 5/2.5/1000 mg and Dapa/Saxa/Met 10/5/1000 mg, respectively, C_{max} was reduced by 38% and 39% for the two strengths, respectively. This reduction in C_{max} under fed condition is consistent with previous findings of dapagliflozin and is not considered clinically meaningful.

Table 5: Comparison of PK parameters of dapagliflozin, saxagliptin and metformin under fasted vs fed condition

	PK parameter	GMR (90%CI) fed vs fasted Dapa/Saxa/Met 5/2.5/1000 mg	GMR (90%CI) fed vs fasted Dapa/Saxa/Met 10/5/1000 mg
Dapagliflozin	C_{max}	0.62 (0.55 – 0.70)	0.61 (0.55 – 0.68)
	AUC_t	0.98 (0.90 – 1.07)	0.95 (0.87 – 1.03)
	AUC	0.98 (0.90 – 1.07)	0.95 (0.87 – 1.04)
Saxagliptin	C_{max}	0.91 (0.77 – 1.06)	0.84 (0.75 – 0.95)
	AUC_t	1.11 (0.67, 1.26)	1.12 (1.02 – 1.23
	AUC	1.10 (0.97 – 1.25)	1.12 (1.02 – 1.23)
Metformin	C_{max}	1.05 (0.95 – 1.17)	0.96 (0.86 – 1.07)
	AUC_t	0.99 (0.88 – 1.10)	0.96 (0.86 – 1.06)
	AUC	0.99 (0.88 – 1.12)	0.94 (0.84 – 1.06)

Source: NDA 210874, Module 2.7; Summary of Biopharmaceutics Review

2.4.3. How is the proposed to-be-marketed formulation linked to the clinical formulation?

The batches used in Study D168AC10001 were identical to the proposed commercial formulations except for the color in the outer film-coat. For Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg, light pink and yellow color tablets were used, respectively, for the BE studies. The proposed commercial drug products will have (b) (4) for Dapa/Saxa/Met 5/2.5/1000 mg and 10/5/1000 mg, respectively. The Applicant communicated the change in color during a Type C meeting dated 01/15/2018. The Agency agreed that adequate batch release, dissolution and stability data would support the change of color in the to-be-marketed product.

2.5. Bioanalytical

2.5.1. What are the analytical methods used to measure dapagliflozin, saxagliptin and metformin in plasma?

Plasma concentrations of dapagliflozin, saxagliptin and metformin were determined by HPLC with MS/MS detection. The validation summary is provided in Table 6, Table 7 and Table 8 for dapagliflozin, saxagliptin and metformin, respectively. The QC sample results for all three analytes met the acceptance criteria, i.e., at least (b) (4)% of the QC results were within (b) (4)% of their nominal concentrations. The PK samples were stored and analyzed within the validated storage stability period and conditions.

Table 6: Validation summary of bioanalytical method for dapagliflozin

Matrix (anticoagulant)	Human plasma (K_3EDTA)
Sample volume	75.0 µL
Analytical method/detection	Protein precipitation + solid-phase extraction/LC-MS/MS
Internal standard	[$^{13}C_6$]Dapagliflozin
Validated range	0.2 ng/mL to 200 ng/mL
Calibration model	Linear regression
Weighting factor	$1/x^2$
Quantitation method	Peak area ratio
Intra-assay accuracy (%Bias)	-10.5% to 8.8%
Intra-assay precision (%CV)	2.0% to 8.3%
Inter-assay accuracy (%Bias)	-5.5% to 2.7%
Inter-assay precision (%RSD)	4.1% to 9.6%
Recovery	93.3%
Freeze-thaw stability	4 cycles at -10°C to -30°C 6 cycles at -60°C to -80°C
Frozen matrix stability	31 days at -10 to -30C 128 days at -60 to -80C
Ambient matrix stability	60 hr at RT

Source: NDA 210874, Module 5.3. DAPAHPP (Reports of Bioanalytical and Analytical Method); Module 2.7. Summary of Biopharmaceutics Studies.

Table 7: Validation summary of bioanalytical method for saxagliptin

Matrix (anticoagulant)	Human plasma (K_2EDTA)
Sample volume	100 µL
Analytical method/detection	Protein precipitation / LC-MS/MS
Internal standard	[^{13}C,D_2]Saxagliptin
Validated range	0.100 ng/mL to 50 ng/mL
Calibration model	Linear regression
Weighting factor	$1/x^2$
Quantitation method	Peak area ratio
Intra-assay accuracy (%Bias)	-2.5% to 17%
Intra-assay precision (%RSD)	1.9% to 7.4%
Inter-assay accuracy (%Bias)	-1.0% to 10.0%
Inter-assay precision (%RSD)	3.0% to 7.4%
Extraction efficiency	96.3%
Freeze-thaw matric stability	4 cycles at -10°C to -30°C

Frozen matrix stability	4 cycles at -60°C to -80°C 30 days at -10°C to -30°C 185 days at -60°C to -80°C
Ambient matrix stability	29 hr at RT

Source: NDA 210874, Module 5.3. SAXAHPP (Reports of Bioanalytical and Analytical Method); Module 2.7. Summary of Biopharmaceutics Studies.

Table 8: Validation summary of bioanalytical method for metformin

Matrix (anticoagulant)	Human plasma (K_3EDTA)
Sample volume	25 µL
Analytical method/detection	Protein precipitation / LC-MS/MS
Internal standard	Metformin-d_6
Validated range	2 ng/mL to 2000 ng/mL
Calibration model	Linear regression
Weighting factor	$1/x^2$
Quantitation method	Peak area ratio
Intra-assay accuracy (%RE)	-5.3% to 10.5%
Intra-assay precision (%CV)	1.1% to 7.3%
Inter-assay accuracy (%RE)	-2.0% to 4.5%
Inter-assay precision (%CV)	3.5% to 6.3%
Extraction efficiency	91.0%
Freeze-thaw matric stability	5 cycles at -10 to -30C and at -60 to -80C
Frozen matrix stability	162 days -20°C and -70°C
Ambient matrix stability	28 hr at RT

Source: NDA 210874, Module 5.3. MFNHPC (Reports of Bioanalytical and Analytical Method); Module 2.7. Summary of Biopharmaceutics Studies.

2.5.2. What are the results for the re-analysis of the incurred samples?

Pharmacokinetic samples of dapagliflozin, saxagliptin and metformin were re-analyzed as part of incurred sample reproducibility assessment, which met the acceptance criteria of (b)(4)% of incurred sample results being within (b)(4)% of the original result.

2.5.3. What are the findings from OSIS inspection?

The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and bioanalytical sites of the pivotal clinical pharmacology Study D168AC00001. Following inspection, OSIS concluded that the clinical data from this study are reliable to support regulatory decision. Refer to OSIS Memorandum (dated 03/14/2019) for further details.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MOHAMMAD S ABSAR
03/27/2019 10:56:44 AM

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03/27/2019 12:53:24 PM