

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205649Orig1s000

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

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	205649
Submission Date(s):	October 29, 2013
Brand Name	Xigduo XR
Generic Name	Dapagliflozin / Metformin HCl XR
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Bristol Myers Squibb
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	<p>Tablets:</p> <ul style="list-style-type: none"> • 5 mg dapagliflozin/500 mg metformin HCl extended-release • 5 mg dapagliflozin/1000 mg metformin HCl extended-release • 10 mg dapagliflozin/500 mg metformin HCl extended-release • 10 mg dapagliflozin/1000 mg metformin HCl extended-release
Proposed Indication	<ul style="list-style-type: none"> • Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.
Dosage & Administration	<ul style="list-style-type: none"> • Individualize the starting dose based on the patient's current treatment. • Administer once daily in the morning with food • Swallow whole. Never crush, cut, or chew. • Do not exceed a daily dose of 10 mg dapagliflozin/2000 mg metformin HCl extended-release. • No dosage adjustment is indicated in patients with mild renal impairment. • Xigduo XR should not be used in patients with moderate to severe renal impairment (defined as eGFR <60 mL/min/1.73 m² or CrCl <60 mL/min) or end-stage renal disease.
Clinical Pharmacology Review Team	Suryanarayana Sista, Lokesh Jain

TABLE OF CONTENTS

1	Executive Summary	5
1.1	Recommendation	5
1.2	Phase IV Commitments.....	5
1.3	Summary of Important Clinical Pharmacology Findings	5
2	Question-Based Review (QBR).....	8
2.1	What are the in vivo Clinical Pharmacology and Biopharmaceutics studies with PK information submitted in the NDA.....	8
2.1.1	What are the highlights of the Xigduo XR drug product as they relate to clinical pharmacology review?.....	14
2.1.2	What is the composition of to-be-marketed formulation of Xigduo XR?.....	14
2.1.3	What are the proposed mechanism of action and therapeutic indications?.....	19
2.1.4	What are the proposed dosages and routes of administration?	20
2.2	General Clinical Pharmacology	20
2.2.1	What is known about the PK characteristics of dapagliflozin and metformin following the administration of commercially listed drugs, Farxiga and Glucophage XR tablets?	20
2.2.2	Were the active moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?.....	21
2.2.3	Compared to single-dose, how do the pharmacokinetics of dapagliflozin and metformin compare following multiple dose administration of Xigduo XR?.....	21
2.3	Intrinsic Factors.....	24
2.3.1	What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?.....	24
2.4	Extrinsic Factors	24
2.4.1	What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?.....	24
2.5	General Biopharmaceutics	25
2.5.1	Was bioequivalence established between dapagliflozin and metformin FDC formulations and individual components?.....	25
2.5.2	What is the effect of food on the bioavailability of dapagliflozin and metformin from the FDC.....	34
2.6	Analytical.....	35
2.6.1	Is the analytical method for Dapagliflozin and Metformin appropriately validated?.....	35
3	Labeling Comments (Preliminary)	37
4	APPENDIX.....	49
	OCP Filing Memo	49

List of Tables

Table 1	Highlights of Bioequivalence, Food-Effect, Steady-State and DDI Information	7
Table 2:	Overview of studies with pharmacokinetic assessments relevant to the clinical pharmacology and biopharmaceutics of Xigduo XR.....	9
Table 3a	Composition of Dapagliflozin 5 mg/Metformin XR 500 mg.....	16
Table 3b	Composition of Dapagliflozin 10 mg/Metformin XR 500 mg	17
Table 3c	Composition of Dapagliflozin 5 mg/Metformin XR 1000 mg	18
Table 3d	Composition of Dapagliflozin 10 mg/Metformin XR 1000 mg	19
Table 4:	Steady-state pharmacokinetic parameters (mean (%CV)) following administration of Xigduo XR tablets (5 mg dapagliflozin/500 mg metformin) every 24 hours for 4 days	22
Table 5:	Steady-state pharmacokinetic parameters (mean (%CV)) following administration of Xigduo XR tablets (10 mg dapagliflozin/1000 mg metformin) every 24 hours for 4 days	23
Table 6:	Summary Statistics for Dapagliflozin Pharmacokinetic Parameters administration of FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg in healthy subjects.....	28
Table 7:	Bioequivalence and Food Effect Comparisons for Dapagliflozin administration of FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg in healthy subjects	29
Table 8:	Summary Statistics for Metformin Pharmacokinetic Parameters administration of FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg in healthy subjects	29
Table 9:	Bioequivalence and Food Effect Comparisons for Metformin administration of FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg in healthy subjects	30
Table 10:	Summary Statistics for Dapagliflozin Pharmacokinetic Parameters following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg.....	32
Table 11:	Bioequivalence and Food Effect Comparisons for Dapagliflozin following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg.....	33
Table 12:	Summary Statistics for Metformin Pharmacokinetic Parameters following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg.....	33
Table 13:	Bioequivalence and Food Effect Comparisons for Metformin following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg.....	34
Table 14	Summary of key descriptive parameters for Dapagliflozin and Metformin bioanalytical assays used in clinical studies	36

List of Figures

Figure 1:	Links between relative bioavailability studies conducted for formulation selection and the pivotal bioequivalence studies	8
Figure 2:	Composition of Xigduo XR tablet	15
Figure 3:	Mean trough dapagliflozin and metformin plasma concentration profile versus time following administration of 5/500 XR FDC tablet	22
Figure 4:	Mean trough dapagliflozin and metformin plasma concentration profile versus time following administration of 10/1000 XR FDC tablet.....	23
Figure 5:	Links Between Pivotal Bioequivalence Studies and <i>In Vitro</i> Dissolution Studies to Support Biowaiver for the To-Be-Marketed Dapagliflozin/Metformin XR FDC Tablets.....	26
Figure 6	Mean plasma concentration time profile of dapagliflozin following FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg.....	27
Figure 7	Mean plasma concentration time profile of metformin following administration of FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg in healthy subjects	28
Figure 8	Mean plasma concentration time profile of dapagliflozin following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg.....	31
Figure 9	Mean plasma concentration time profile of metformin following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg.....	32

1 Executive Summary

Xigduo XR being developed by Bristol-Myers Squibb, and to be marketed by AstraZeneca Pharmaceuticals LP, is a sodium-glucose cotransporter 2 (SGLT2) inhibitor and biguanide fixed-dose combination (FDC) product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

If approved, Xigduo will be the first SGLT2/biguanide FDC to enter the market.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted under NDA 205649 and recommends approval

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Dapagliflozin/metformin hydrochloride extended-release film-coated tablets (Xigduo XR) are manufactured in strengths of 5 mg/500 mg, 10 mg/500 mg, 5 mg/1000 mg, and 10 mg/1000 mg, and contain 5 mg or 10 mg of dapagliflozin and 500 mg or 1000 mg of metformin hydrochloride.

The proposed dosing regimen is that healthcare providers should individualize the starting dose of Xigduo XR based on the patient's current treatment. Xigduo XR should be taken once daily in the morning with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin.

Two pivotal studies, one with the 5/500 XR FDC (Dapagliflozin+Metformin) *versus* 5 mg dapagliflozin and 500 mg Glucophage XR administered together, and the other with 10/1000 XR FDC (Dapagliflozin+Metformin) *versus* 10 mg dapagliflozin and 2x500 mg Glucophage XR administered together, were conducted to address the following:

(a) **Bioequivalence (BE):**

- i. Study MB102100 demonstrated BE of 5/500 (Dapagliflozin+Metformin) *versus* individual components 5 mg dapagliflozin and 500 mg Glucophage XR administered together under fed conditions.
- ii. Study MB102092 demonstrated BE of 10/500 (Dapagliflozin+Metformin) *versus* individual components 10 mg dapagliflozin and 2x500 mg Glucophage XR administered together under fed conditions.

(b) **Food-Effect:** Both studies MB102100 and MB102092 incorporated a fasting arm of the FDCs to evaluate food-effect on the pharmacokinetics of dapagliflozin and metformin from the FDC. Food decreased the C_{max} of dapagliflozin; however, AUCs were similar for fasting and fed treatments. Metformin pharmacokinetics were unaffected by food.

(c) **Steady-state:** Steady-state pharmacokinetics (PK) of dapagliflozin and metformin in the fed state following administration of the 10/1000 XR FDC tablet (study

MB102092) or 5/500 XR FDC tablet (study MB102100) were evaluated. Extended-release characteristics for metformin were exhibited. Total and peak exposures of dapagliflozin and metformin were similar at steady-state compared to single-dose.

Biowaiver: The pivotal BE program conducted with the highest strength FDC and lowest strength FDC utilized a bracketing approach. *In vitro* dissolution data was provided along with a biowaiver request for the intermediate XR FDC strengths, 5/1000 mg and 10/500 mg. The biowaiver request and *in vitro* dissolution data were reviewed by the ONDQA reviewer Dr. Tien Mien Chen (see review dated 7/2/2014 in DARRTS).

Drug-Drug interaction (DDI): DDI information of dapagliflozin on metformin and metformin on dapagliflozin is available from Dapagliflozin NDA 20-2293. Dapagliflozin is metabolized to form the inactive metabolite BMS-801576 via UGT1A9 which is the major metabolic pathway for dapagliflozin in humans. Metformin is predominantly excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolite has been identified in humans) nor undergo biliary excretion. Based on the characteristics of these 2 compounds, it was not anticipated that there would be any pharmacokinetic drug-drug interaction. As expected, the data from the DDI study (MB102026) demonstrated that dapagliflozin and metformin did not affect the PK of the other compound when given together. Therefore these 2 compounds can be administered together if needed.

Key BE, food-effect, steady-state and DDI information of Xigduo XR are summarized in [Table 1](#).

Table 1 Highlights of Bioequivalence, Food-Effect, Steady-State and DDI Information

Study	PK Parameter	Bioequivalence		Food-Effect		Steady-state		DDI	
		Dapagliflozin	Metformin	Dapagliflozin	Metformin	Dapagliflozin	Metformin	Dapagliflozin	Metformin
MB102100 (5/500 XR FDC vs. individual components)	C _{max}	94.4 – 108.6	92.0 – 103.2	↓ 34%	↔	Slight increase	↔		
	AUC _{0-t}	99.0 – 104.7	92.8 – 103.8	↓ 9%	↔				
	AUC _{0-∞}	98.8 – 105.0	93.0 – 104.2	↓ 9%	↔				
	AUC _{0-τ}					Slight increase	↔		
	T _{max}	↔	↔	↓	↔	↔	↔		
MB102092 (10/1000 XR FDC vs. individual components)	C _{max}	86.8 – 101.0	95.7 – 104.7	↓ 34%	↔	↔	↔		
	AUC _{0-t}	94.8 – 99.5	92.7 – 103.4	↓ 8%	↔				
	AUC _{0-∞}	95.0 – 99.5	92.1 – 103.1	↓ 8%	↔				
	AUC _{0-τ}					↔	↔		
	T _{max}	↔	↔	↓	↓	↔	↔		
MB102026 (Dapagliflozin/Metformin DDI)	C _{max}							84.8 – 102.4	86.6 – 104.9
	AUC _{0-t}							95.1 – 106.3	93.6 – 107.0
	AUC _{0-∞}							94.5 – 105.3	93.3 – 107.5
	T _{max}							↔	↔

(Source: Xigduo XR NDA (20-5649), Module 5.3.1.2, Study MB102100, Table 11.2-1, page 50; Table 11.2-2, page 53; Table 11.3-1, page 58; Table 11.3-2, page 61
Xigduo XR NDA (20-5649), Module 5.3.1.2, Study MB102092, Table 11.2-1, page 48; Table 11.2-2, page 51; Table 11.3-1, page 56; Table 11.3-2, page 59
Farxiga NDA (20-2293), Module 5.3.2.2, Study MB102026, Table 9.2.1B, page 56; Table 9.2.2B, page 59)

2 Question-Based Review (QBR)

2.1 What are the *in vivo* Clinical Pharmacology and Biopharmaceutics studies with PK information submitted in the NDA

The clinical pharmacology and Biopharmaceutics program performed to evaluate the bioequivalence and relative bioavailability of the Xigduo XR fixed-dose combination (FDC) compared to the mono components included 5 trials. All studies were conducted in healthy volunteers. In addition to the 2 pivotal bioequivalence (BE) studies comparing the FDC against the mono components from which PK data were available, the NDA program also comprised 1 metformin formulation finding Phase 1 trial in healthy subjects, and 2 relative bioavailability Phase 1 trials in healthy subjects to compare the bioavailability of the FDC against the mono components, leading up to the pivotal studies, (Table 2). A schematic of the Clinical Pharmacology/Biopharmaceutics program is shown in Figure 1.

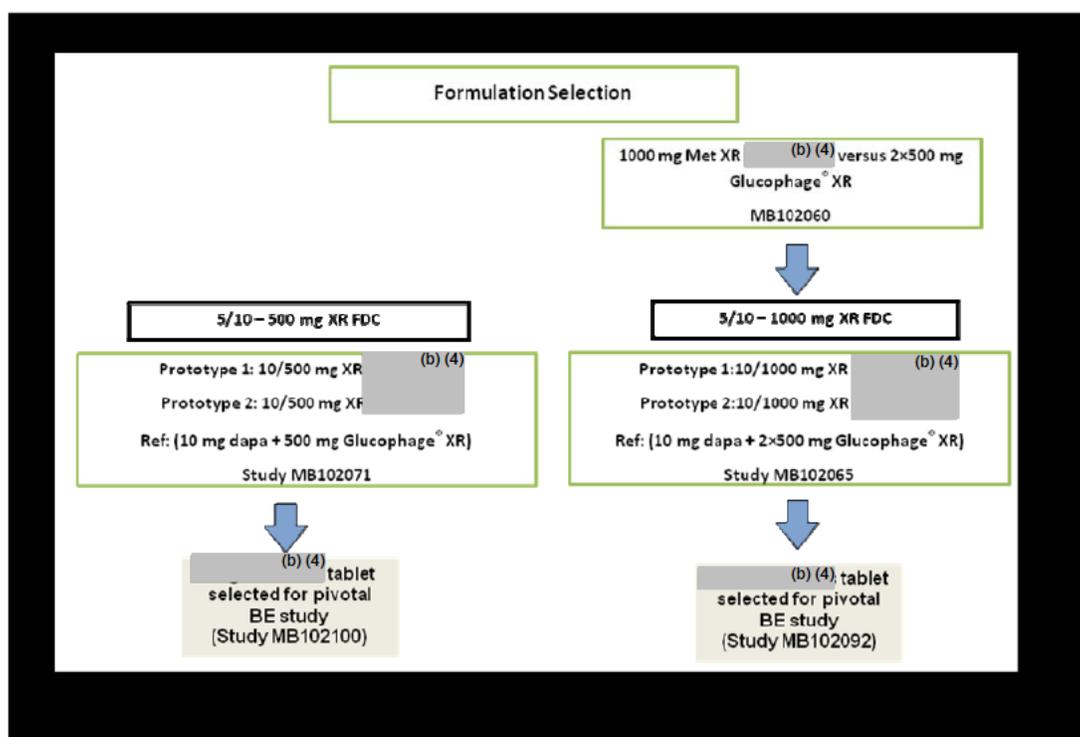


Figure 1: Links between relative bioavailability studies conducted for formulation selection and the pivotal bioequivalence studies

(Source: Xigduo XR NDA, Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods (930063960, v.1.0), page 18)

Table 2: Overview of studies with pharmacokinetic assessments relevant to the clinical pharmacology and biopharmaceutics of Xigduo XR

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Pivotal Studies							
Phase I BE	MB102092	<p>Primary: To demonstrate the bioequivalence of dapagliflozin and metformin administered as the 10-mg dapagliflozin/1000-mg extended-release (XR) metformin fixed-dose combination (10/1000 XR FDC) tablet and a 10-mg dapagliflozin tablet coadministered with two 500-mg Glucophage® XR (metformin XR) tablets (hereafter referred to as the individual component [IC] tablets) to healthy subjects in the fed state</p> <p>Secondary:</p> <ul style="list-style-type: none"> To characterize the single-dose and steady-state pharmacokinetics (PK) of dapagliflozin and metformin following administration of the 10/1000 XR FDC tablet to healthy subjects in the fed state 	Open-label, randomized, 4-period, 4-treatment, crossover study with a washout between each dose in Periods 1, 2, and 3 of at least 4 days	<ul style="list-style-type: none"> Treatment A: A single oral dose of IC tablets (one 10-mg dapagliflozin tablet and two 500-mg metformin XR tablets) administered in the fed state (bioequivalence reference treatment). Treatment B: A single oral dose of the 10/1000 XR FDC tablet administered in the fed state (bioequivalence test treatment). Treatment C: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state (food-effect assessment). Treatment D: Once-daily oral doses of the 10/1000 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment). 	36 subjects randomized, 35 subjects completed the study	Healthy M or F, age 18-55 years, with a BMI of 18-32 kg/m ²	<p>Treatments A, B and C: single-dose</p> <p>Treatment D: multiple-dose for 4 days</p>

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
		<ul style="list-style-type: none"> To assess the effect of a meal (light-fat) on the single-dose PK of dapagliflozin and metformin administered in the 10/1000 XR FDC tablet in healthy subjects <p>To assess, in healthy subjects, the safety and tolerability of the IC tablets administered in the fed state, and that of single doses (administered in the fed and fasted states) and multiple doses (administered in the fed state) of the 10/1000 XR FDC tablet.</p>					
Phase I BE	MB102100	<p><u>Primary:</u> To demonstrate the bioequivalence of dapagliflozin and metformin administered as a 5-mg dapagliflozin/500-mg extended-release (XR) metformin fixed-dose combination (5/500 XR FDC) tablet and a 5-mg dapagliflozin tablet coadministered with one 500-mg Glucophage® XR (metformin XR) tablet to healthy subjects in the fed</p>	Open-label, randomized, 4-period, 4-treatment, crossover study with a washout between each dose in Periods 1, 2, and 3 of at least 4 days	<ul style="list-style-type: none"> Treatment A: A single oral dose of IC tablets (one 5-mg dapagliflozin tablet and one 500-mg metformin XR tablet) administered in the fed state (bioequivalence reference treatment). Treatment B: A single oral dose of the 5/500 XR FDC tablet administered in the fed state (bioequivalence test treatment). Treatment C: A 	36 subjects randomized, 36 subjects completed the study	Healthy M or F, age 18-55 years, with a BMI of 18-32 kg/m ²	<p>Treatments A, B and C: single-dose</p> <p>Treatment D: multiple-dose for 4 days</p>

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
		<p>state.</p> <p>Secondary:</p> <ul style="list-style-type: none"> To characterize the single-dose and steady-state pharmacokinetics (PK) of dapagliflozin and metformin following administration of the 5/500 XR FDC tablet to healthy subjects in the fed state. To assess the effect of a meal (light-fat) on the single-dose PK of dapagliflozin and metformin administered in the 5/500 XR FDC tablet in healthy subjects. <p>To assess, in healthy subjects, the safety and tolerability of the IC tablets administered in the fed state, and that of single doses (administered in the fed and fasted states) and multiple doses (administered in the fed state) of the 5/500 XR FDC tablet.</p>		<p>single oral dose of the 5/500 XR FDC tablet administered in the fasted state (food-effect assessment).</p> <ul style="list-style-type: none"> Treatment D: Once-daily oral doses of the 5/500 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment). 			
Supportive Studies							
Phase I Relative BA	MB102060	<p>Primary:</p> <p>Assess relative bioavailability of one compressed tablet</p>	Open-label, randomized, 3-period, 3-treatment,	<ul style="list-style-type: none"> Treatment A: Single dose of Glucophage XR 2 x 500 mg tablets 	15 subjects randomized, 15 subjects completed the study	Healthy M and F), 18 to 45 years of age with a body mass index (BMI) of	Single dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
		<p>prototype containing reduced-mass metformin XR 1000 mg relative to Glucophage XR 2 x 500 mg tablets when administered to healthy subjects in a fasted condition</p> <p>Secondary:</p> <ul style="list-style-type: none"> Assess the effect of food on the compressed tablet prototype containing reduced-mass metformin XR 1000 mg in healthy subjects. Assess the safety and tolerability of metformin when administered as Glucophage XR 2 x 500 mg tablets and when administered as the compressed tablet prototype containing reduced-mass metformin 1000 mg XR. 	unbalanced crossover study	<p>(fasted)</p> <ul style="list-style-type: none"> Treatment B: Single dose of compressed tablet prototype containing metformin reduced-mass XR 1000 mg (hereafter referred to as metformin reduced-mass XR tablet) (fasted) Treatment C: Single dose of metformin reduced-mass XR 1 x 1000 mg tablet (fed) 		18 to 32 kg/m ² inclusive	
Phase I Relative BA	MB102065	Assess the relative bioavailability (BA) of dapagliflozin and metformin from the 2 FDC formulations, comprised of 10 mg dapagliflozin and 1000 mg metformin XR, relative to coadministration of a dapagliflozin 10	Open-label, randomized, 3-period, 3-treatment, crossover study with a washout of at least 7 days between 2 consecutive doses	<ul style="list-style-type: none"> Treatment A: FDC tablet of dapagliflozin 10 mg and metformin XR 1000 mg (FDC1), fasted Treatment B: FDC tablet of dapagliflozin 10 mg and reduced mass (RM) 	44 subjects enrolled ; 15 subjects randomized, 13 subjects completed the study	Healthy M or F, age 18-45 years, with a BMI of 18-32 kg/m ²	Single-dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
		mg tablet and 2 x 500 mg Glucophage XR tablets, in healthy subjects in a fasted state.		metformin XR 1000 mg (FDC2), fasted <ul style="list-style-type: none"> Treatment C: Coadministration of a dapagliflozin 10 mg tablet and Glucophage XR 2 x 500 mg tablets, fasted 			
Phase I Relative BA	MB102071	To assess the relative bioavailability of dapagliflozin and metformin from two FDC formulations comprising 10 mg dapagliflozin and 500 mg metformin XR, relative to coadministration of a dapagliflozin 10 mg tablet and a 500 mg Glucophage® XR tablet, in healthy subjects in a fasted state	Open-label, randomized, 3-period, 3-treatment, unbalanced cross-over study with a washout of at least 7 days between 2 consecutive doses	<ul style="list-style-type: none"> Treatment A: FDC tablet of dapagliflozin 10 mg and metformin XR 500 mg (FDC1), fasted Treatment B: FDC tablet of dapagliflozin 10 mg and reduced mass metformin XR 500 mg (FDC2), fasted Treatment C: Coadministration of a dapagliflozin 10 mg tablet and Glucophage XR 500 mg tablet, fasted 	36 subjects enrolled ; 15 subjects randomized, 14 subjects completed the study	Healthy M or F, age 18-45 years, with a BMI of 18-32 kg/m ²	Single-dose

The efficacy and safety of Xigduo XR was obtained from dapagliflozin NDA (20-2293), where the safety and tolerability of dapagliflozin both as monotherapy and in combination with other therapies for T2DM, including metformin, were documented and evaluated.

The dapagliflozin clinical development program from NDA 20-2293 included 12 Phase 3 studies that support the safety and tolerability of dapagliflozin/metformin XR FDC tablets. For additional details, please refer to the safety and efficacy evaluation of dapagliflozin and metformin from the FDCs by the Medical officer, Dr. Kaveeta Vasisht (see review dated 7/11/2014 in DARRTS).

2.1.1 What are the highlights of the Xigduo XR drug product as they relate to clinical pharmacology review?

Dapagliflozin/metformin XR FDC tablets are (b) (4) a (b) (4) tablet configuration using (b) (4) dapagliflozin and metformin (b) (4) dapagliflozin (b) (4) is formulated for immediate release, whereas the metformin (b) (4) is formulated to provide extended release. The formulation compositions for the (b) (4) the FDC are slightly different than the compositions utilized for the single entity dapagliflozin (Farxiga, BMS/AZ) or metformin XR (Glucophage XR, BMS) products, respectively.

2.1.2 What is the composition of to-be-marketed formulation of Xigduo XR?

Metformin XR (Glucophage XR) tablets are currently available in 500 mg and 750 mg strengths with a maximum daily dose of 2000 mg to be taken with the evening meal. In order to provide more convenience to patients, a 1000 mg metformin XR tablet formulation was developed by the sponsor (b) (4) tablets. (b) (4)

Formulation:

Dapagliflozin/metformin hydrochloride extended-release film-coated tablets (Xigduo XR) are manufactured in strengths of 5 mg/500 mg, 10 mg/500 mg, 5 mg/1000 mg, and 10 mg/1000 mg, and contain 5 mg or 10 mg of dapagliflozin and 500 mg or 1000 mg of metformin hydrochloride. The formulations are shown in [Tables 3a-3d](#). A schematic of the dapagliflozin/metformin XR tablet is shown in [Figure 2](#).



Figure 2: Composition of Xigduo XR tablet

(Source: Xigduo XR NDA, Module 2.7.2, Summary of Clinical Pharmacology Studies (930063942, v.1.0), page 8)

Table 3a Composition of Dapagliflozin 5 mg/Metformin XR 500 mg

Component	Quality Standard	Function	Quantity per Tablet (mg)	Quantity per Tablet (% w/w)
(b) (4)				(b) (4)
Metformin Hydrochloride (b) (4)	In-house ^b	Active		
Carboxymethylcellulose Sodium (b) (4)	USP USP, Ph.Eur.	(b) (4)		
Hypromellose 2208	USP, Ph.Eur.			
Hypromellose 2910	USP			
Microcrystalline Cellulose (b) (4)	NF, Ph.Eur.			
Silicon Dioxide	NF			
Magnesium Stearate	NF, Ph.Eur.			
(b) (4)				
Dapagliflozin Propanediol ^d	In-house ^e	Active		
(b) (4)	NF, Ph.Eur.	(b) (4)		
Lactose Anhydrous	NF, Ph.Eur.			
Croscopovidone	NF, Ph.Eur.			
(b) (4)	NF NF, Ph.Eur.			
(b) (4)		(t)		
Film-Coating Layer				
(b) (4)	In-house ^k USP, Ph.Eur.	(b) (4)		
Total Tablet Weight			1367.07	100.00
(b) (4)				

USP – United States Pharmacopocia
 NF – National Formulary
 Ph.Eur. – European Pharmacopocia

^a (b) (4) metformin hydrochloride, USP, (b) (4)

(b) (4)

^d Dapagliflozin propanediol is (b) (4) containing 1:1:1 ratio of the active moiety (dapagliflozin), (s)-(-)-1,2-propanediol, and water. The amount of dapagliflozin in the 5 mg strength tablet is theoretically equivalent to (b) (4) of the input dapagliflozin propanediol.

^e In-house requirements for dapagliflozin propanediol are listed as part of an established BMS Testing Standard Specification.

(b) (4)

^g Microcrystalline cellulose (b) (4) (b) (4)

ⁱ (b) (4)

^j (b) (4) contains Polyvinyl Alcohol (b) (4) USP, Ph.Eur. (b) (4) polyethylene Glycol (b) (4) Ph.Eur. (b) (4) Titanium Dioxide USP, Ph.Eur. (b) (4) and FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake (b) (4) (b) (4)

^k In-house requirements for (b) (4) are listed as part of an established BMS Testing Standard Specification; all of the components of the (b) (4) meet the applicable compendial requirements.

^l The amount of coating material is based on (b) (4) (b) (4)

(Source: Xigduo XR NDA eCTD module 3.2.P.1; Table 3.2.P.1.T02, page 1)

Table 3b Composition of Dapagliflozin 10 mg/Metformin XR 500 mg

Component	Quality Standard	Function	Quantity per Tablet (mg)	Quantity per Tablet (% w/w)
(b) (4)				
Metformin Hydrochloride (b) (4)	In-house ^b	Active	(b) (4)	(b) (4)
Carboxymethylcellulose Sodium (b) (4)	USP	(b) (4)		
Hypromellose 2208	USP, Ph.Eur.			
Hypromellose 2910	USP			
Microcrystalline Cellulose (b) (4)	NF, Ph.Eur.			
Silicon Dioxide	NF			
Magnesium Stearate	NF, Ph.Eur.			
(b) (4)				
Dapagliflozin Propanediol ^d	In-house ^e	Active	(b) (4)	
(b) (4)	NF, Ph.Eur.			
Lactose Anhydrous	NF, Ph.Eur.			
Croscopovidone	NF, Ph.Eur.			
(b) (4)	NF			
(b) (4)	NF, Ph.Eur.			
(b) (4)				
(b) (4)	In-house ^k			
(b) (4)	USP, Ph.Eur.			
(b) (4)				
Total Tablet Weight			1367.07	100.00

(b) (4)
 USP – United States Pharmacopocia
 NF – National Formulary
 Ph.Eur. – European Pharmacopocia

^a (b) (4) metformin hydrochloride, USP, (b) (4)

(b) (4)

^d Dapagliflozin propanediol is (b) (4) containing 1:1:1 ratio of the active moiety (dapagliflozin), (S)-(+)-1,2-propanediol, and water. The amount of dapagliflozin in the 10 mg strength tablet is theoretically equivalent to (b) (4)% of the input dapagliflozin propanediol.

^e In-house requirements for dapagliflozin propanediol are listed as part of an established BMS Testing Standard Specification.

^f (b) (4)

^g Microcrystalline cellulose (b) (4)

^h (b) (4)

ⁱ (b) (4)

^j (b) (4) Polyvinyl Alcohol (b) (4) USP, Ph.Eur.

^k (b) (4) Titanium Dioxide USP, Ph.Eur. (b) (4) Polyethylene Glycol (b) (4) Ph.Eur. (b) (4) Talc USP, Ph.Eur. (b) (4) and (b) (4) Iron Oxide NF (b) (4)

^l In-house requirements for (b) (4) are listed as part of an established BMS Testing Standard Specification; all of the components of the (b) (4) meet the applicable compendial requirements.

^l The amount of coating material is based on (b) (4)

(Source: Xigduo XR NDA eCTD module 3.2.P.1; Table 3.2.P.1.T03, page 1)

Table 3c Composition of Dapagliflozin 5 mg/Metformin XR 1000 mg

Component	Quality Standard	Function	Quantity per Tablet (mg)	Quantity per Tablet (% w/w)
(b) (4)				(b) (4)
Metformin Hydrochloride (b) (4)	In-house ^b	Active		
Carboxymethylcellulose Sodium (b) (4)	USP	(b) (4)		
(b) (4)	USP, Ph.Eur.			
Hypromellose 2208	USP, Ph.Eur.			
Silicon Dioxide	NF			
Magnesium Stearate	NF, Ph.Eur.			
(b) (4)				
Dapagliflozin Propanediol ^d	In-house ^e	Active		
Microcrystalline Cellulose (b) (4)	NF, Ph.Eur.	(b) (4)		
Lactose Anhydrous	NF, Ph.Eur.			
Croscopovidone	NF, Ph.Eur.			
(b) (4)	NF			
(b) (4)	NF, Ph.Eur.			
(b) (4)		(b) (4)		
(b) (4)	In-house ^k			
(b) (4)	USP, Ph.Eur.			
Total Tablet Weight			1645.13	100.00

(b) (4)
 USP = United States Pharmacopoeia
 NF = National Formulary
 Ph.Eur. = European Pharmacopoeia

^a (b) (4) (b) (4) metformin hydrochloride, USP. (b) (4)

(b) (4) (b) (4)

(b) (4)

^d Dapagliflozin propanediol is (b) (4) containing 1:1:1 ratio of the active moiety (dapagliflozin), (S)-(+)-1,2-propanediol, and water. The amount of dapagliflozin in the 5 mg strength tablet is theoretically equivalent to (b) (4) of the input dapagliflozin propanediol.

^e In-house requirements for dapagliflozin propanediol are listed as part of an established BMS Testing Standard Specification.

(b) (4)

^g Microcrystalline cellulose (b) (4) (b) (4)

^h The target amount of total magnesium stearate is (b) (4) w/w of the dapagliflozin layer. (b) (4)

ⁱ (b) (4) (b) (4) Polyvinyl Alcohol (b) (4) USP, Ph.Eur. (b) (4) (b) (4) Polycethylene Glycol (b) (4) (b) (4) Ph.Eur. (b) (4) Titanium Dioxide USP, Ph.Eur. (b) (4) (b) (4) Talc USP, Ph.Eur. (b) (4) (b) (4) Iron Oxide NF (b) (4)

^k In-house requirements for (b) (4) are listed as part of an established BMS Testing Standard Specification; all of the components of the (b) (4) meet the applicable compendial requirements.

^l The amount of coating material is based on a (b) (4) (b) (4)

(Source: Xigduo XR NDA eCTD module 3.2.P.1; Table 3.2.P.1.T04, page 1)

Table 3d Composition of Dapagliflozin 10 mg/Metformin XR 1000 mg

Component	Quality Standard	Function	Quantity per Tablet (mg)	Quantity per Tablet (% w/w)
(b) (4)				
Metformin Hydrochloride (b) (4)	In-house ^b	Active	(b) (4)	(b) (4)
(b) (4)				
Carboxymethylcellulose Sodium (b) (4)	USP	(b) (4)		
	USP, Ph.Eur.			
Hypromellose 2208	USP, Ph.Eur.			
Silicon Dioxide	NF			
Magnesium Stearate	NF, Ph.Eur.			
(b) (4)				
Dapagliflozin Propanediol ^d	In-house ^e	Active	(b) (4)	(b) (4)
Microcrystalline Cellulose (b) (4)	NF, Ph.Eur.	(b) (4)		
Lactose Anhydrous	NF, Ph.Eur.			
Croscopovidone	NF, Ph.Eur.			
(b) (4)	NF			
	NF, Ph.Eur.			
(b) (4)				
(b) (4)	In-house ^k			(b) (4)
	USP, Ph.Eur.			
(b) (4)				(b) (4)
Total Tablet Weight			1645.13	100.00
(b) (4)				

USP – United States Pharmacopoeia
 NF – National Formulary
 Ph.Eur. = European Pharmacopoeia

^a (b) (4) metformin hydrochloride, USP, (b) (4)
 (b) (4)
 (b) (4)

^d Dapagliflozin propanediol is (b) (4) containing 1:1:1 ratio of the active moiety (dapagliflozin), (S)-(+)-1,2-propanediol, and water. The amount of dapagliflozin in the 10 mg strength tablet is theoretically equivalent to (b) (4) of the input dapagliflozin propanediol.

^e In-house requirements for dapagliflozin propanediol are listed as part of an established BMS Testing Standard Specification.

(b) (4)
 (b) (4)

^f Microcrystalline cellulose (b) (4) (b) (4)

^h The target amount of total magnesium stearate is (b) (4) % w/w of the dapagliflozin layer.

ⁱ (b) (4)
^j (b) (4) Polvinyl Alcohol (b) (4) USP, Ph.Eur.
 (b) (4) Titanium Dioxide USP, Ph.Eur. (b) (4) Polyethylene Glycol (b) (4)
 Ph.Eur. (b) (4) Talc USP, Ph.Eur. (b) (4) and (b) (4) Iron Oxide NF (b) (4)
 (b) (4)

^k In-house requirements for (b) (4) are listed as part of an established BMS Testing Standard Specification, all of the components of the (b) (4) meet the applicable compendial requirements.

^l The amount of coating material is based on (b) (4) (b) (4)

(Source: Xigduo XR NDA eCTD module 3.2.P.1; Table 3.2.P.1.T05, page 1)

2.1.3 What are the proposed mechanism of action and therapeutic indications?

Dapagliflozin: Majority of the reabsorption of filtered glucose from the tubular lumen is mediated by sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules. Dapagliflozin is a stable, competitive, reversible, selective and orally active 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.

Metformin: 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.

2.1.4 What are the proposed dosages and routes of administration?

The general recommendation is to individualize the starting dose based on the patient's current treatment. The dose should be administered once daily in the morning with food.

In addition, the following recommendations are proposed by the sponsor:

- Swallow whole. Never crush, cut, or chew.
- Do not exceed a daily dose of 10 mg dapagliflozin/2000 mg metformin HCl extended-release.
- No dosage adjustment is indicated in patients with mild renal impairment. Xigduo XR should not be used in patients with moderate to severe renal impairment (defined as eGFR <60 mL/min/1.73 m² or CrCl <60 mL/min) or end-stage renal disease.

2.2 General Clinical Pharmacology

2.2.1 What is known about the PK characteristics of dapagliflozin and metformin following the administration of commercially listed drugs, Farxiga and Glucophage XR tablets?

Dapagliflozin:

The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. The C_{max} and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment. The mean plasma terminal half-life (t_{1/2}) for dapagliflozin is approximately 12.9 hours following a single oral dose of Farxiga 10 mg. The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [¹⁴C]-dapagliflozin dose and is the predominant drug-related component in human plasma. Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [¹⁴C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug.

Metformin:

The absolute bioavailability of a Glucophage 500 mg tablet given under fasting conditions is approximately 50% to 60%. Although the extent of metformin absorption (as measured by AUC) from the glucophage XR tablet increased by approximately 50% when given with food, there was no

effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of glucophage XR. Studies using single oral doses of glucophage 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. At steady state, the AUC and C_{max} are less than dose proportional for glucophage XR within the range of 500 mg to 2000 mg administered once daily. Following a single oral dose of glucophage XR, C_{max} is achieved with a median value of 7 hours and a range of 4 hours to 8 hours. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of glucophage, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally $<1 \mu\text{g/mL}$. Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

2.2.2 Were the active moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?

Yes. Dapagliflozin and metformin were measured in plasma to assess the PK parameters.

2.2.3 Compared to single-dose, how do the pharmacokinetics of dapagliflozin and metformin compare following multiple dose administration of Xigduo XR?

Multiple dose pharmacokinetics of dapagliflozin and metformin following the administration of Xigduo XR were assessed in two studies. In study MB102100, steady-state PK of dapagliflozin and metformin were evaluated following administration of the 5/500 XR FDC tablet to healthy subjects in the fed state once daily for 4 days. In study MB102092, steady-state PK of dapagliflozin and metformin were evaluated following administration of the 10/1000 XR FDC tablet to healthy subjects in the fed state once daily for 4 days.

Study MB102100:

The geometric mean trough plasma concentrations of dapagliflozin and metformin increased slightly with time from Day 2 to Day 5 following once-daily dosing of the 5/500 XR FDC tablet in the fed state ([Figure 3](#)). Following 4 days of administration of the 5/500 XR FDC tablet in the fed state, the 0 to 24-hour mean profiles of dapagliflozin and metformin were slightly higher on Day 4 compared to the mean profiles following a single dose administration. Review of the individual metformin single-dose and multiple-dose plasma concentration-time profiles showed no evidence of dose dumping. In study MB102100, repeated once-daily dosing for 4 days did not change the PK of dapagliflozin or metformin. Steady state pharmacokinetic parameters for dapagliflozin and metformin are summarized in [Table 4](#).

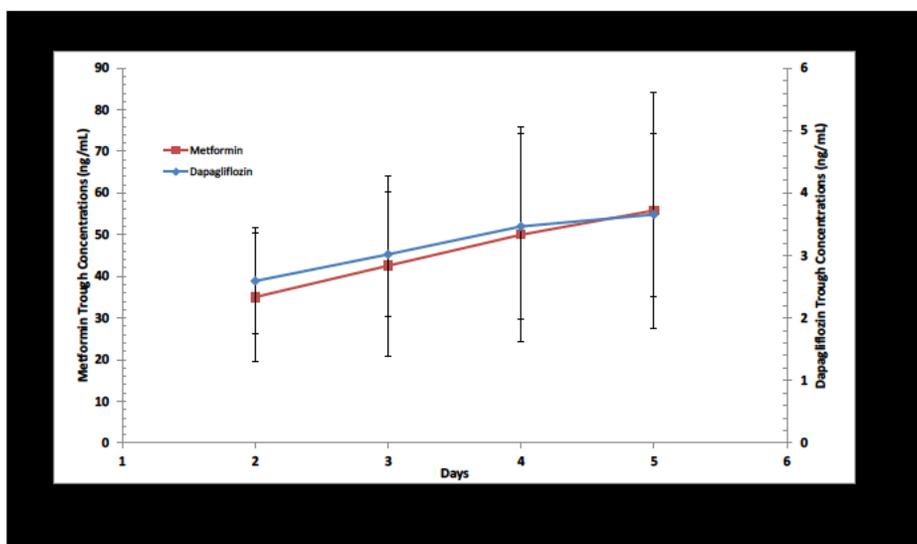


Figure 3: Mean trough dapagliflozin and metformin plasma concentration profile versus time following administration of 5/500 XR FDC tablet

Table 4: Steady-state pharmacokinetic parameters (mean (%CV)) following administration of Xigduo XR tablets (5 mg dapagliflozin/500 mg metformin) every 24 hours for 4 days

PK Parameters	Dapagliflozin (N = 36) ^a	Metformin (N = 36) ^a
Day 1		
AUC _{0-∞} (ng.h/mL)	246 (23)	5042 (25)
AUC _{0-t} (ng.h/mL)	228 (23)	4878 (25)
C _{max} (ng/mL)	46.5 (27)	631 (22)
T _{max} (ng/mL) ^b	2.00 (0.52 – 3.02)	4.00 (3.00 – 6.03)
Days 2 through 5		
Day 2 C _{min} (ng/mL)	2.59 (33)	35.0 (44)
Day 3 C _{min} (ng/mL)	3.02 (33)	42.6 (51)
Day 4 C _{min} (ng/mL)	3.47 (43)	50.0 (52)
Day 5 C _{min} (ng/mL)	3.66 (36)	55.8 (51)
Day 5		
AUC _{0-τ} (ng.h/mL)	272 (22)	5188 (28)
C _{max,ss} (ng/mL)	51.6 (21)	623 (24)
T _{max,ss} (ng/mL)	2.00 (0.50 – 3.00)	4.00 (3.00 – 8.00)

^an=18 for steady-state evaluation

^bMedian (Range) for T_{max}

(Source: Xigduo XR NDA Module 5.3.1.2, Study MB102100, Table 11.2-1, page 50, Table 11.3-1, page 58; Table 14.2.1.1, page 82; Table 14.2.1.2, page 84-85)

Reviewer Comments: Following 4 days of repeated dosing, the single- and multiple-dose PK of metformin were similar. There were no unexpected early peaks in the individual metformin single-dose and multiple-dose concentration-time profiles, indicating no evidence of dose dumping. Following multiple dosing for 4 days, dapagliflozin C_{max} was approximately 11% higher than that following a single dose, and AUC_(0-τ) was approximately 11% higher than AUC_(0-∞) following a single dose, indicating minimal accumulation. Similar findings were reported in the NDA for dapagliflozin.

Study MB102092:

In study MB102092, following 4 days of once-daily dosing of the 10/1000 XR FDC tablet in the fed state, both C_{max} and T_{max} of metformin were similar to the corresponding value following single dose administration. The geometric mean AUC_{τ} following repeated dosing (9550 ng.h/mL) appeared to be similar compared to the geometric mean $AUC_{0-\infty}$ following a single dose administration (8965 ng.h/mL), suggesting metformin PK was not altered following 4 days of dosing, with no evidence of dose dumping. Repeated once-daily dosing for 4 days did not appear to change the PK of dapagliflozin in this study. The trough level of metformin increased slightly from Day 2 to Day 3, appeared to be similar on Days 3 and 4, and increased slightly from Day 4 to Day 5 following once daily dosing of the 10/1000 XR FDC tablet in the fed state. Trough concentrations of dapagliflozin and metformin are presented in [Figure 4](#). Steady state pharmacokinetic parameters for dapagliflozin and metformin are summarized in [Table 5](#).

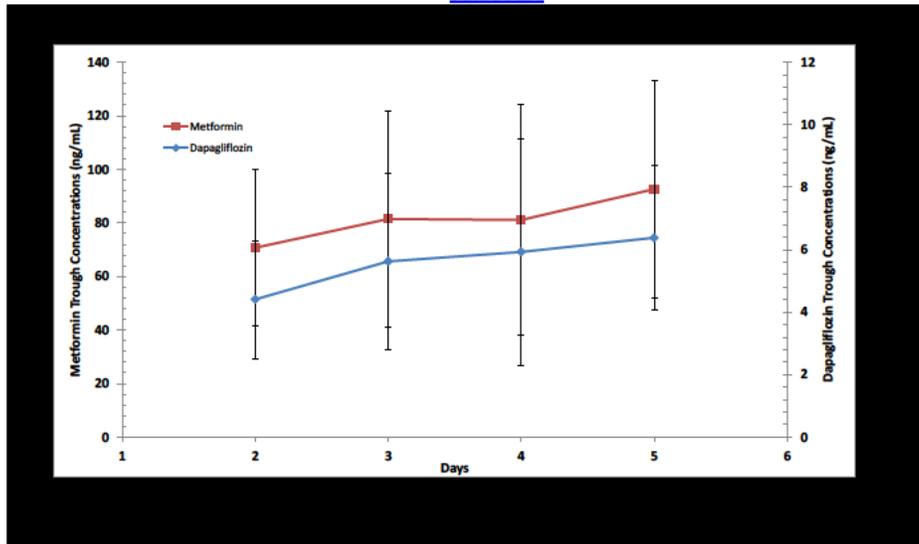


Figure 4: Mean trough dapagliflozin and metformin plasma concentration profile versus time following administration of 10/1000 XR FDC tablet

Table 5: Steady-state pharmacokinetic parameters (mean (%CV)) following administration of Xigduo XR tablets (10 mg dapagliflozin/1000 mg metformin) every 24 hours for 4 days

PK Parameters	Dapagliflozin (N = 36) ^a	Metformin (N = 36) ^a
Day 1		
$AUC_{0-\infty}$ (ng.h/mL)	489 (27)	8970(33)
AUC_{0-t} (ng.h/mL)	464 (26)	8730 (33)
C_{max} (ng/mL)	93.7 (28)	1100 (33)
T_{max} (ng/mL) ^b	2.00 (1.00 - 4.02)	4.00 (3.00 - 8.03)
Days 2 through 5		
Day 2 C_{min} (ng/mL)	4.41 (43)	70.7 (41)
Day 3 C_{min} (ng/mL)	5.63 (50)	81.5 (50)
Day 4 C_{min} (ng/mL)	5.93 (61)	81.1 (53)
Day 5 C_{min} (ng/mL)	6.38 (36)	92.6 (44)
Day 5		
$AUC_{0-\tau}$ (ng.h/mL)	507 (27)	9550 (24)
$C_{max,ss}$ (ng/mL)	92.5 (24)	1180 (18)
$T_{max,ss}$ (ng/mL)	2.00 (1.00 - 3.00)	4.00 (3.00 - 6.00)

^an=18 for steady-state evaluation

^bMedian (Range) for T_{max}

(Source: Xigduo XR NDA Module 5.3.1.2, Study MB102092, Table 11.2-1, page 48, Table 11.3-1, page 56; Table Table 14.2.1.1, page 81, Table 14.2.1.2, page 83-84)

Reviewer Comments: Following 4 days of repeated dosing, the single- and multiple-dose PK of metformin were similar. There were no unexpected early peaks in the individual metformin single-dose and multiple-dose concentration-time profiles, indicating no evidence of dose dumping. Following multiple dosing for 4 days, dapagliflozin C_{max} was similar to that following a single dose, and $AUC_{(0-7)}$ was approximately 4% higher than $AUC_{(0-\infty)}$ following a single dose, indicating minimal accumulation. Similar findings were reported in the NDA for dapagliflozin.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No dedicated study was conducted with Xigduo XR to evaluate the pharmacokinetics in special populations such as geriatric, hepatic impaired and renal impaired patients. Since this is a 505(b)(2) application, the Applicant referred to information regarding special population (geriatric and renal) and drug interaction from the NDA for Farxiga (Dapagliflozin, NDA 20-2293), where a pool of 21 double-blind, active- and placebo-controlled clinical safety and efficacy studies were conducted with dapagliflozin as monotherapy or in combination with other antidiabetic therapies.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, smoking and alcohol on Xigduo XR use were not evaluated. The sponsor conducted a specific study to investigate the effect of food on the PK of Xigduo XR. This is discussed in the next section below.

2.5 General Biopharmaceutics

The sponsor evaluated a (b) (4) metformin formulation as a potential replacement for the (b) (4) metformin XR core for each metformin strength (500 and 1000 mg). Results from this pilot study indicated the following:

- a. FDC is bioequivalent to mono-components under fasted condition
- b. Food affects the C_{max} for metformin but has no significant effect on AUC of metformin. However, for chronically administered drugs such as metformin, AUC is a better predictor of efficacy and the observed change in C_{max} may not be clinically relevant.
- c. The sponsor could use the (b) (4) metformin formulation in developing the dapagliflozin+metformin XR FDC

The sponsor further evaluated the FDC formulations in 2 additional pilot studies.

Study MB102065:

The plasma concentration-time profiles of dapagliflozin were generally similar when administered as the 10/1000 FDC XR tablets or as individual tablets co-administered in the fasted state. For dapagliflozin, estimates of bioequivalence calculated as the 90% CIs of the ratios for geometric means for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} were entirely contained within 0.80 to 1.25 limits following administration of both FDC formulations.

Metformin exposure was 15 to 20% higher from the 2 prototype 10/1000 XR FDC formulations compared to the individual components administered together.

Study MB102071:

The plasma concentration-time profiles of dapagliflozin were generally similar when administered as the 10/500 FDC XR tablets or as individual tablets co-administered in the fasted state. For dapagliflozin, estimates of bioequivalence calculated as the 90% CIs of the ratios for geometric means for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} were entirely contained within 0.80 to 1.25 limits following administration of both FDC formulations.

Systemic metformin exposure was 8% to 10% lower from the (b) (4) FDC compared with metformin from the individual components administered together. For metformin following administration of the (b) (4) FDC formulation, the 90% CIs for the (b) (4) FDC:individual components geometric mean ratios fell within 0.8 to 1.25 for C_{ma} , $AUC_{(0-\infty)}$, and $AUC_{(0-t)}$ indicating that the rate and extent of absorption of metformin from the (b) (4) FDC was similar to that from the single-ingredient products with the same strength of 500 mg metformin.

Information from the 3 pilot studies helped the sponsor develop the final formulations for the pivotal BE studies.

2.5.1 Was bioequivalence established between dapagliflozin and metformin FDC formulations and individual components?

The sponsor designed the dapagliflozin/metformin XR FDC formulation strengths used in the BE studies in concordance with suggestions by the Agency (IND 106,890, submissions dated 07-Jun-2010 and 24-Sept-2010). The schematic for pivotal BE studies for the 5/500 and 10/1000 mg dapagliflozin/metformin XR FDC formulations and *in vitro* dissolution data in to support of a

biowaiver approach for the 10/500 and 5/1000 mg dapagliflozin/metformin XR to-be-marketed FDC tablets is shown in [Figure 5](#).

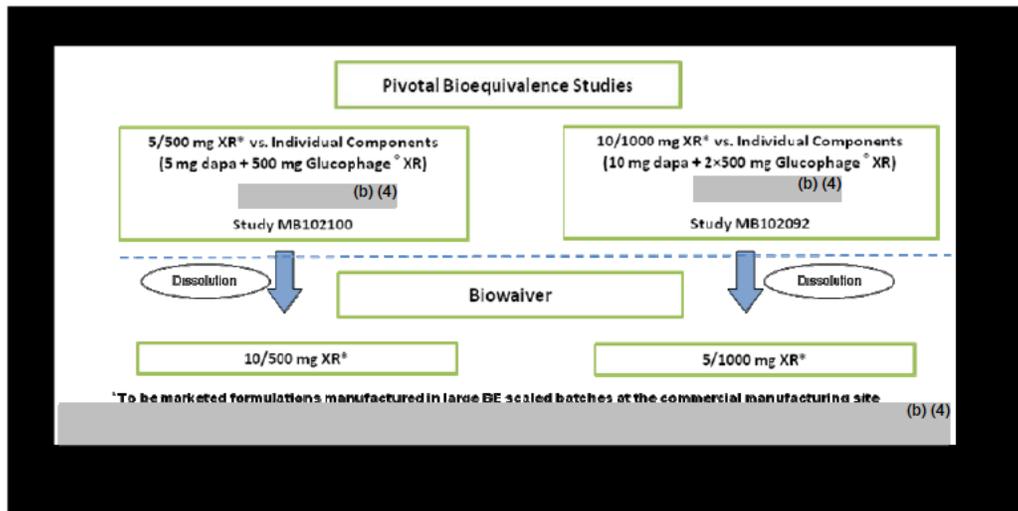


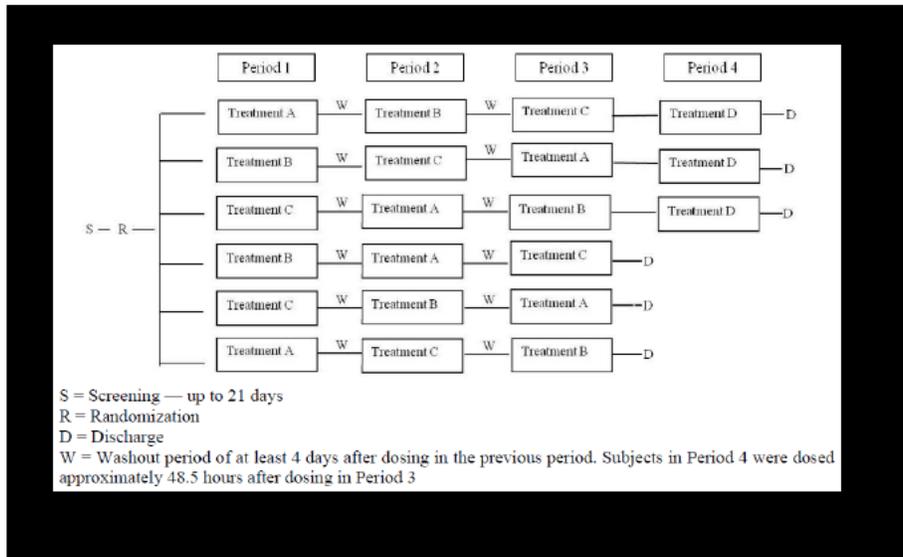
Figure 5: Links Between Pivotal Bioequivalence Studies and *In Vitro* Dissolution Studies to Support Biowaiver for the To-Be-Marketed Dapagliflozin/Metformin XR FDC Tablets

(Source: *Xigduo XR NDA Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Figure 1.3.1, page 27*)

Two studies using the to-be-marketed formulations (according to the sponsor - same embossing, color, and commercial-scale manufacturing lot size and site as for the to-be-marketed proposed commercial formulations) were conducted to evaluate fed-state BE/food effect/steady-state PK with the 10 mg dapagliflozin/1000 mg metformin XR (Study MB102092) and the 5 mg dapagliflozin/500 mg metformin XR (Study MB102100) FDC formulations compared to their individual components (5 or 10 mg dapagliflozin tablets and 1 or 2 x 500 mg Glucophage XR tablets) administered simultaneously. The 2 pivotal BE studies are described below.

Study MB102092:

This was an open-label, randomized, 4-period, 4-treatment, crossover study in 36 healthy fasted and fed subjects. Treatments A, B, and D were administered 30 minutes after the start of a light-fat meal and Treatment C was administered in the fasted state. The 36 subjects were randomized to 1 of 6 sequences (ABC, BCA, CAB, BAC, CBA, or ACB). Subjects randomized to sequences ABC, BCA, or CAB subsequently received Treatment D to assess the steady-state PK of the 10/1000 XR FDC tablet. Subjects randomized to sequences BAC, CBA, or ACB were discharged at the end of Period 3. Periods 1, 2, and 3 were each 2 days in duration and Period 4 was 5 days in duration. There was a washout period of at least 4 days after dosing in Periods 1 and 2. Subjects who were enrolled in Period 4 were dosed approximately 48.5 hours after dosing in Period 3.



- Treatment A:** A single oral dose of IC tablets (one 10-mg dapagliflozin tablet and two 500-mg metformin XR tablets) administered in the fed state (bioequivalence reference treatment).
- Treatment B:** A single oral dose of the 10/1000 XR FDC tablet administered in the fed state (bioequivalence test treatment).
- Treatment C:** A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state (food-effect assessment).
- Treatment D:** Once-daily oral doses of the 10/1000 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment).

(Source: Xigduo XR NDA Module 5.3.1.2, Study MB102092, Figure 9.1-1, page 22)

The mean (\pm SD) dapagliflozin and metformin plasma concentration versus time profiles from the study are presented in [Figures 6](#) and [7](#), respectively. Summary statistics by treatment for dapagliflozin and metformin PK parameters are provided in [Tables 6](#) and [7](#), respectively. Statistical analyses of PK parameter, C_{max} , $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ of dapagliflozin and metformin are presented in [Tables 8](#) and [9](#), respectively.

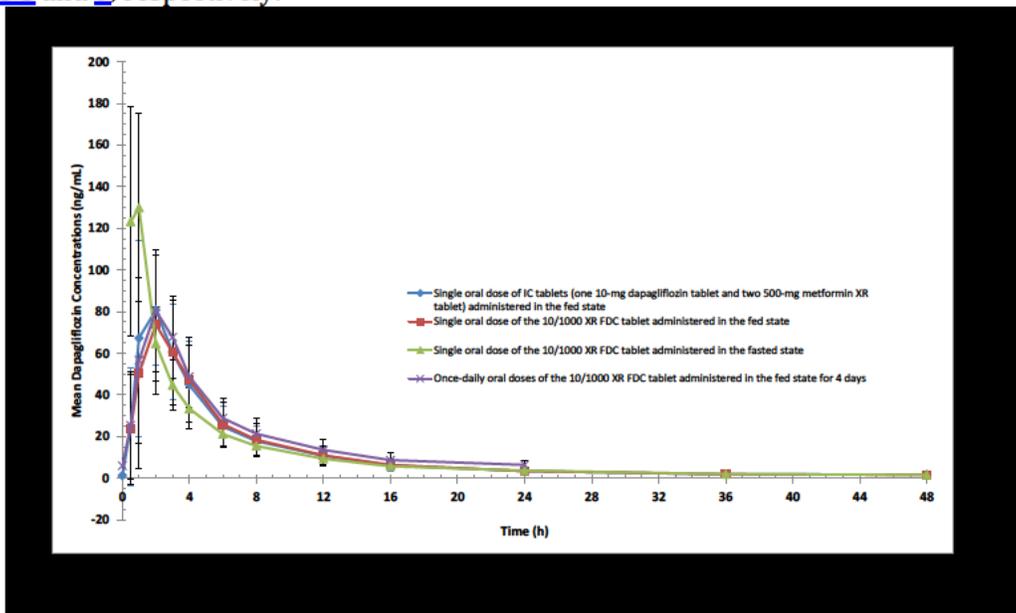


Figure 6 Mean plasma concentration time profile of dapagliflozin following FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg

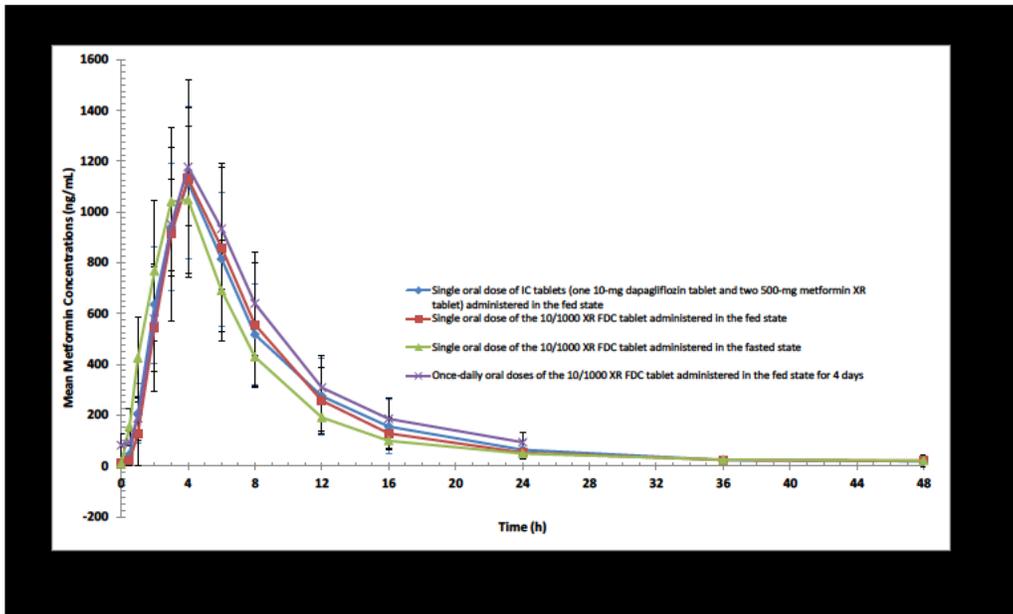


Figure 7 Mean plasma concentration time profile of metformin following administration of FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg in healthy subjects

Table 6: Summary Statistics for Dapagliflozin Pharmacokinetic Parameters administration of FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg in healthy subjects

Treatment	Dapagliflozin Pharmacokinetic Parameters					
	C _{max} (ng/mL) GM [n] (CV%)	AUC _(0-t) (ng.h/mL) GM [n] (CV%)	AUC _(0-∞) (ng.h/mL) GM [n] (CV%)	T _{max} (h) Median [n] (Min-Max)	t _{1/2} (h) Mean [n] (SD)	AUC _(0-τ) (ng.h/mL) GM [n] (CV%)
A	99.9 [35] (27)	475 [35] (28)	501 [35] (28)	2.00 [35] (1.00-4.02)	11.3 [35] (5.83)	
B	93.7 [36] (28)	464 [36] (26)	489 [36] (27)	2.00 [36] (1.00-4.02)	11.3 [36] (4.61)	
C	142 [35] (34)	501 [35] (29)	528 [35] (29)	0.53 [35] (0.50-1.05)	11.3 [35] (4.86)	
D	92.5 [18] (24)			2.00 [18] (1.00-3.00)		507 [18] (27)

Abbreviations: GM = geometric mean; n = number of nonmissing observations; CV% = coefficient of variation; SD = standard deviation
 Treatment A: A single oral dose of IC tablets (one 10-mg dapagliflozin tablet and two 500-mg metformin XR tablets) administered in the fed state.
 Treatment B: A single oral dose of the 10/1000 XR FDC tablet administered in the fed state.
 Treatment C: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state.
 Treatment D: Once-daily oral doses of the 10/1000 XR FDC tablet administered in the fed state for 4 days.
 (Source: Report of Study MB-102092; Table 11.2-1, Page 48)

Table 7: Bioequivalence and Food Effect Comparisons for Dapagliflozin administration of FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg in healthy subjects

Treatment and Comparison	AUC _(0-∞) (ng.h/mL) Adjusted GM (n)	C _{max} (ng/mL) Adjusted GM (n)	AUC _(0-t) (ng.h/mL) Adjusted GM (n)
A	504 (35)	100 (35)	477 (35)
B	489 (36)	93.7 (36)	464 (36)
C	531 (35)	143 (35)	504 (35)
Ratio of Adjusted GM (90% CI)			
B vs A	0.971 (0.948, 0.995)	0.937 (0.868, 1.010)	0.972 (0.950, 0.995)
B vs A (Potency corrected) ^a	0.961 (0.938, 0.985)	0.927 (0.860, 1.000)	0.963 (0.940, 0.985)
B vs C	0.922 (0.902, 0.942)	0.656 (0.605, 0.711)	0.921 (0.900, 0.941)

GM = geometric mean; n = number of nonmissing observations

Treatment A: A single oral dose of IC tablets (one 10-mg dapagliflozin tablet and two 500-mg metformin XR tablet) administered in the fed state.

Treatment B: A single oral dose of the 10/1000 XR FDC tablet administered in the fed state.

Treatment C: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state.

^a Potency-corrected results were obtained by multiplying the adjusted geometric mean ratio and 90% CI by the correction factor, where correction factor = measured content of reference treatment / measured content of test treatment. For these calculations, the factor was 9.9 mg /10 mg = 0.99.

(Source: Report of Study MB-102092; Table 11.2-2, Page 51)

Table 8: Summary Statistics for Metformin Pharmacokinetic Parameters administration of FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg in healthy subjects

Treatment	Metformin Pharmacokinetic Parameters					
	C _{max} (ng/mL) GM [n] (CV%)	AUC _(0-t) (ng.h/mL) GM [n] (CV%)	AUC _(0-∞) (ng.h/mL) GM [n] (CV%)	T _{max} (h) Median [n] (Min-Max)	t _{1/2} (h) Mean [n] (SD)	AUC _(0-τ) (ng.h/mL) GM [n] (CV%)
A	1100 [35] (27)	8980 [35] (31)	9290 [35] (30)	4.00 [35] (3.00-6.00)	11.1 [35] (6.46)	
B	1100 [36] (33)	8730 [36] (33)	8970 [34] (33)	4.00 [36] (3.00-8.03)	12.4 [34] (6.91)	
C	1080 [35] (25)	8290 [35] (21)	8740 [32] (22)	3.03 [35] (2.00-4.03)	12.9 [32] (7.03)	
D	1180 [18] (18)			4.00 [18] (3.00-6.00)		9550 [18] (24)

Abbreviations: GM = geometric mean; n = number of nonmissing observations; CV% = coefficient of variation; SD = standard deviation

Treatment A: A single oral dose of IC tablets (one 10-mg dapagliflozin tablet and two 500-mg metformin XR tablets) administered in the fed state.

Treatment B: A single oral dose of the 10/1000 XR FDC tablet administered in the fed state.

Treatment C: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state.

Treatment D: Once-daily oral doses of the 10/1000 XR FDC tablet administered in the fed state for 4 days.

(Source: Report of Study MB-102092; Table 11.3-1, Page 56)

Table 9: Bioequivalence and Food Effect Comparisons for Metformin administration of FDC formulation consisting of 10 mg dapagliflozin and 1000 mg metformin XR and coadministration of dapagliflozin 10 mg and glucophage XR 2x500 mg in healthy subjects

Treatment and Comparison	AUC _(0-∞) (ng.h/mL) Adjusted GM (n)	C _{max} (ng/mL) Adjusted GM (n)	AUC _(0-t) (ng.h/mL) Adjusted GM (n)
A	9270 (35)	1100 (35)	8960 (35)
B	9080 (34)	1100 (36)	8730 (36)
C	8840 (32)	1080 (35)	8280 (35)
Ratio of Adjusted GM (90% CI)			
B vs A	0.979 (0.927, 1.034)	1.001 (0.957, 1.047)	0.974 (0.921, 1.031)
B vs A (Potency corrected) ^a	0.961 (0.910, 1.015)	0.983 (0.940, 1.028)	0.957 (0.905, 1.012)
B vs C	1.026 (0.959, 1.099)	1.016 (0.926, 1.114)	1.054 (0.980, 1.134)

GM = geometric mean; n = number of nonmissing observations

Treatment A: A single oral dose of IC tablets (one 10-mg dapagliflozin tablet and two 500-mg metformin XR tablet) administered in the fed state.

Treatment B: A single oral dose of the 10/1000 XR FDC tablet administered in the fed state.

Treatment C: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state.

^a Potency-corrected results were obtained by multiplying the adjusted geometric mean ratio and 90% CI by the correction factor, where correction factor = measured content of reference treatment / measured content of test treatment. For these calculations, the factor was 9.9 mg /10 mg = 0.99.

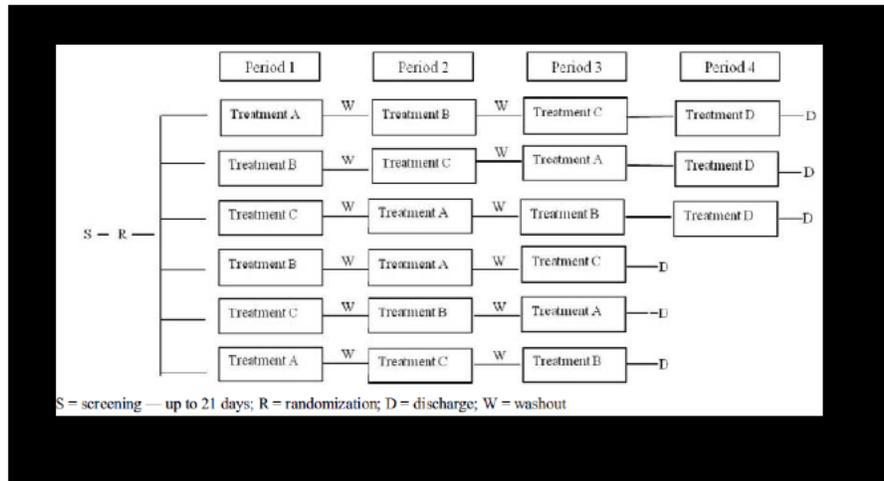
(Source: Report of Study MB-102092; Table 11.3-2, Page 59)

Reviewer Comments:

The sponsor demonstrated bioequivalence between the 10/1000 XR FDC tablet and the IC tablets for both dapagliflozin and metformin under fed conditions, thus supporting the use of the FDC tablet instead of the IC tablets in T2DM patients.

Study MB102100:

This was an open-label, randomized, 4-period, 4-treatment, crossover study in 36 healthy fasted and fed subjects. Treatments A, B, and D were administered 30 minutes after the start of a light-fat meal and Treatment C was administered in the fasted state. The 36 subjects were randomized to 1 of 6 sequences (ABC, BCA, CAB, BAC, CBA, or ACB). Subjects randomized to sequences ABC, BCA, or CAB subsequently received Treatment D to assess the steady-state PK of the 5/500 XR FDC tablet. Subjects randomized to sequences BAC, CBA, or ACB were discharged at the end of Period 3. Periods 1, 2, and 3 were each 2 days in duration and Period 4 was 5 days in duration. There was a washout period of at least 4 days after dosing in Periods 1 and 2. Subjects who were enrolled in Period 4 were dosed approximately 48.5 hours after dosing in Period 3.



- Treatment A: A single oral dose of IC tablets (one 5-mg dapagliflozin tablet and one 500-mg metformin XR tablets) administered in the fed state (bioequivalence reference treatment).
- Treatment B: A single oral dose of the 5/500 XR FDC tablet administered in the fed state (bioequivalence test treatment).
- Treatment C: A single oral dose of the 5/500 XR FDC tablet administered in the fasted state (food-effect assessment).
- Treatment D: Once-daily oral doses of the 5/500 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment).

(Source: Xigduo XR NDA Module 5.3.1.2, Study MB102100, Figure 9.1-1, page 23)

The mean (\pm SD) dapagliflozin and metformin plasma concentration versus time profiles from the study are presented in [Figures 8](#) and [9](#), respectively. Summary statistics by treatment for dapagliflozin and metformin PK parameters are provided in [Tables 10](#) and [11](#), respectively. Statistical analyses of PK parameter, C_{max} , $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ of dapagliflozin and metformin are presented in [Tables 12](#) and [13](#), respectively.

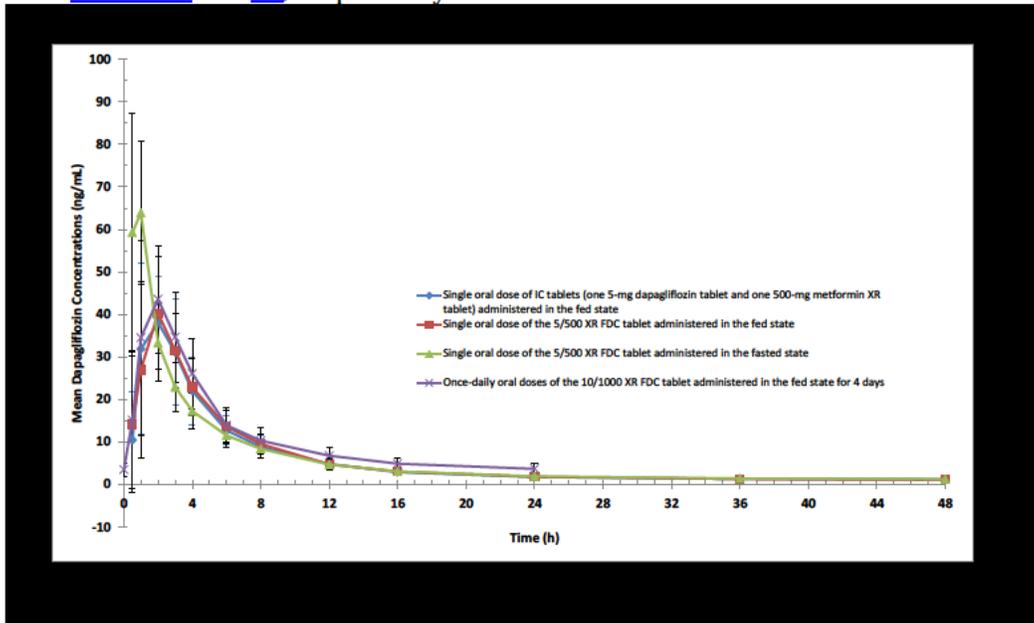


Figure 8 Mean plasma concentration time profile of dapagliflozin following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg

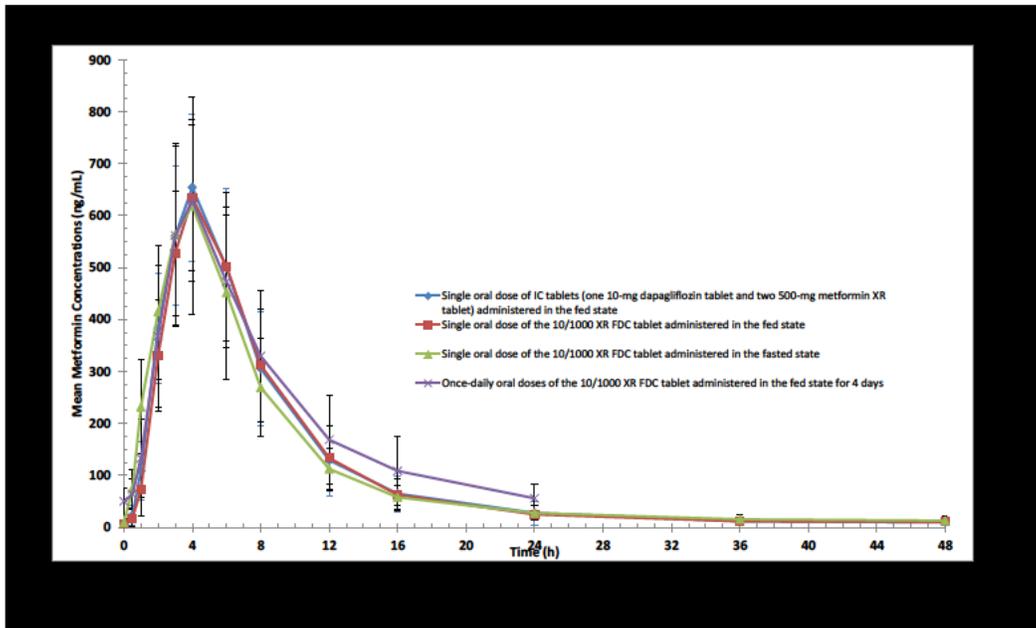


Figure 9 Mean plasma concentration time profile of metformin following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg

Table 10: Summary Statistics for Dapagliflozin Pharmacokinetic Parameters following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg

Treatment	Dapagliflozin Pharmacokinetic Parameters					
	C_{max} (ng/mL) GM[n] (CV%)	T_{max} (h) median[n] (min-max)	$AUC_{(0-t)}$ (ng.h/mL) GM[n] (CV%)	$AUC_{(0-\infty)}$ (ng.h/mL) GM[n] (CV%)	$t_{1/2}$ (h) mean[n] (SD)	$AUC_{(0-\tau)}$ (ng.h/mL) GM[n] (CV%)
A	45.9 [36] (25)	2.00 [36] (0.50 - 3.03)	224 [36] (25)	238 [35*] (25)	9.03 [35] (4.80)	NA NA
B	46.5 [36] (27)	2.00 [36] (0.52 - 3.02)	228 [36] (23)	246 [36] (23)	10.2 [36] (7.75)	NA NA
C	70.6 [36] (25)	1.00 [36] (0.48 - 2.00)	252 [36] (26)	271 [36] (25)	10.2 [36] (5.48)	NA NA
D	51.6 [18] (21)	2.00 [18] (0.50 - 3.00)	NA NA	NA NA	NA NA	272 [18] (22)

Abbreviations: GM = geometric mean; n = number of nonmissing observations; CV% = coefficient of variation; SD = standard deviation; NA = Not applicable

* $AUC_{(0-\infty)}$ and $t_{1/2}$ of 1 subject were excluded from summary of Treatment A due to AUC extrapolated > 20%.

Treatment A: A single oral dose of IC tablets (one 5-mg dapagliflozin tablet and one 500-mg metformin XR tablet) administered in the fed state.

Treatment B: A single oral dose of the 5/500 XR FDC tablet administered in the fed state.

Treatment C: A single oral dose of the 5/500 XR FDC tablet administered in the fasted state.

Treatment D: Once-daily oral doses of the 5/500 XR FDC tablet administered in the fed state for 4 days.

(Source: Report of Study MB-102100; Table 11.2-1, Page 50)

Table 11: Bioequivalence and Food Effect Comparisons for Dapagliflozin following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg

Treatment and Comparison	C _{max} (ng/mL) Adjusted GM (n)	AUC _(0-t) (ng.h/mL) Adjusted GM (n)	AUC _(0-∞) (ng.h/mL) Adjusted GM (n)
A	45.9 (36)	224 (36)	242 (35)
B	46.5 (36)	228 (36)	246 (36)
C	70.6 (36)	252 (36)	271 (36)
Ratio of Adjusted GM (90% CI)			
B vs A	1.012 (0.944, 1.086)	1.018 (0.990, 1.047)	1.019 (0.988, 1.050)
B vs A (Potency corrected) ^a	1.027 (0.957, 1.101)	1.032 (1.004, 1.062)	1.033 (1.002, 1.065)
B vs C	0.659 (0.614, 0.706)	0.905 (0.880, 0.931)	0.907 (0.884, 0.931)

GM = geometric mean; n = number of nonmissing observations

AUC_(0-∞) of 1 subject was excluded from Treatment A due to AUC extrapolated > 20%.

Treatment A: A single oral dose of IC tablets (one 5-mg dapagliflozin tablet and one 500-mg metformin XR tablet) administered in the fed state.

Treatment B: A single oral dose of the 5/500 XR FDC tablet administered in the fed state.

Treatment C: A single oral dose of the 5/500 XR FDC tablet administered in the fasted state.

^a Potency-corrected results were obtained by multiplying the adjusted geometric mean ratio and 90% CI by the correction factor, where correction factor = measured content of reference treatment (4.98 mg) / measured content of test treatment (4.91 mg). For these calculations, the factor was 4.98/4.91 = 1.014.

(Source: Report of Study MB-102100; Table 11.2-2, Page 53)

Table 12: Summary Statistics for Metformin Pharmacokinetic Parameters following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg

Treatment	Dapagliflozin Pharmacokinetic Parameters					
	C _{max} (ng/mL) GM[n] (CV%)	T _{max} (h) median[n] (min-max)	AUC _(0-t) (ng.h/mL) GM[n] (CV%)	AUC _(0-∞) (ng.h/mL) GM[n] (CV%)	t _{1/2} (h) mean[n] (SD)	AUC _(0-τ) (ng.h/mL) GM[n] (CV%)
A	647 [36] (23)	4.00 [36] (3.00 - 6.03)	4971 [36] (31)	5121 [36] (31)	11.2 [36] (7.82)	NA NA
B	631 [36] (22)	4.00 [36] (3.00 - 6.03)	4878 [36] (25)	5042 [36] (25)	10.6 [36] (9.07)	NA NA
C	608 [36] (31)	4.00 [36] (3.00 - 4.05)	4820 [36] (30)	4992 [35*] (30)	13.1 [35*] (9.22)	NA NA
D	623 [18] (24)	4.00 [18] (3.00 - 8.00)	NA NA	NA NA	NA NA	5188 [18] (28)

Abbreviations: GM = geometric mean; n = number of nonmissing observations; CV% = coefficient of variation; SD = standard deviation; NA = Not applicable

* AUC_(0-∞) and t_{1/2} of 1 subject were excluded from summary of Treatment C due to AUC extrapolated > 20%.

Treatment A: A single oral dose of IC tablets (one 5-mg dapagliflozin tablet and one 500-mg metformin XR tablet) administered in the fed state.

Treatment B: A single oral dose of the 5/500 XR FDC tablet administered in the fed state.

Treatment C: A single oral dose of the 5/500 XR FDC tablet administered in the fasted state.

Treatment D: Once-daily oral doses of the 5/500 XR FDC tablet administered in the fed state for 4 days.

(Source: Report of Study MB-102100; Table 11.3-1, Page 58)

Table 13: Bioequivalence and Food Effect Comparisons for Metformin following FDC formulation consisting of 5 mg dapagliflozin and 500 mg metformin XR and coadministration of dapagliflozin 5 mg and glucophage XR 500 mg

Treatment and Comparison	C _{max} (ng/mL) Adjusted GM (n)	AUC _(0-t) (ng.h/mL) Adjusted GM (n)	AUC _(0-∞) (ng.h/mL) Adjusted GM (n)
A	647 (36)	4971 (36)	5121 (36)
B	631 (36)	4878 (36)	5042 (36)
C	608 (36)	4820 (36)	5091 (35)
Ratio of Adjusted GM (90% CI)			
B vs A	0.975 (0.920, 1.032)	0.981 (0.928, 1.038)	0.985 (0.930, 1.042)
B vs A (Potency corrected) ^a	0.957 (0.903, 1.014)	0.964 (0.911, 1.019)	0.967 (0.914, 1.023)
B vs C	1.037 (0.949, 1.133)	1.012 (0.948, 1.080)	0.990 (0.926, 1.059)

GM = geometric mean; n = number of nonmissing observations

AUC_(0-∞) of 1 subject was excluded from Treatment A due to AUC extrapolated > 20%.

Treatment A: A single oral dose of IC tablets (one 5-mg dapagliflozin tablet and one 500-mg metformin XR tablet) administered in the fed state.

Treatment B: A single oral dose of the 5/500 XR FDC tablet administered in the fed state.

Treatment C: A single oral dose of the 5/500 XR FDC tablet administered in the fasted state.

^a Potency-corrected results were obtained by multiplying the adjusted geometric mean ratio and 90% CI by the correction factor, where correction factor = measured content of reference treatment (4.98 mg) / measured content of test treatment (4.91 mg). For these calculations, the factor was 4.98/4.91 = 1.014.

(Source: Report of Study MB-102100; Table 11.3-2, Page 61)

Reviewer Comments:

The sponsor demonstrated bioequivalence between the 5/500 XR FDC tablet and the IC tablets for both dapagliflozin and metformin under fed conditions, thus supporting the use of the FDC tablet instead of the IC tablets in T2DM patients.

2.5.2 What is the effect of food on the bioavailability of dapagliflozin and metformin from the FDC

Studies MB-102092 and MB-102100 also evaluated the effect of food on the bioavailability of dapagliflozin and metformin.

Dapagliflozin:

In study MB-102092, following administration of the 10/1000 XR FDC tablet, a food effect on dapagliflozin PK was observed. There was a 34% reduction in C_{max} and a 8% reduction in both AUC_(0-t) and AUC_(0-∞).

In study MB-102100, following administration of the 5/500 XR FDC tablet, a food effect on dapagliflozin PK was observed. There was a 34% reduction in C_{max} and a 9% reduction in both AUC_(0-t) and AUC_(0-∞).

Metformin:

In study MB-102092, following administration of the 10/1000 XR FDC tablet with a light-fat meal, there was no food effect on metformin PK.

In study MB-102100, following administration of the 5/500 XR FDC tablet with a light-fat meal, there was no food effect on metformin PK.

Reviewer Comments:

The food-effect (decreased C_{max} and AUC) observed for dapagliflozin in both the studies with 10/1000 XR and 5/500 XR FDC tablets is consistent with previous findings with dapagliflozin (Farxiga, NDA 20-2293). In that NDA, the sponsor reported that the food-induced reductions of this magnitude in dapagliflozin C_{max} did not affect the inhibition of glucose reabsorption within the dapagliflozin dose range of 5 to 10 mg. Therefore, the observed food effect for the dapagliflozin component of the FDC tablet is unlikely to be of clinical importance.

2.6 Analytical

2.6.1 Is the analytical method for Dapagliflozin and Metformin appropriately validated?

Dapagliflozin in human plasma was measured using a LC-MS/MS assay. The method was validated for a range of 1.00 to 200 ng/mL, based on the analysis of 0.150 mL of plasma. Human plasma containing Dapagliflozin (sponsor's internal code for dapagliflozin is BMS-512148) and the internal standard, [$^{13}\text{C}_6$]BMS-512148, was extracted by solid phase extraction. An aliquot of the extract was injected onto a Sciex API 4000 LC-MS-MS in positive ion mode equipped with an HPLC column. The peak area of the m/z 407→329 BMS-512148 product ion was measured against the peak area of the m/z 413→323 [$^{13}\text{C}_6$]BMS-512148 internal standard product ion. The assays were validated for analyzing the moieties of interest in plasma samples in terms of recovery, linearity, accuracy, precision and sensitivity.

Metformin in human plasma was measured using a LC-MS/MS assay. The method is applicable to quantitation within a nominal metformin range of 2.00 to 1000 ng/mL and requires a 50.0- μL human plasma aliquot. Analysis was conducted by HPLC with MS/MS detection. A 50.0- μL matrix aliquot was fortified with 25 μL of 500 ng/mL internal standard working solution and diluted with 500 μL of water. Analytes were isolated through solid phase extraction using a Waters Oasis WCX 10-mg, 96-well SPE plate and eluted with 350 μL of 2.0% formic acid in acetonitrile. The eluate was then further diluted with 1.00 mL of 2.0% formic acid in acetonitrile prior to being analyzed via HPLC with MS/MS detection. The assays were validated for analyzing the moieties of interest in plasma samples in terms of recovery, linearity, accuracy, precision and sensitivity.

A summary of key descriptive parameters for the bioanalytical assays used in clinical studies is listed in [Table 14](#).

Table 14 Summary of key descriptive parameters for Dapagliflozin and Metformin bioanalytical assays used in clinical studies

Study Number/Report Number	Study Title	Analytical Laboratory	Sample Matrix	Assay Range	LLOQ	Accuracy	Precision
Protocol MB102060/ Test Facility study no (b) (4) Project PZT	Study No. MB102060: Determination of Metformin in Human Plasma	PPD	Plasma	Metformin 2.00 to 1000 ng/mL	Metformin 2.00 ng/mL	Metformin 95.54% - 105.23% at 5.00 – 2000 ng/mL	Metformin 2.10% - 2.88% at 5.00 – 2000 ng/mL
Protocol MB102065/ Test Facility study no. DCN 01931PH	Determination of BMS-512148 in Human K2-EDTA Plasma by LC-MS-MS	Cedra Corporation	Plasma	<u>Dapagliflozin</u> 1.00 to 200 ng/mL	<u>Dapagliflozin</u> 1.00 ng/mL	<u>Dapagliflozin</u> 94.7% to 99.4% at 3.00 – 1000 ng/mL	<u>Dapagliflozin</u> -0.6% to -5.3% at 3.00 – 1000 ng/mL
Protocol MB102065/ Test Facility study no (b) (4) Project GXU	Quantitation of Metformin in Human Plasma via HPLC with MS/MS Detection	PPD	Plasma	Metformin 2.00 to 1000 ng/mL	Metformin 2.00 ng/mL	Metformin 98.75% - 102.56% at 5.00 – 1000 ng/mL	Metformin 1.01% 3.09% at 5.00 – 1000 ng/mL
Protocol MB102071/ Test Facility study no. DCN 02685C5	Determination of BMS-512148 in Human EDTA Plasma by LC-MS-MS	Cedra Corporation	Plasma	<u>Dapagliflozin</u> 1.00 to 200 ng/mL	<u>Dapagliflozin</u> 1.00 ng/mL	<u>Dapagliflozin</u> 100.6% to 107.0% at 3.00 – 1000 ng/mL	<u>Dapagliflozin</u> 3.8% to 4.4% at 3.00 – 1000 ng/mL
Protocol MB102071/ Test Facility study no (b) (4) Project SNV	Quantitation of Metformin in Human Plasma via HPLC with MS/MS Detection	PPD	Plasma	Metformin 2.00 to 2000 ng/mL	Metformin 2.00 ng/mL	Metformin 96.79% - 100.12% at 5.00 – 750 ng/mL	Metformin 2.17% 3.98% at 5.00 – 750 ng/mL
Protocol MB102092/ Test Facility study no. Document Control Number 3006171	Determination of BMS-512148 in Human K2-EDTA Plasma by LC-MS/MS	Worldwide Clinical Trials	Plasma	<u>Dapagliflozin</u> 1.00 to 200 ng/mL	<u>Dapagliflozin</u> 1.00 ng/mL	<u>Dapagliflozin</u> 93.8% to 98.7% at 3.00 – 1000 ng/mL	<u>Dapagliflozin</u> -1.3% to -6.30% at 3.00 – 1000 ng/mL
Protocol MB102092/ Test Facility study no (b) (4) Project MXX	Quantitation of Metformin in Human Plasma via HPLC with MS/MS Detection	PPD	Plasma	Metformin 2.00 to 2000 ng/mL	Metformin 2.00 ng/mL	Metformin 93.21% - 106.01% at 5.00 – 1550 ng/mL	Metformin 4.08% - 6.79% at 5.00 – 1550 ng/mL
Protocol MB102100/ Test Facility study no. Document Control Number 3006173	Determination of BMS-512148 in Human K2-EDTA Plasma by LC-MS/MS	Worldwide Clinical Trials	Plasma	<u>Dapagliflozin</u> 1.00 to 200 ng/mL	<u>Dapagliflozin</u> 1.00 ng/mL	<u>Dapagliflozin</u> 95.3% to 102.5% at 3.00 – 160 ng/mL	<u>Dapagliflozin</u> 3.3% to -6.9% at 3.00 – 160 ng/mL
Protocol MB102100/ Test Facility study no (b) (4) Project BYX	Quantitation of Metformin in Human Plasma via HPLC with MS/MS Detection	PPD	Plasma	Metformin 2.00 to 2000 ng/mL	Metformin 2.00 ng/mL	Metformin 94.08% - 107.21% at 5.00 – 1550 ng/mL	Metformin 2.67% - 6.11% at 5.00 – 1550 ng/mL

3 Labeling Comments (Preliminary)

The following are the labeling recommendations relevant to clinical pharmacology for NDA 204961. The ~~red~~ ~~strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XIGDUO XR

XIGDUO XR combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a biguanide.

Dapagliflozin

(b) (4)

(b) (4)

Metformin hydrochloride

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. (b) (4) metformin does not produce hypoglycemia in either patients with type 2 diabetes or in healthy subjects, except in unusual circumstances [see *Warnings and Precautions (5.8)*], and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

12.2 Pharmacodynamics

General

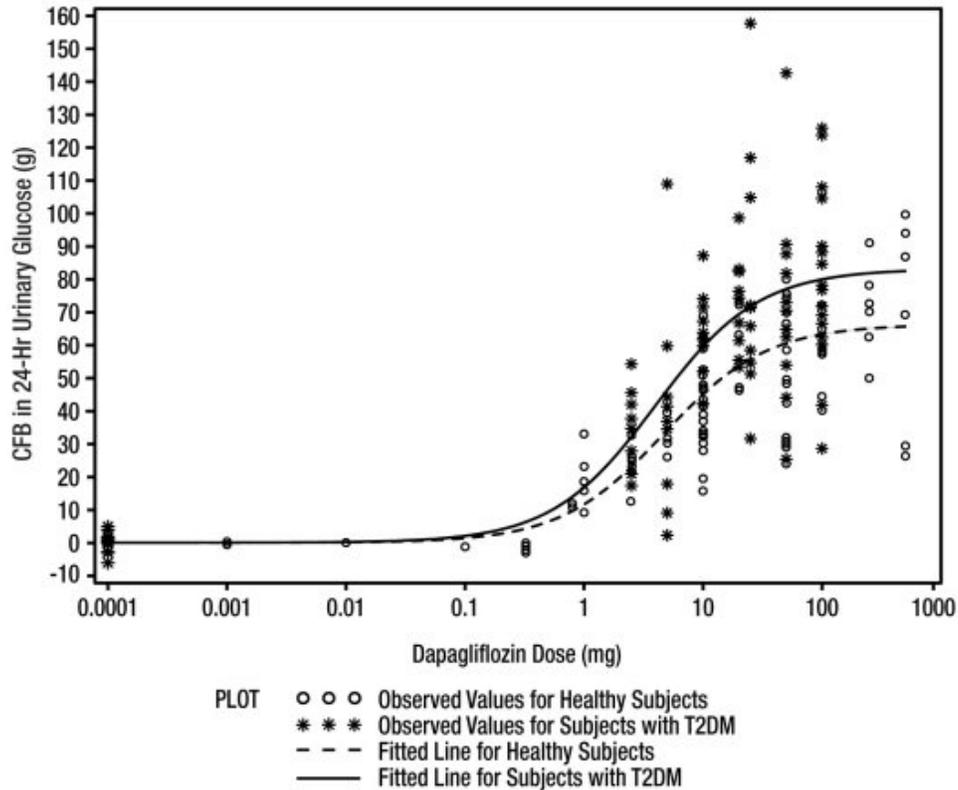
Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin (see Figure 1).

(b) (4)

[Redacted content]

Figure 1: Scatter Plot and Fitted Line of Change from Baseline in 24-Hour Urinary Glucose Amount versus Dapagliflozin Dose in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus (T2DM) (Semi-Log Plot)



Cardiac Electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended dose) dapagliflozin in healthy subjects.

12.3 Pharmacokinetics

XIGDUO XR

XIGDUO XR combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin (FORXIGA®) and metformin hydrochloride extended-release (GLUCOPHAGE® XR) administered together as individual tablets.

The administration of XIGDUO XR in healthy subjects after a standard meal compared to the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin extended-release. Compared to the fasted state, the standard meal resulted in 34.5% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of dapagliflozin. This effect of food is not considered

to be clinically meaningful. Food has no relevant effect on the pharmacokinetics of metformin when administered as XIGDUO XR combination tablets.

Absorption

Dapagliflozin

[REDACTED] (b) (4)

Metformin hydrochloride

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. The extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food. There was no effect of food on C_{max} and T_{max} of metformin.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metformin hydrochloride

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes.

Metabolism

Dapagliflozin

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 [REDACTED] dominant drug-related component in human plasma. [REDACTED] (b) (4)

Metformin hydrochloride

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, [< less than](#) 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. [The mean plasma terminal half-life \(t_{1/2}\) for dapagliflozin is 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects.](#)

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Renal Impairment

XIGDUO XR

Use of metformin in patients with renal impairment increases the risk for lactic acidosis. Because XIGDUO XR contains metformin, XIGDUO XR is contraindicated in patients with moderate to severe renal impairment [see *Contraindications (4)* and *Warnings and Precautions (5.3)*]. No dose adjustment of XIGDUO XR is required in patients with mild renal impairment [see *Use in Specific Populations (8.6)*].

Dapagliflozin

At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher renal glucose clearance or 24-hour glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes and mild, moderate, and severe

renal impairment was 42%, 80%, and 90% lower, respectively, than patients with type 2 diabetes with normal renal function, (b) (4)

(b) (4) t of hemodialysis on dapagliflozin exposure is not known. (b) (4)

Metformin hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Impairment

XIGDUO XR

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Because XIGDUO XR contains metformin, XIGDUO XR should generally be avoided in patients with hepatic impairment [see *Warnings and Precautions (5.4)*].

Dapagliflozin

In patients with mild and moderate hepatic impairment (Child-Pugh Classes A and B), mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose administration of 10 mg dapagliflozin. These differences were not considered to be clinically meaningful, (b) (4)

(b) (4) In patients with severe hepatic impairment (Child-Pugh Class C), mean C_{max} and AUC of dapagliflozin were 40% and 67% higher, respectively, as compared to healthy matched controls. (b) (4)

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Geriatric

Dapagliflozin

Based on a population pharmacokinetic analysis, age does not have a clinically meaningful effect on systemic exposures of dapagliflozin (b) (4) thus no dose adjustment is recommended.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

XIGDUO XR should not be initiated in patients of any age unless measurement of creatinine clearance demonstrates that renal function is only normal or mildly impaired [see *Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.6), and Clinical Studies (14.6)*].

Pediatric

Pharmacokinetics of XIGDUO XR in the pediatric population has not been studied.

Gender

Dapagliflozin

Based on a population pharmacokinetic analysis, gender does not have a clinically meaningful effect on systemic exposures of dapagliflozin (b) (4) thus no dose adjustment is recommended.

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and patients with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Race

Dapagliflozin

Based on a population pharmacokinetic analysis, race (White, Black, or Asian) does not have a clinically meaningful effect on systemic exposures of dapagliflozin and thus no dose adjustment is recommended.

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

Body Weight

Dapagliflozin

Based on a population pharmacokinetic analysis, body weight does not have a clinically meaningful effect on systemic exposures of dapagliflozin (b) (4) thus, no dose adjustment is recommended.

Drug Interactions

Specific pharmacokinetic drug interaction studies with XIGDUO XR have not been performed, although, such studies have been conducted with the individual dapagliflozin and metformin components.

In Vitro Assessment of Drug Interactions

Dapagliflozin

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP 1A2, 2B6, or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

(b) (4)

Effects of Other Drugs on Metformin

Table (b) (4) shows the effect of other coadministered drugs on metformin.

Table (b) (4): Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug (Dose Regimen)*	Metformin (Dose Regimen)*	Metformin	
		Change [†] in AUC [‡]	Change [†] in C _{max}
No dosing adjustments required for the following:			
Glyburide (5 mg)	850 mg	9% [§]	↓7% [§]
Furosemide (40 mg)	850 mg	↑(b) (4) 15% [§]	↑22% [§]
Nifedipine (10 mg)	850 mg	↑(b) (4) 9%	↑(b) (4) 20%
Propranolol (40 mg)	850 mg	↓10%	↓6%
Ibuprofen (400 mg)	850 mg	↑5% [§]	↑7% [§]
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution. [See <i>Warnings and Precautions</i> (5.9) and <i>Drug Interactions</i> (7.1).]			
Cimetidine (400 mg)	850 mg	↑40%	↑(b) (4) 0%

* All metformin and coadministered drugs were given as single doses.

† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

‡ AUC = AUC(INF).

§ Ratio of arithmetic means.

Effects of Metformin on Other Drugs

Table (b) (4) shows the effect of metformin on other coadministered drugs.

Table (b) (4): Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug (Dose Regimen)*	Metformin (Dose Regimen)*	Coadministered Drug	
		Change [†] in AUC [‡]	Change [†] in C _{max}
No dosing adjustments required for the following:			
Glyburide (5 mg)	850 mg	↓22% [§]	↓37% [§]
Furosemide (40 mg)	850 mg	↓12% ^{(b) (4) §}	↓31% [§]
Nifedipine (10 mg)	850 mg	↑10% [¶]	↑8%
Propranolol (40 mg)	850 mg	↑1% [¶]	↑2%
Ibuprofen (400 mg)	850 mg	↓3% [#]	↑1% [#]
Cimetidine (400 mg)	850 mg	↓5% [¶]	↑1%

* All metformin and coadministered drugs were given as single doses.

[†] Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

[‡] AUC = AUC(INF) unless otherwise noted.

[§] Ratio of arithmetic means, p-value of difference <0.05.

[¶] AUC(0-24 hr) reported.

[#] Ratio of arithmetic means.

Effects of Other Drugs on Dapagliflozin

Table (b) (4) shows the effect of coadministered drugs on dapagliflozin [see *Drug Interactions (7)*]. No dose adjustments are recommended for dapagliflozin.

Table (b) (4): Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Dapagliflozin	
		Change [†] in AUC [‡]	Change [†] in C _{max}
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	↓1%	↓7%
Pioglitazone (45 mg)	50 mg	0%	↑9%
Sitagliptin (100 mg)	20 mg	↑8%	↓4%
Glimepiride (4 mg)	20 mg	↓1%	↑1%
Voglibose (0.2 mg three times daily)	10 mg	↑1%	↑4%
Cardiovascular Agents			
Hydrochlorothiazide (25 mg)	50 mg	↑7%	↓1%

Table 5: Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Dapagliflozin	
		Change [†] in AUC [‡]	Change [†] in C _{max}
No dosing adjustments required for the following:			
Bumetanide (1 mg)	10 mg once daily for 7 days	↑5%	↑8%
Valsartan (320 mg)	20 mg	↑2%	↓12%
Simvastatin (40 mg)	20 mg	↓1%	↓2%
Anti-Infective Agent			
Rifampin (600 mg once daily for 6 days)	10 mg	↓22%	(b) (4) ↓7%
Non-Steroidal Anti-Inflammatory Agent			
Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours)	10 mg	↑51%	↑13%

* Single dose unless otherwise noted.

† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

‡ AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

Effects of Dapagliflozin on Other Drugs

Table (b)
(4) shows the effect of dapagliflozin on other coadministered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

**Table (b)
(4): Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs**

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Coadministered Drug	
		Change [†] in AUC [‡]	Change [†] in C _{max}
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	0%	↓5%
Pioglitazone (45 mg)	50 mg	0%	↓7%
Sitagliptin (100 mg)	20 mg	↑1%	↓11%
Glimepiride (4 mg)	20 mg	↑13%	↑4%
Cardiovascular Agents			
Hydrochlorothiazide (25 mg)	50 mg	↓1%	↓5%
Bumetanide (1 mg)	10 mg once daily for 7 days	↑13%	↑13%
Valsartan (320 mg)	20 mg	↑5%	↓6%
Simvastatin (40 mg)	20 mg	↑19%	↓6%

Table 6: Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Coadministered Drug	
		Change [†] in AUC [‡]	Change [†] in C _{max}
No dosing adjustments required for the following:			
Digoxin (0.25 mg)	20 mg loading dose then 10 mg once daily for 7 days	0%	↓1%
Warfarin (25 mg)	20 mg loading dose then 10 mg once daily for 7 days	↑3%	↑7%
<i>S</i> -warfarin		↑6%	↑8%
<i>R</i> -warfarin			

* Single dose unless otherwise noted.

† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

‡ AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

4 APPENDIX

OCP Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205649	Brand Name	XIGDUO XR
OCP Division (I, II, III, IV, V)	II	Generic Name	Dapagliflozin + Metformin XR FDC
Medical Division	DMEP	Drug Class	SGLT-2 inhibitor and biguanide combination product
OCP Reviewer	Suryanarayana Sista, Ph.D.	Indication(s)	Treatment of Type 2 diabetes
OCP Team Leader	Lokesh Jain, Ph.D.	Dosage Form	oral tablet
Pharmacometrics Reviewer		Dosing Regimen	see below*
Date of Submission	10/29/2013	Route of Administration	oral
Estimated Due Date of OCP Review	08/29/2014	Sponsor	Bristol-Myers Squibb / AstraZeneca
Medical Division Due Date		Priority Classification	505 (b)(1) Standard
PDUFA Due Date	10/29/2014		

- * In patients currently not treated with metformin, initiate treatment with 2.5 mg linagliptin/500 mg metformin hydrochloride twice daily
- * In patients already treated with metformin, start with 2.5 mg linagliptin and the current dose of metformin taken at each of the two daily meals (e.g. a patient on metformin 1000 mg twice daily would be started on 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily with meals).
- * Patients already treated with linagliptin and metformin individual components may be switched to Jentadueto containing the same doses of each component

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	7		
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2		022336D, LCMS 153.5
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
<i>in-vivo</i> effects on primary drug:				
<i>in-vivo</i> effects of primary drug:				
<i>in-vitro</i> :				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

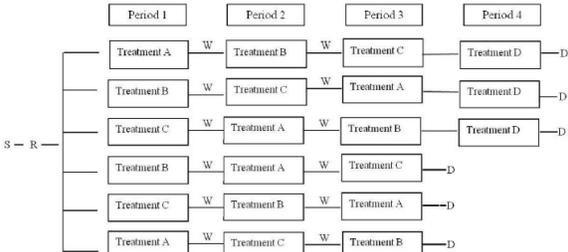
Clinical Pharmacology and Biopharmaceutics Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	3		MB102060, MB102071, MB102065
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		MB102092, MB102100
replicate design; single / multi dose:				
Food-drug interaction studies		2*		MB102092, MB102100
Bio-waiver request based on BCS				Not Applicable
BCS class				Not Applicable
Dissolution study to evaluate alcohol induced dose-dumping	X	1		This study will be evaluated by ONDQA
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			(b) (4), pediatric plan for dapagliflozin cross-referred
Literature References	X	21		
Total Number of Studies		7		

*These studies have been counted earlier under traditional design; single / multi dose

Brief summary about the submission:

Bristol-Myers Squibb and AstraZeneca are seeking US marketing approval for Dapagliflozin+Metformin XR FDC tablets (Proposed Trade Name: Xigduo XR) under the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. The proposed indication of Xigduo XR tablets is "adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate". This NDA is supported by data from five biopharmaceutic studies (3 prototype formulation testings and 2 pivotal fed (light fat meal) bioequivalence/food effect/steady-state PK studies):

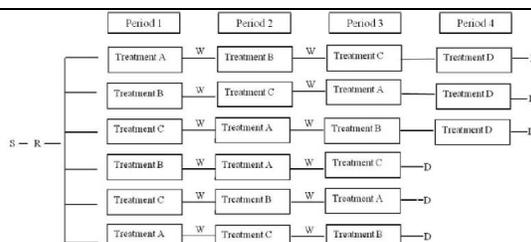
Type of Study / Study Identifier Location of Study Report	Objective(s) of the Study	Study Design
Phase I Relative Bioavailability Study / MB102060 Section 5.3.1.2	<p>Primary: To assess relative bioavailability of one compressed tablet prototype containing reduced-mass metformin XR 1000 mg relative to Glucophage XR 2 x 500 mg tablets when administered to healthy subjects in a fasted condition.</p> <p>Secondary: (a) to assess the effect of food on the compressed tablet prototype containing reduced-mass metformin XR 1000 mg in healthy subjects, and (b) to assess the safety and tolerability of metformin when administered as Glucophage XR 2 x 500 mg tablets and when administered as the compressed tablet prototype containing reduced-mass metformin 1000 mg XR.</p>	<p>Open-label, randomized, 3-period, 3-treatment, unbalanced crossover study in healthy subjects. On Day 1 of Period 1, subjects were randomized to receive oral (PO) doses of the following 3 treatments in 1 of 6 treatment sequences:</p> <ul style="list-style-type: none"> • Treatment A: Single dose of Glucophage XR 2 x 500 mg tablets (fasted) • Treatment B: Single dose of metformin reduced-mass XR 1 x 1000 mg tablet (fasted) • Treatment C: Single dose of metformin reduced-mass XR 1 x 1000 mg tablet (fed)
Phase I Relative Bioavailability Study / MB102071 Section 5.3.1.2	<p>Primary: To assess the relative bioavailability of dapagliflozin and metformin from two FDC formulations comprising 10 mg dapagliflozin and 500 mg metformin XR, relative to coadministration of a dapagliflozin 10 mg tablet and a 500 mg Glucophage XR tablet, in healthy subjects in a fasted state.</p> <p>Secondary: To assess the safety and tolerability of dapagliflozin 10 mg and metformin 500 mg coadministered to healthy subjects in a fasted state.</p>	<p>Open-label, randomized, 3-period, 3-treatment, unbalanced cross-over study in healthy subjects. On Day -1 of Period 1, subjects were randomized to receive 1 of the following 3 treatments in 1 of 6 treatment sequences:</p> <ul style="list-style-type: none"> • Treatment A = FDC tablet of dapagliflozin 10 mg and metformin XR 500 mg (FDC1), fasted • Treatment B = FDC tablet of dapagliflozin 10 mg and reduced mass metformin XR 500 mg (FDC2), fasted • Treatment C = Coadministration of a dapagliflozin 10 mg tablet and a Glucophage XR 500 mg tablet, fasted
Phase I Relative Bioavailability Study / MB102065 Section 5.3.1.2	<p>Primary: The primary objective of this study was to assess the relative bioavailability (BA) of dapagliflozin and metformin from the 2 FDC formulations,</p>	<p>Open-label, randomized, 3-period, 3-treatment, unbalanced cross-over study in healthy subjects. On Day -1 of Period 1, subjects were randomized to receive 1 of the following 3 treatments in 1 of 6 treatment sequences:</p> <ul style="list-style-type: none"> • Treatment A: FDC tablet of dapagliflozin 10 mg

	<p>comprised of 10 mg dapagliflozin and 1000 mg metformin XR, relative to coadministration of a dapagliflozin 10 mg tablet and 2 x 500 mg Glucophage XR tablets, in healthy subjects in a fasted state.</p> <p>Secondary: The secondary objective of this study was to assess the safety and tolerability of dapagliflozin 10 mg and metformin 1000 mg coadministered to healthy subjects in a fasted state.</p>	<p>and metformin XR 1000 mg (FDC1), fasted</p> <ul style="list-style-type: none"> • Treatment B: FDC tablet of dapagliflozin 10 mg and RM metformin XR 1000 mg (FDC2), fasted • Treatment C: Coadministration of dapagliflozin 10 mg tablet and Glucophage XR 2 x 500 mg tablets, fasted
<p>Phase I Fed-state Bioequivalence Study / MB102092 Section 5.3.1.2</p>	<p>Primary: To demonstrate the bioequivalence of dapagliflozin and metformin administered as the 10-mg dapagliflozin/1000-mg extended-release (XR) metformin fixed-dose combination tablet and a 10-mg dapagliflozin tablet coadministered with two 500-mg Glucophage XR tablets to healthy subjects in the fed state.</p> <p>Secondary: (a) to characterize the single-dose and steady-state PK of dapagliflozin and metformin following administration of the 10/1000 XR FDC tablet to healthy subjects in the fed state, (b) to assess the effect of a meal (light-fat) on the single-dose PK of dapagliflozin and metformin administered in the 10/1000 XR FDC tablet in healthy subjects, and (c) to assess, in healthy subjects, the safety and tolerability of the individual component tablets administered in the fed state, and that of single doses (administered in the fed and fasted states) and multiple doses (administered in the fed state) of the 10/1000 XR FDC tablet</p>	<p>Open-label, randomized, 4-period, 4-treatment, crossover study in healthy fasted and fed subjects.</p>  <p>S = Screening — up to 21 days R = Randomization D = Discharge W = Washout period of at least 4 days after dosing in the previous period. Subjects in Period 4 were dosed approximately 48.5 hours after dosing in Period 3</p> <ul style="list-style-type: none"> • Treatment A: A single oral dose of IC tablets (one 10-mg dapagliflozin tablet and two 500-mg metformin XR tablets) administered in the fed state (bioequivalence reference treatment). • Treatment B: A single oral dose of the 10/1000 XR FDC tablet administered in the fed state (bioequivalence test treatment). • Treatment C: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state (food-effect assessment). • Treatment D: Once-daily oral doses of the 10/1000 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment).
<p>Phase I Fed-state Bioequivalence Study</p>	<p>Primary: To demonstrate the bioequivalence of dapagliflozin and metformin</p>	<p>Open-label, randomized, 4-period, 4-treatment, crossover study in healthy fasted and fed subjects.</p>

/ MB102100
Section 5.3.1.2

administered as a 5-mg dapagliflozin/500-mg extended-release (XR) metformin FDC tablet and a 5-mg dapagliflozin tablet coadministered with one 500-mg Glucophage XR tablet to healthy subjects in the fed state.

Secondary: (a) to characterize the single-dose and steady-state PK of dapagliflozin and metformin following administration of the 5/500 XR FDC tablet to healthy subjects in the fed state., (b) to assess the effect of a meal (light-fat) on the single-dose PK of dapagliflozin and metformin administered in the 5/500 XR FDC tablet in healthy subjects, and (c) to assess, in healthy subjects, the safety and tolerability of the individual component tablets administered in the fed state, and that of single doses (administered in the fed and fasted states) and multiple doses (administered in the fed state) of the 5/500 XR FDC tablet.



S = screening — up to 21 days; R = randomization; D = discharge; W = washout

- Treatment A: A single oral dose of IC tablets (one 5-mg dapagliflozin tablet and one 500-mg metformin XR tablet) administered in the fed state (bioequivalence reference treatment).
- Treatment B: A single oral dose of the 5/500 XR FDC tablet administered in the fed state (bioequivalence test treatment).
- Treatment C: A single oral dose of the 5/500 XR FDC tablet administered in the fasted state (food-effect assessment).
- Treatment D: Once-daily oral doses of the 5/500 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment).

NDA 20-5649 [505 (b)(1)] Dapagliflozin/ Metformin XR FDC Bristol-Myers Squibb

Clinical Pharmacology Review Team:

Sury Sista
Lokesh Jain (TL)

Overview: FDC Formulation

- Dapagliflozin/metformin XR FDC tablets are (b) (4) a (b) (4) tablet configuration (b) (4) dapagliflozin and metformin (b) (4). The dapagliflozin (b) (4) formulated for immediate release, whereas the metformin (b) (4) formulated to provide extended release.

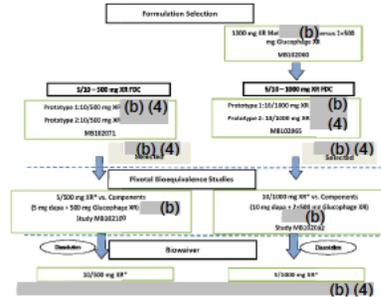


(b) (4)

Overview: Clinical Pharmacology Program

- Clinical Pharmacology program:** 5 Phase 1 studies; (12 Phase 3 studies were submitted earlier to the dapagliflozin NDA 20-2293)
 - Relative Bioavailability studies (n = 3)
 - Bioequivalence Studies (n = 2)

Figure 1: Links between Pilot (Relative Bioavailability), Bioequivalence Studies, In Vitro Dissolution Studies and the To-Be-Marketed Dapagliflozin/Metformin XR FDC Tablets



Sponsor's Product Development Rationale

- The need for multiple daily antidiabetic medications to achieve and sustain adequate glycosylated hemoglobin A1c (HbA_{1c}) control often leads to poor adherence.
- A new therapeutic combination of dapagliflozin and metformin, available as one tablet, would provide an important treatment option for patients with T2DM, and could improve patient compliance.
- Dapagliflozin is a competitive, reversible, orally active inhibitor of sodium glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption.
- Metformin, a biguanide, is a well-characterized medicine that has been in widespread use for decades. It is the first line agent of choice for T2DM.
- Dapagliflozin's mechanism of action (MOA) is different from, and complementary to, the mechanisms of action of Metformin, resulting in the direct and insulin-independent elimination of glucose by the kidney.
- The two drugs with complementary MOAs, and with clinically important effects on HbA_{1c}, FPG, PPG and weight loss are expected to maintain glycemic control in patients who have difficulty with maintaining glycemic control on metformin alone, or in combination with other oral antidiabetic drugs or insulin.
- The sponsors have developed dapagliflozin/metformin XR FDC tablets with the following dose strengths: (i) 5 mg dapagliflozin/500 mg metformin XR, (ii) 5 mg dapagliflozin/1000 mg metformin XR, (iii) 10 mg dapagliflozin/500 mg metformin XR, (iv) and 10 mg dapagliflozin/1000 mg metformin XR.

Sponsor's Product Development Rationale

Available Combinations Matrix:

Approved Daily Doses of Individual Components of Dapagliflozin and Metformin IR and XR*		Suggested Dapagliflozin/Metformin XR FDC Dosing
Dapagliflozin	Metformin IR or XR	
5 mg	500 mg	5/500 FDC
	750 mg	5/500 FDC or 5/1000 FDC**
	850 mg	5/500 FDC or 5/1000 FDC**
	1000 mg	5/1000 FDC
	1500 mg	5/1000 FDC + Met XR 500
	1700 mg (2 tabs of 850 mg)	5/1000 FDC + Met XR 500 or 5/1000 FDC + 2 tabs of Met XR 500**
10 mg	500 mg	10/500 FDC
	750 mg	10/500 FDC or 10/1000 FDC**
	850 mg	10/500 FDC or 10/1000 FDC**
	1000 mg	10/1000 FDC
	1500 mg	10/1000 FDC + Met XR 500
	1700 mg (2 tabs of 850 mg)	10/1000 FDC + Met XR 500 or 2 tabs of 5/1000 FDC**
	2000 mg	2 tabs of 5/1000 FDC

*Available doses for metformin IR are: 500 mg, 850 mg, or 1000 mg.
Available doses for metformin XR are: 500 mg or 750 mg
**Depending on desired glycemic goal

5

Overview: Bioequivalence

Pivotal BE Study MB102092

Protocol	Study Description	Treatments	Number of Subjects	Bioequivalence Criteria Met? (Treatment B/A)			
				Dapagliflozin		Metformin	
				C _{max}	AUC	C _{max}	AUC
MB102092	Bioequivalence Study of a Fixed-Dose Combination Tablet of 10-mg Dapagliflozin/1000-mg Metformin XR Relative to a Single 10-mg Dapagliflozin Tablet and Two 500-mg GLUCOPHAGE XR Tablets Coadministered to Healthy Subjects in the Fed and Fasted States and Steady-State Pharmacokinetic Assessment of the Fixed-Dose Combination of 10-mg Dapagliflozin/1000-mg Metformin XR.	4 period x 4 treatment Treatment A: A single oral dose of 10-mg Dapagliflozin/1000-mg Metformin XR (one 10-mg dapagliflozin tablet and two 500-mg metformin XR tablets) administered in the fed state (bioequivalence reference treatment) Treatment B: A single oral dose of the 10/1000 XR FDC tablet administered in the fed state (bioequivalence test treatment) Treatment C: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state (food-effect assessment) Treatment D: Once-daily oral doses of the 10/1000 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment)	36 (fasting)	Yes	Yes	Yes	Yes
			Number of Subjects	Food Effect [Treatment B/C] FE (50%CI) are provided if comparability criteria not met			
				Dapagliflozin		Metformin	
				C _{max}	AUC	C _{max}	AUC
			36	0.656 (0.605, 0.711)	Yes	Yes	Yes

6

Overview: Bioequivalence

Pivotal BE Study MB102100

Protocol	Study Description	Treatments	Number of Subjects	Bioequivalence Criteria Met? (Treatment B/A)			
				Dapagliflozin		Metformin	
				C _{max}	AUC	C _{max}	AUC
MB102100	Bioequivalence Study of a Fixed-Dose Combination Tablet of 5-mg Dapagliflozin/500-mg Metformin XR Relative to a Single 5-mg Dapagliflozin Tablet and a Single 500-mg GLUCOPHAGE XR Tablet Coadministered to Healthy Subjects in the Fed and Fasted States and Steady-State Pharmacokinetic Assessment of the Fixed-Dose Combination of 5-mg Dapagliflozin/500-mg Metformin XR.	4 period x 4 treatment: Treatment A: A single oral dose of 10 tablets (one 5-mg dapagliflozin tablet and a 500-mg metformin XR tablet) administered in the fed state (bioequivalence reference treatment) Treatment B: A single oral dose of the 5/500 XR FDC tablet administered in the fed state (bioequivalence test treatment) Treatment C: A single oral dose of the 5/500 XR FDC tablet administered in the fasted state (food-effect assessment) Treatment D: Once-daily oral doses of the 5/500 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment)	36 (fasting)	Yes	Yes	Yes	Yes
			Number of Subjects	Food Effect [Treatment B/C] FE (90%CI) provided if comparability criteria not met			
				Dapagliflozin		Metformin	
				C _{max}	AUC	C _{max}	AUC
			36	0.859 (0.614, 0.796)	Yes	Yes	Yes

Compared to the fasted state, a light-fat meal decreased the C_{max} of dapagliflozin by 35% when administered as the FDC tablet and did not have an effect on AUC₀₋₄ and AUC_∞ of dapagliflozin in the FDC. As the daily amount of glucose excreted in the urine is dependent upon dapagliflozin AUC and not the peak concentration, changes in dapagliflozin C_{max} is not expected to influence dapagliflozin's safety, tolerability and efficacy hence dapagliflozin may be taken without regard to meals.

7

Pediatric Plan

Sponsor Request

- The sponsors are currently evaluating the PK/PD of dapagliflozin in pediatric patients aged 10 to 17 years old with T2DM (Study MB102091).

(b) (4)

(b) (4)

Key Questions: Mid Cycle Deliverables

- Was bioequivalence between the individual components and the FDC established?

Conclusions

- This NDA is filable from OCP perspective
- OSI inspection will be requested for the pivotal BE studies

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Data in original NDA for dapagliflozin (20-2293)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	Data in original NDA for dapagliflozin (20-2293)
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	Rationale for dapagliflozin in NDA 20-2293. Rationale for available FDC strengths submitted with current application.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	Data in original dapagliflozin NDA (20-2293).
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	Data in original dapagliflozin NDA (20-2293).
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	Data in original dapagliflozin NDA (20-2293).
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	Data in original dapagliflozin NDA (20-2293).
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comment to Sponsor:
None

Suryanarayana M. Sista	09 Dec, 2013
Reviewing Clinical Pharmacologist	Date
Lokesh Jain	09 Dec, 2013
Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURYNARAYANA M SISTA
07/14/2014

LOKESH JAIN
07/14/2014

ONDQA BIOPHARMACEUTICS REVIEW

NDA#: 205649/N000
Submission Date: 10/30/13 and 01/24/14
Related IND: 108690
Brand Name: TBD
Generic Name: Dapagliflozin (Dapa)+Metformin HCl (Met)
Formulation: FDC (Fixed dose combination) of Dapa IR (Immediate release) and Met XR (Extended release) bilayer oral tablets
Strength: Dapa 5 mg/Met500 mg, Dapa10 mg/Met500 mg, Dapa5 mg/Met1000 mg, and Dapa10 mg/Met1000 mg (four strengths)
Applicant: BMS (Bristol-Meyers-Squibb)
Type of submission: 505(b)(1); original (N000)
Reviewer: Tien-Mien Chen, Ph.D.

SYNOPSIS

Background

Dapa is being developed by BMS and Astra-Zeneca (AZ) as a therapeutic agent for treatment of type 2 diabetes mellitus (T2DM) under IND 68,652. AstraZeneca's NDA 202293 for Farxiga (Dapa IR tablets 5 mg and 10 mg) as a single component NME (new molecular entity) was submitted to the FDA for review on 12/29/10, and approved on 01/08/14. Dapa is reported as a highly selective active inhibitor of the human renal sodium glucose co-transporter (SGLT-2), the major transporter responsible for renal reabsorption of glucose, thereby promoting its urinary excretion.

Met HCl is a biguanide antidiabetic agent that is a compendial drug. Met XR tablets are currently approved in the United States for the treatment of T2DM including BMS branded Glucophage XR, 500 mg and 750 mg tablets (NDA 21202).

Current Submission

On 10/30/13, BMS submitted NDA 205649 for film-coated Dapa/Met XR FDC (b) (4) oral tablets (four strengths), 5 mg/500 mg (Dapa5/Met500 XR), 10 mg/500 mg (Dapa10/Met500 XR), 5 mg/1000 mg (Dapa5/Met1000 XR) and 10 mg/1000 mg (Dapa10/Met1000 XR). The proposed formulations of the four strengths (b) (4) . On 01/24/14, the Applicant responded to the Agency's information request dated 01/14/14.

NDA 205649 reportedly included 12 Phase 3 studies that support the efficacy and safety for the Dapa/Met XR FDC tablets. Five biopharmaceutics studies contributed three BA (relative bioavailability) and two BE (bioequivalence) studies. The two pivotal BE studies were conducted to link the commercial TBM (to-be-marketed) formulations with

individual components for the highest and the lowest strengths, i.e., Dapa10/Met1000 XR tablets (Study No. MB102092) and Dapa5/Met500 XR tablets (Study No. MB102100). The above pivotal BE studies were similarly designed as 4x4 studies to assess the food effect and the steady-state PK (pharmacokinetics) as well. The above 5 bioavailability studies are currently under review by the Office Clinical Pharmacology (OCP).

Also, submitted to the NDA were 1). Dissolution method development report, 2). Proposed dissolution method and acceptance criteria, and 3). The *in vitro* alcohol dose-dumping study results. A Biowaiver request was also submitted for the two middle strengths, Dapa10/Met500 XR and Dapa5/Met1000 XR tablets, which have not been tested clinically. Supporting comparative dissolution profile data were submitted for the two middle strengths compared with both the highest and the lowest strengths. The *in vitro* study results and the biowaiver request are reviewed here by the Biopharmaceutics/ONDQA.

Biopharmaceutics Review

The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution method development report, proposed dissolution method and acceptance criteria, *in vitro* alcohol dose-dumping study, and the comparative dissolution profile data to support the biowaiver for the two middle strengths.

Reviewer's Comments:

The Applicant's proposed dissolution method and its acceptance criteria are reviewed and found acceptable as shown below (in Comment Section) for implementation on stability and release testing.

The *in vitro* alcohol dose-dumping study demonstrated that there is no alcohol dose-dumping potential, therefore, no *in vivo* alcohol dose-dumping human PK study is needed. Finally, the biowaiver with supporting comparative dissolution profile data for the two middle strengths, Dapa10/Met500 XR and Dapa5/Met1000 XR tablets, which had not been tested clinically, is reviewed and found acceptable. Therefore, the biowaiver request is granted!

RECOMMENDATION

From the Biopharmaceutics perspective, this NDA is recommended for approval.

COMMENT (Needs to be conveyed to the Applicant):

Your proposed dissolution method and its acceptance criteria as shown below are reviewed and accepted for implementation on the stability and release testing upon approval.

USP Apparatus: 1 (Basket, 20 mesh) with 100 rpm
Medium: pH 6.8 Phosphate buffer, 1000 mL at 37°C
Acceptance
Criteria: For Dapa: Q= (b) (4) % at 30 min
For Met: 1 hr: (b) (4) %
3 hrs: %
10 hrs: (b) (4) %

Tien-Mien Chen, Ph.D.
ONDQA Biopharmaceutics Reviewer

06/27/14

Date

Tapash Ghosh, Ph.D.
ONDQA Biopharmaceutics Team Leader

07/02/14

Date

CC: DARRTS/NDA No.205649/N000\RLostritto

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Dapa is reported as a highly selective active inhibitor of the human renal sodium glucose co-transporter (SGLT-2), the major transporter responsible for renal reabsorption of glucose, thereby promoting its urinary excretion. Dapa is being developed by BMS and Astra-Zeneca (AZ) as a therapeutic agent for treatment of type 2 diabetes mellitus (T2DM) under IND 68,652. AstraZeneca's NDA 202293 for Farxiga (Dapa IR tablets 5 mg and 10 mg) as a single component NME (new molecular entity) was submitted to the FDA for review on 12/29/10, and was approved on 01/08/14.

Met HCl is a biguanide antidiabetic agent that is a compendial drug. Met HCl, which is supplied (b) (4)

Met XR tablets are currently approved in the United States for the treatment of T2DM including BMS branded Glucophage XR, 500 mg and 750 mg tablets (NDA 21202).

CURRENT SUBMISSION

On 10/30/13, BMS submitted NDA 205649 for Dapa/Met XR FDC oral tablets (four strengths). On 01/24/14, the Applicant responded to the Agency's information request dated 01/14/14.

Dapa DS (drug substance) is manufactured at the BMS facility in Swords, Ireland. Its DS documentation (b) (4) is to be referred to the Dapa DS details in the NDA 202293. For this NDA 205649, BMS and AZ are seeking marketing approval for the FDC of Dapa/Met XR tablets administered once daily [QD] to improve glycemic control in patients with T2DM.

The Dapa/Met film-coated XR FDC (b) (4) tablets (Dapa/Met XR) contain Dapa and Met HCl in strengths of 5 mg/500 mg (Dapa5/Met500 XR), 10 mg/500 mg (Dapa10/Met500 XR), 5 mg/1000 mg (Dapa5/Met1000 XR) and 10 mg/1000 mg (Dapa 10/Met1000 XR) and will be manufactured at the BMS facility at Humacao, Puerto Rico and packaged in high-density polyethylene (HDPE) bottles and aluminum/aluminum (Alu/Alu) blisters (b) (4)

The proposed formulations of the four strengths (b) (4)

NDA 205649 reportedly included 12 Phase 3 studies that support the efficacy and safety for the Dapa/Met XR FDC tablets. In addition, five biopharmaceutics studies contributed three BA and two BE data for the Dapa/Met XR FDC tablets. The two pivotal BE studies were conducted to link the commercial TBM formulations with individual components for the highest and the lowest strengths, i.e., Dapa10/Met1000 XR (Study No. MB102092) and Dapa5/Met500 XR (Study No. MB102100). The above pivotal BE studies were similarly designed as 4x4 studies to assess the food effect and the steady-state PK as well. The above 5 bioavailability studies are currently under review by the Office Clinical Pharmacology (OCP).

Also, submitted to the NDA were 1). Dissolution method development report, 2). Proposed dissolution method and acceptance criteria, and 3). The *in vitro* alcohol dose-dumping study results. A biowaiver request with supporting comparative dissolution profile data was submitted for the two middle strengths, Dapa10/Met500 XR and Dapa5/Met1000 XR tablets when compared with both the highest and the lowest strengths. The *in vitro* study results and the biowaiver request are reviewed here by the Biopharmaceutics/ONDQA.

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution method development report, proposed dissolution method and acceptance criteria, *in vitro* alcohol dose-dumping study, and the comparative dissolution profile data to support the biowaiver for the two middle strengths.

FORMULATION COMPARISONS

Figure 1. The Scheme of the Dapa/Met XR (b) (4) Tablets



The composition and formulations of the final TBM of Dapa/Met XR FDC tablets are shown below. The four strengths (b) (4)

(b) (4)

Table 1. Composition and Formulation of the Final TBM of Dapa/Met XR FDC Tablets

Dapa/Met XR Strength (mg/mg):		5/500 (BE)	10/500 (Biowaiver)	5/1000 (Biowaiver)	10/1000 (BE)
Component ^a	Function	Quantity per Tablet (mg)			
(b) (4)		(b) (4)			
Metformin HCl	Active				
(b) (4)					
Carboxymethylcellulose Sodium	(b) (4)				
(b) (4)					
Hypromellose 2208					
Hypromellose 2910					
MCC (b) (4)					
Silicon Dioxide					
Magnesium Stearate					
(b) (4)					
(b) (4)					
Dapagliflozin Propanediol ^d	Active				
(b) (4)	(b) (4)				
Lactose Anhydrous					
Crospovidone					
(b) (4)					
(b) (4)	(b) (4)				
(b) (4)	(b) (4)				
Total Tablet Weight		1367.07	1367.07	1645.13	1645.13

(b) (4)
MCC = microcrystalline cellulose

^a The quality standard requirements for the components are the same as provided in Section 3.2.P.1, *Description and Composition of the Drug Product*.

^b (b) (4) metformin hydrochloride, USP, (b) (4)

- (b) (4)
- u Dapagliflozin propanediol is (b) (4) containing 1:1:1 ratio of the active moiety (dapagliflozin), (s)-(+)-1,2-propanediol, and water. (b) (4)
- f Microcrystalline cellulose (b) (4)
- g The target amount of total magnesium stearate is (b) (4)
- h (b) (4)
- i The (b) (4) color coating materials listed below were used as supplied by (b) (4). Compositional information for the coating materials is provided in Section 3.2.P.1, *Description and Composition of the Drug Product*.
- Orange (b) (4) (Dapa 5/Met XR 500)
- Pink (b) (4) (Dapa 10/Met XR 500)
- Pink (b) (4) (Dapa 5/Met XR 1000)
- Yellow (b) (4) (Dapa 10/Met XR 1000)

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERIA

The proposed dissolution method and the dissolution acceptance criteria for Dapa/Met XR FDC Tablets are shown below.

USP Apparatus:	1 (Basket, 20 mesh) with 100 rpm
Medium:	pH 6.8 Phosphate buffer, 1000 mL at 37°C
Acceptance Criteria:	For Dapa: Q= (b) (4) % at 30 min For Met: 1 hr: (b) (4) % 3 hrs: (b) (4) % 10 hrs: (b) (4) %

Dissolution Method Development Report:

Dapa is reported as a BCS class III DS and its solubility is around 2.1-2.2 mg/mL at various pH media (pHs 1.0, 4.5, and 6.8). Dapa is a non-ionizable compound; thus, its aqueous solubility and partition coefficient are not affected by changes in pH as shown below.

Figure 2. Mean Dissolution Profiles of Dapa (Dapa5/Met500 XR Tablets) in Three Dissolution Media (Biobatch No. 1L633771)

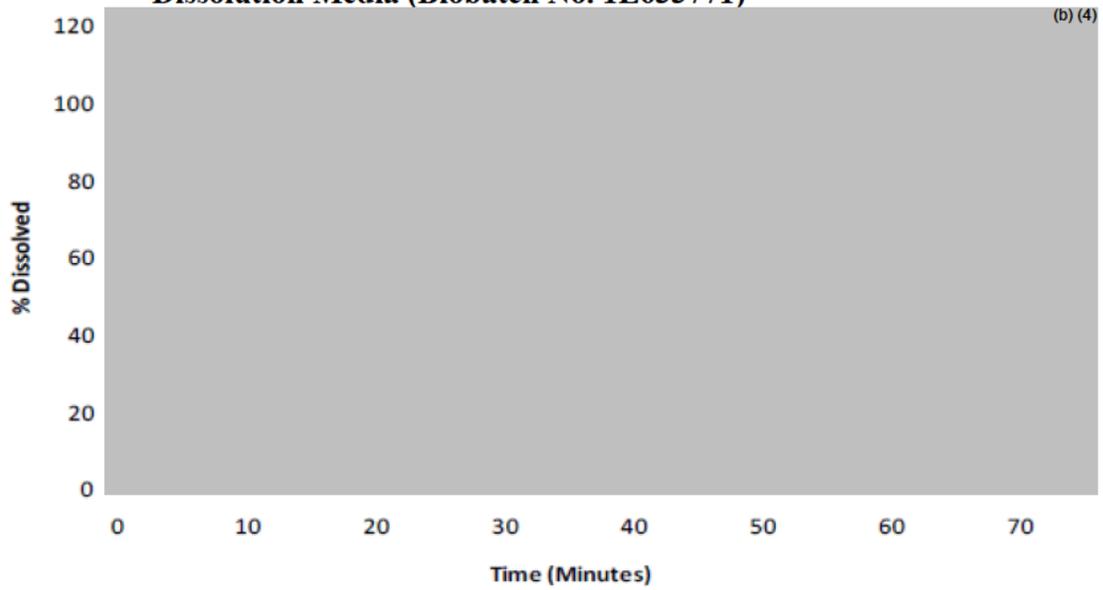


Figure 3. Mean Dissolution Profiles of Dapa (Dapa10/Met1000 XR Tablets) in Three Dissolution Media (Biobatch No. 1L633770)

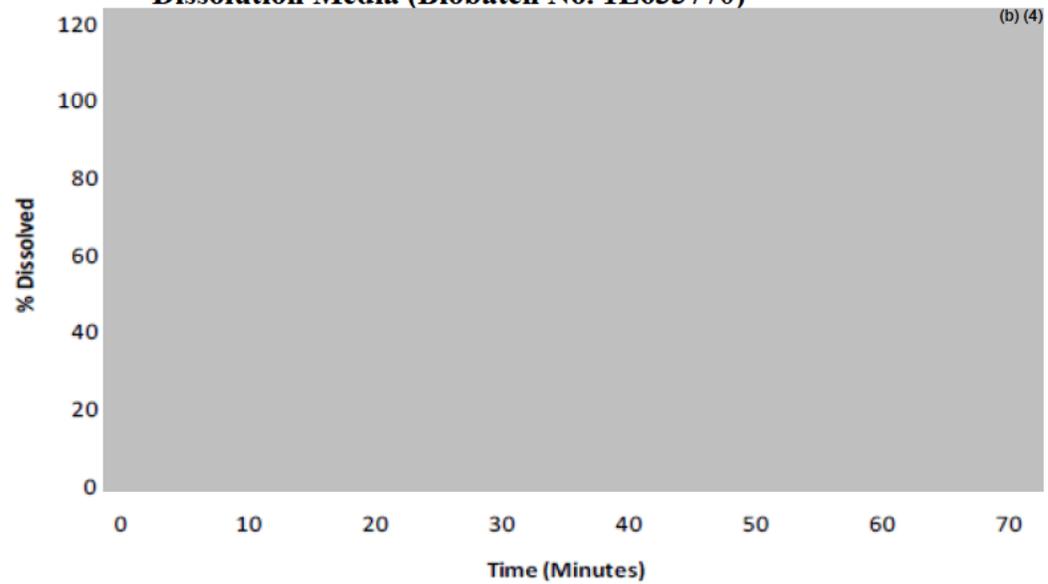
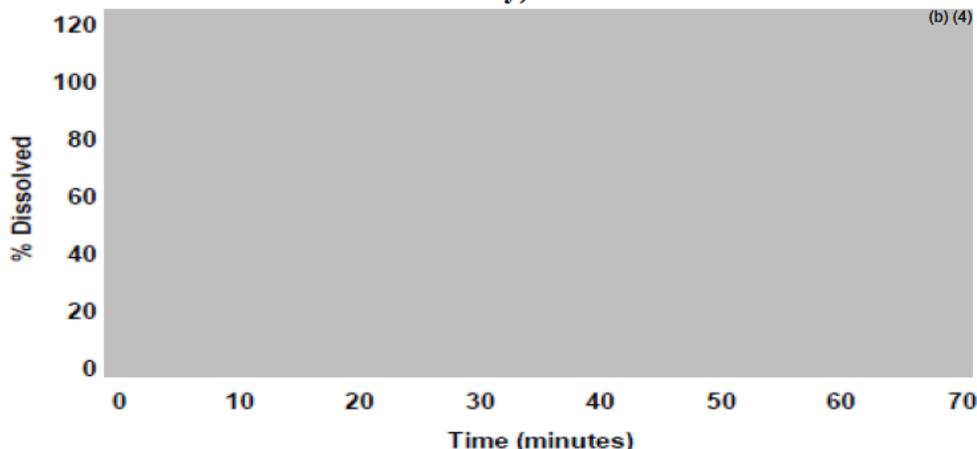


Figure 4. Dapa Dissolution Profile Comparison of Dapa 10 mg Single Entity LTSS Tablet (Batch No. 77571-010) and Dapa10/Met1000 XR Tablet (Biobatch No. 9K53082 for a BA study)



As expected, not only for similar dissolution profiles in different pH media, the dissolution of Dapa is not affected by the method, e.g., paddle vs. basket, or mesh 40 vs. mesh 20 tested). Therefore, the dissolution method development was focused mainly on the Met XR ^{(b) (4)}. The report is summarized below:

- A single method for dissolution of Dapa and Met was explored and developed for late phase and registration stability use.
- A dissolution method similar to the compendial Met XR products (currently approved Glucophage XR 500 and 750 mg) methodology was achieved.
- UPS Apparatus I (basket) with 100 rpm and II (paddle) with 75 rpm were tested.
- Media of pH 4.5 and 6 were tested.
- Basket with 40 mesh and 20 mesh were tested.
- The proposed dissolution method was test for discriminating power using the Met1000 ^{(b) (4)}

[Redacted text block]

1. USP Apparatus Selection:

The currently FDA approved dissolution methods for the Glucophage XR 500 and 750 mg tablets are shown below.

Table 2. Dissolution Methods for the Currently Approved Glucophage XR Tablets

Tablets	USP Apparatus	Spindle Rotation Speed	Media Volume	Temp	Medium
500 mg Glucophage [®] XR	Paddles (Apparatus II)	100 rpm	1000 mL	37°C	pH 6.8 Phosphate Buffer
750 mg Glucophage [®] XR	Baskets (Apparatus I)	100 rpm	1000 mL	37°C	pH 6.8 Phosphate Buffer

Glucophage XR 500 tablets were tested using both methods and results demonstrated similarity between the above two methods. A single dissolution method was thus explored for Met XR.

The following methods tested for Dapa/Met XR tablets are shown below.

Table 3. Dissolution Method (with Different pHs) Tested

Drug Substance	Dapa 10/Met XR 1000	Dapa 10/Met XR 500
Dapagliflozin	USP Apparatus I (Basket, 40-mesh), 100 rpm pH 6.8 Phosphate Buffer	USP Apparatus II (Paddle), 75 rpm pH 4.5 Acetate Buffer
Metformin XR	(used for both dapagliflozin and metformin)	USP Apparatus I (Basket, 40-mesh), 100 rpm pH 6.8 Phosphate Buffer

Note: USP Apparatus II (paddle) with 75 rpm in pH 4.5 Acetate Buffer is the currently FDA approved dissolution for Dapa.

Similar dissolution results were further demonstrated for Met XR as compared to Glucophage XR 500 and 750 mg tablets:

Table 4. Dissolution Results Obtained

(b) (4)

The basket (USP Apparatus 1) with 100 rpm was, however, selected for development of dissolution conditions for Met for the following reasons:

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4. Dissolution Acceptance Criteria:

The Applicant proposed the following dissolution acceptance criteria.

Acceptance

Criteria:

For Dapa: Q= (b) (4) % at 30 min

For Met: 1 hr: (b) (4) %

3 hrs: (b) (4) %

10 hrs: (b) (4) %

- a. For Dapa: Since Dapa is reported as a BCS Class III DS demonstrating (b) (4) % dissolved in 30 min, Q= (b) (4) % at 30 min was proposed and found acceptable.
- b. For Met: Since the dissolution method development used Glucophage XR's method as a starting point, the same dissolution acceptance criteria are similarly proposed for this combo tablets. The mean dissolution profile and mean % of Met XR dissolved obtained from both the biobatches (Nos. 1L63770 and 1L63771) employed in the pivotal BE studies and the two middle strengths, Dapa10/Met500 XR (batch No. 1H59771) and Dapa5/Met1000 XR (batch No. 1H59770) confirm the proposed dissolution acceptance criteria. Please see mean comparative dissolution data of Dapa and Met XR in Appendix for details.

Therefore, the above proposed dissolution acceptance criteria for Dapa and Met XR are reviewed and found acceptable.

Reviewer's Comment:

The Applicant's dissolution method development report and the proposed dissolution method and its acceptance criteria are reviewed and found acceptable.

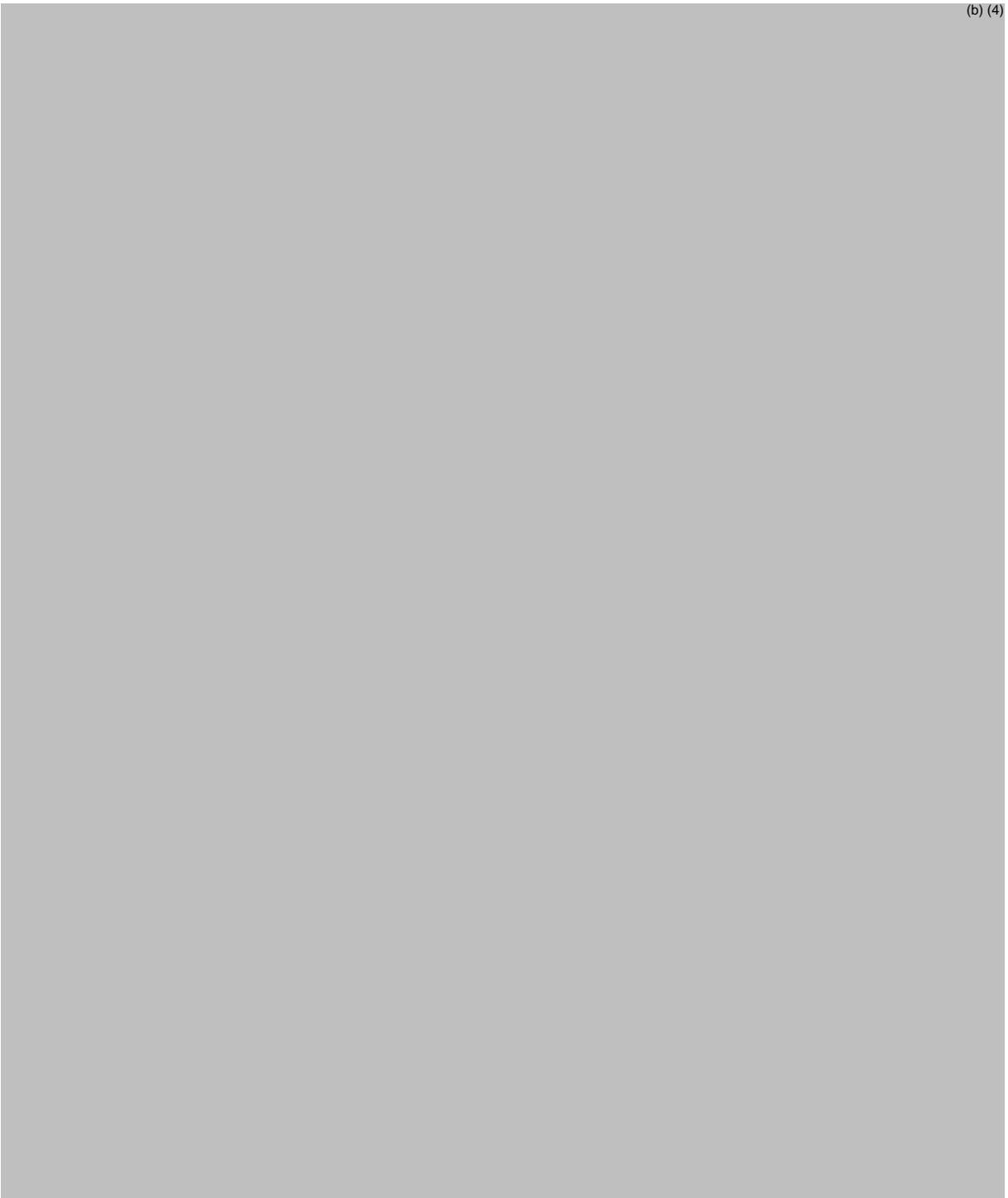
Biowaiver Request:

Two middle strengths, Dapa5/Met1000 XR and Dapa10/Met500 XR tablets had not been tested clinically. A biowaiver request with supporting comparative dissolution profile data was submitted and reviewed here. The Applicant responded on 01/24/14 to Agency's information request dated 01/14/14 regarding the rearrangement and reanalysis on the comparative dissolution profile data.

Both Dapa5/Met500 XR (The Lowest Strength; Batch No. 1L63771) and Dapa10/Met1000 XR (The Highest Strength; Batch No. 1L63770) were the biobatches employed in the pivotal BE studies (Nos. MB102100 and MB102092, respectively). The results are shown below.

- A. Dapa10/Met500 mg XR Tablet Compared with Dapa5/Met500 mg XR Tablet (Red curve) and Dapa10/Met1000 mg XR Tablet (Blue curve).

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Note: Dapa is reported as a BCS class III DS which dissolved (b) (4)% in (b) (4) min. The biowaiver request and the comparative dissolution profile data of two middle strengths compared with the lowest and the highest strengths are reviewed, however, the mean comparative dissolution profiles for Dapa are not presented here (in Appendix instead). Please also see Applicant's response dated 01/24/14 for details.

Reviewer's Comments:

The similarity factor (f2) values calculated are all >50 indicating the similarity of the two middle strengths to the highest and the lowest strengths in three dissolution media tested. Therefore, the biowaiver request for these two middle strengths is granted.

In Vitro Alcohol Dose-Dumping Study:

The results of *in vitro* alcohol dose dumping study were submitted:

- Both the highest and the lowest strengths were employed.
- The alcohol of 0, 5, 10, and 25% were tested and
- The proposed dissolution method was used.

Table 9. Dapa/Met XR FDC Tablets (Batch Nos.) and Alcohol Concentrations Employed

Test Article	Batch Number	Control (0% Ethanol)	5% Ethanol	10% Ethanol	25% Ethanol
Dapa 5/Met XR 500	89114-103-1	X	X	X	X
Dapa 10/Met XR 1000	89114-107	X	X	X	X

The results are summarized below.

Figure 12. Mean *In Vitro* Dissolution Profiles of Metformin from Dapa5/Met500 XR Tablets (The Lowest) at 0%, 5%, 10%, and 25% (v/v) Ethanol (n = 6 tab. per Ethanol Conc.)

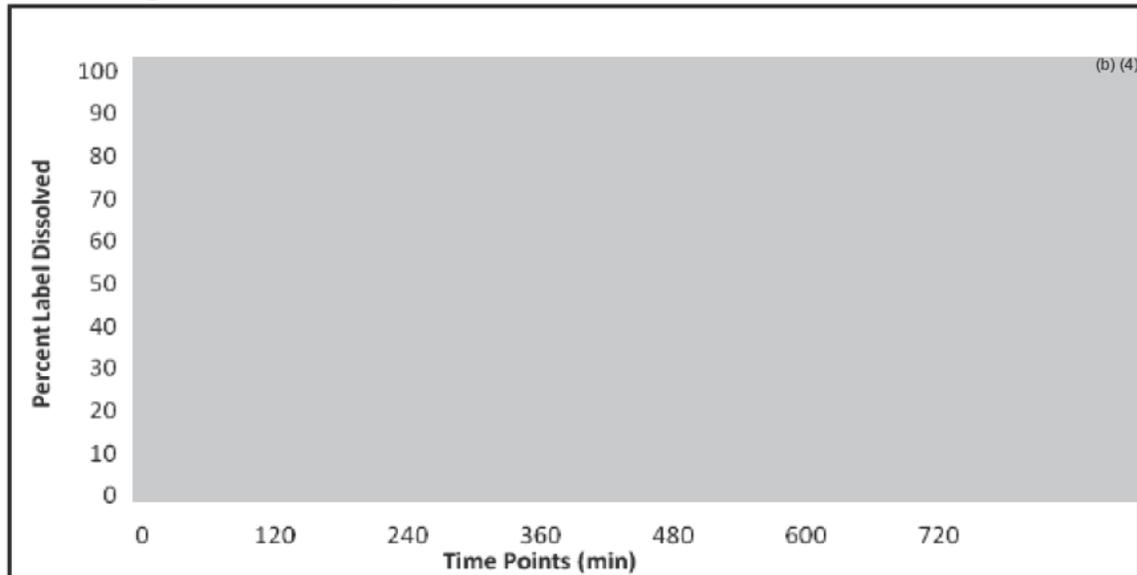


Figure 13. Mean *In Vitro* Dissolution Profiles of Metformin from Dapa10/Met1000 XR Tablets (The Highest) at 0, 5, 10, and 25% (v/v) Ethanol (n = 6 tab. per Ethanol Conc.)

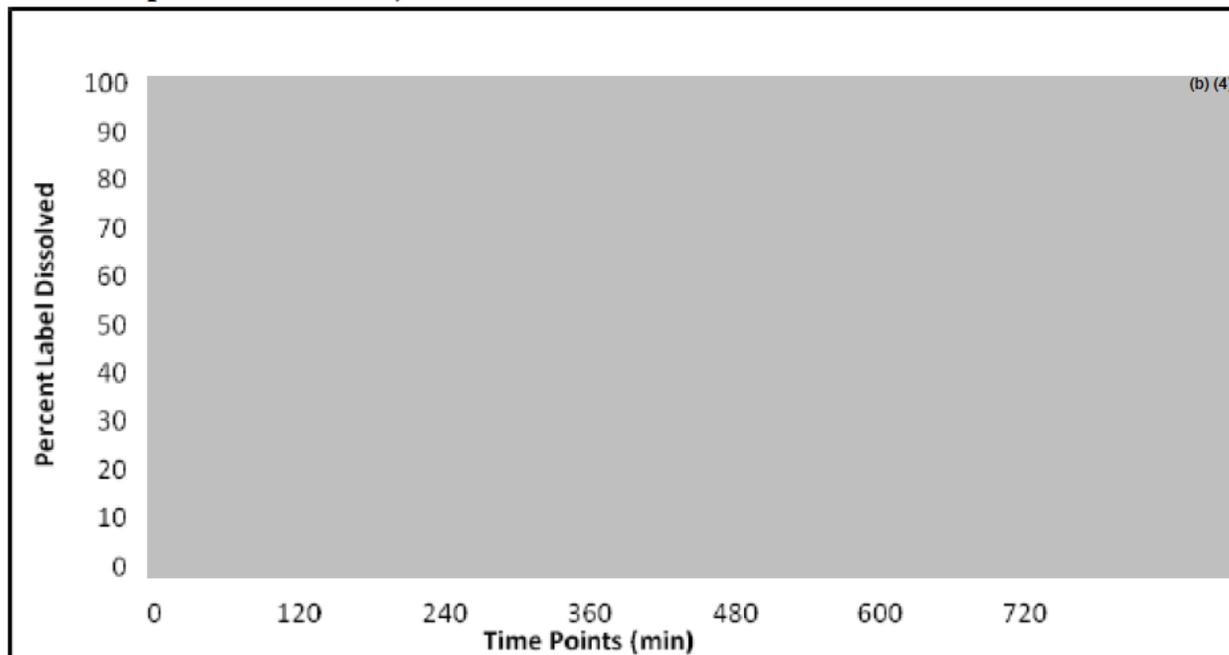


Table 10. Summary of f_2 Calculation for Met Dissolution Results in Media of Alcohol Concs. (5, 10, and 25%) vs. The Control (0%)

Test Article	Ethanol	Average Percent Dissolved										Similarity Factor (f_2)
		10 min	15 min	30 min	45 min	60 min	180 min	360 min	600 min	720 min		
Dapa 5/Met XR 500	0%	(b) (4)										---
	5%	(b) (4)										92
	10%	(b) (4)										72
	25%	(b) (4)										47
Dapa 10/Met XR 1000	0%	(b) (4)										---
	5%	(b) (4)										84
	10%	(b) (4)										74
	25%	(b) (4)										60

Reviewer's Comment:

The f_2 value for the comparison of profiles in the 25% ethanol against the control (0%) media was 47 for the lowest strength (Figure) showing a slower rate than the control which suggests that the high concentration of ethanol (25%) may be impacting Met solubility. However, a similar case was not seen for the highest strength of Dapa10/Met1000 XR (Figure 2). The reasons are not known.

The above *in vitro* results indicate that there is no alcohol dose-dumping potential for this drug product although the highest alcohol (40%) proposed was not employed. In conclusion, an *in vivo* alcohol dose-dumping study seemed not needed.

Overall Comment:

The dissolution method development report, the biowaiver request, and the *in vitro* alcohol dose-dumping study results are reviewed and found acceptable. The Applicant's proposed dissolution method and its acceptance criteria should be implemented for future stability and release testing.

**NDA 205649/N000 for Dapa/Met XR Tablets,
5/500, 10/500, 5/1000, and 10/1000 mg**

Appendix

**Mean Comparative Dissolution Data
Supporting Biowaiver**

Table .Dissolution Comparison for Metformin in Dapa 10/Met XR 500 with Dapa 5/Met XR 500 (Lowest Strength) and Dapa 10/Met XR 1000 mg Tablets (Highest Strength)

Dissolution Media	Sample Description	Metformin Average Percent Dissolved (%RSD, n=12)										Similarity Factor (f _s)																				
		10 minutes	15 minutes	30 minutes	45 minutes	60 minutes	180 minutes	360 minutes	600 minutes	720 minutes																						
50 mM Potassium Phosphate (pH 6.8)	Dapa 10/Met XR 500 (Test)	(b) (4)										NA																				
	Dapa 5/Met XR 500 (Reference)											98																				
	Dapa 10/Met XR 1000 (Reference)											72																				
50 mM Sodium Acetate (pH 4.5)	Dapa 10/Met XR 500 (Test)											(b) (4)										NA										
	Dapa 5/Met XR 500 (Reference)																					96										
	Dapa 10/Met XR 1000 (Reference)																					69										
0.1N HCl (pH 1.2)	Dapa 10/Met XR 500 (Test)																					(b) (4)										NA
	Dapa 5/Met XR 500 (Reference)																															92
	Dapa 10/Met XR 1000 (Reference)																															95

Table .Dissolution Comparison for Metformin in Dapa 5/Met XR 1000 with Dapa 5/Met XR 500 (Lowest Strength) and Dapa 10/Met XR 1000 mg Tablets (Highest Strength)

Dissolution Media	Sample Description	Metformin Average Percent Dissolved (%RSD, n=12)										Similarity Factor (f _s)																				
		10 minutes	15 minutes	30 minutes	45 minutes	60 minutes	180 minutes	360 minutes	600 minutes	720 minutes																						
50 mM Potassium Phosphate (pH 6.8)	Dapa 5/Met XR 1000 (Test)	(b) (4)										NA																				
	Dapa 5/Met XR 500 (Reference)											84																				
	Dapa 10/Met XR 1000 (Reference)											76																				
50 mM Sodium Acetate (pH 4.5)	Dapa 5/Met XR 1000 (Test)											(b) (4)										NA										
	Dapa 5/Met XR 500 (Reference)																					81										
	Dapa 10/Met XR 1000 (Reference)																					81										
0.1N HCl (pH 1.2)	Dapa 5/Met XR 1000 (Test)																					(b) (4)										NA
	Dapa 5/Met XR 500 (Reference)																															86
	Dapa 10/Met XR 1000 (Reference)																															88

Dissolution Media	Sample Description	Dapagliflozin Average Percent Dissolved (% RSD, n=12)					Similarity Factor (f_2)										
		10 minutes	15 minutes	30 minutes	45 minutes	60 minutes											
50 mM Potassium Phosphate (pH 6.8)	Dapa 10/Met XR 500 (Test)	(b) (4)					NA ^a										
	Dapa 5/Met XR 500 (Reference)																
	Dapa 10/Met XR 1000 (Reference)																
50 mM Sodium Acetate (pH 4.5)	Dapa 10/Met XR 500 (Test)											NA ^a					
	Dapa 5/Met XR 500 (Reference)																
	Dapa 10/Met XR 1000 (Reference)																
0.1N HCl (pH 1.2)	Dapa 10/Met XR 500 (Test)																NA ^a
	Dapa 5/Met XR 500 (Reference)																
	Dapa 10/Met XR 1000 (Reference)																

^a f_2 similarity factor not calculated as greater than (b) (4) is dissolved as early as the (b) (4) minute sampling point

Dissolution Media	Sample Description	Dapagliflozin Average Percent Dissolved (% RSD, n=12)					Similarity Factor (f_2)										
		10 minutes	15 minutes	30 minutes	45 minutes	60 minutes											
50 mM Potassium Phosphate (pH 6.8)	Dapa 5/Met XR 1000 (Test)	(b) (4)					NA ^a										
	Dapa 5/Met XR 500 (Reference)																
	Dapa 10/Met XR 1000 (Reference)																
50 mM Sodium Acetate (pH 4.5)	Dapa 5/Met XR 1000 (Test)											NA ^a					
	Dapa 5/Met XR 500 (Reference)																
	Dapa 10/Met XR 1000 (Reference)																
0.1N HCl (pH 1.2)	Dapa 5/Met XR 1000 (Test)																NA ^a
	Dapa 5/Met XR 500 (Reference)																
	Dapa 10/Met XR 1000 (Reference)																

^a f_2 similarity factor not calculated as greater than (b) (4) is dissolved as early as the (b) (4) minute sampling point

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIEN MIEN CHEN
07/02/2014

TAPASH K GHOSH
07/02/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205649	Brand Name	XIGDUO XR
OCP Division (I, II, III, IV, V)	II	Generic Name	Dapagliflozin + Metformin XR FDC
Medical Division	DMEP	Drug Class	SGLT-2 inhibitor and biguanide combination product
OCP Reviewer	Suryanarayana Sista, Ph.D.	Indication(s)	Treatment of Type 2 diabetes
OCP Team Leader	Lokesh Jain, Ph.D.	Dosage Form	oral tablet
Pharmacometrics Reviewer		Dosing Regimen	see below ^a
Date of Submission	10/29/2013	Route of Administration	oral
Estimated Due Date of OCP Review	08/29/2014	Sponsor	Bristol-Myers Squibb / AstraZeneca
Medical Division Due Date		Priority Classification	505 (b)(1) Standard
PDUFA Due Date	10/29/2014		

- ^a • In patients currently not treated with metformin, initiate treatment with 2.5 mg linagliptin/500 mg metformin hydrochloride twice daily
- In patients already treated with metformin, start with 2.5 mg linagliptin and the current dose of metformin taken at each of the two daily meals (e.g., a patient on metformin 1000 mg twice daily would be started on 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily with meals).
- Patients already treated with linagliptin and metformin individual components may be switched to Jentadueto containing the same doses of each component

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	7		
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2		022336D, LCMS 153.5
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
<i>in-vivo</i> effects on primary drug:				
<i>in-vivo</i> effects of primary drug:				
<i>in-vitro</i> :				

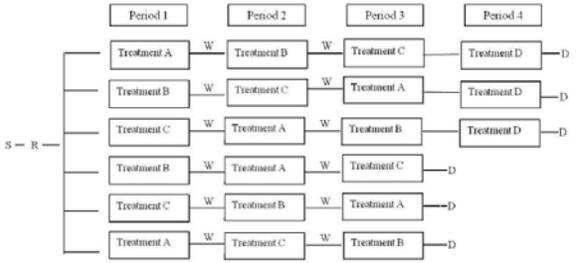
Clinical Pharmacology and Biopharmaceutics Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	3		MB102060, MB102071, MB102065
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		MB102092, MB102100
replicate design; single / multi dose:				
Food-drug interaction studies		2^a		MB102092, MB102100
Bio-waiver request based on BCS				Not Applicable
BCS class				Not Applicable
Dissolution study to evaluate alcohol induced dose-dumping	X	1		This study will be evaluated by ONDQA
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			(b) (4), pediatric plan for dapagliflozin cross-referred
Literature References	X	21		
Total Number of Studies		7		

^aThese studies have been counted earlier under traditional design; single / multi dose

Brief summary about the submission:

Bristol-Myers Squibb and AstraZeneca are seeking US marketing approval for Dapagliflozin+Metformin XR FDC tablets (Proposed Trade Name: Xigduo XR) under the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. The proposed indication of Xigduo XR tablets is "adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate". This NDA is supported by data from five biopharmaceutic studies (3 prototype formulation testings and 2 pivotal fed (light fat meal) bioequivalence/food effect/steady-state PK studies):

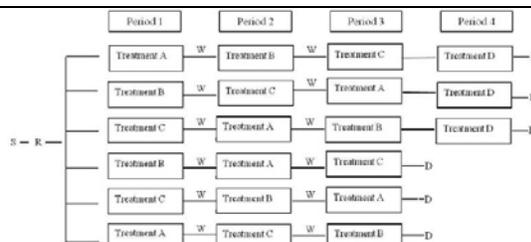
Type of Study / Study Identifier Location of Study Report	Objective(s) of the Study	Study Design
Phase I Relative Bioavailability Study / MB102060 Section 5.3.1.2	<p>Primary: To assess relative bioavailability of one compressed tablet prototype containing reduced-mass metformin XR 1000 mg relative to Glucophage XR 2 x 500 mg tablets when administered to healthy subjects in a fasted condition.</p> <p>Secondary: (a) to assess the effect of food on the compressed tablet prototype containing reduced-mass metformin XR 1000 mg in healthy subjects, and (b) to assess the safety and tolerability of metformin when administered as Glucophage XR 2 x 500 mg tablets and when administered as the compressed tablet prototype containing reduced-mass metformin 1000 mg XR.</p>	<p>Open-label, randomized, 3-period, 3-treatment, unbalanced crossover study in healthy subjects. On Day 1 of Period 1, subjects were randomized to receive oral (PO) doses of the following 3 treatments in 1 of 6 treatment sequences:</p> <ul style="list-style-type: none"> • Treatment A: Single dose of Glucophage XR 2 x 500 mg tablets (fasted) • Treatment B: Single dose of metformin reduced-mass XR 1 x 1000 mg tablet (fasted) • Treatment C: Single dose of metformin reduced-mass XR 1 x 1000 mg tablet (fed)
Phase I Relative Bioavailability Study / MB102071 Section 5.3.1.2	<p>Primary: To assess the relative bioavailability of dapagliflozin and metformin from two FDC formulations comprising 10 mg dapagliflozin and 500 mg metformin XR, relative to coadministration of a dapagliflozin 10 mg tablet and a 500 mg Glucophage XR tablet, in healthy subjects in a fasted state.</p> <p>Secondary: To assess the safety and tolerability of dapagliflozin 10 mg and metformin 500 mg coadministered to healthy subjects in a fasted state.</p>	<p>Open-label, randomized, 3-period, 3-treatment, unbalanced cross-over study in healthy subjects. On Day -1 of Period 1, subjects were randomized to receive 1 of the following 3 treatments in 1 of 6 treatment sequences:</p> <ul style="list-style-type: none"> • Treatment A = FDC tablet of dapagliflozin 10 mg and metformin XR 500 mg (FDC1), fasted • Treatment B = FDC tablet of dapagliflozin 10 mg and reduced mass metformin XR 500 mg (FDC2), fasted • Treatment C = Coadministration of a dapagliflozin 10 mg tablet and a Glucophage XR 500 mg tablet, fasted
Phase I Relative Bioavailability Study / MB102065 Section 5.3.1.2	<p>Primary: The primary objective of this study was to assess the relative bioavailability (BA) of dapagliflozin and metformin from the 2 FDC formulations,</p>	<p>Open-label, randomized, 3-period, 3-treatment, unbalanced cross-over study in healthy subjects. On Day -1 of Period 1, subjects were randomized to receive 1 of the following 3 treatments in 1 of 6 treatment sequences:</p> <ul style="list-style-type: none"> • Treatment A: FDC tablet of dapagliflozin 10 mg

	<p>comprised of 10 mg dapagliflozin and 1000 mg metformin XR, relative to coadministration of a dapagliflozin 10 mg tablet and 2 x 500 mg Glucophage XR tablets, in healthy subjects in a fasted state.</p> <p>Secondary: The secondary objective of this study was to assess the safety and tolerability of dapagliflozin 10 mg and metformin 1000 mg coadministered to healthy subjects in a fasted state.</p>	<p>and metformin XR 1000 mg (FDC1), fasted</p> <ul style="list-style-type: none"> • Treatment B: FDC tablet of dapagliflozin 10 mg and RM metformin XR 1000 mg (FDC2), fasted • Treatment C: Coadministration of dapagliflozin 10 mg tablet and Glucophage XR 2 x 500 mg tablets, fasted
<p>Phase I Fed-state Bioequivalence Study / MB102092 Section 5.3.1.2</p>	<p>Primary: To demonstrate the bioequivalence of dapagliflozin and metformin administered as the 10-mg dapagliflozin/1000-mg extended-release (XR) metformin fixed-dose combination tablet and a 10-mg dapagliflozin tablet coadministered with two 500-mg Glucophage XR tablets to healthy subjects in the fed state.</p> <p>Secondary: (a) to characterize the single-dose and steady-state PK of dapagliflozin and metformin following administration of the 10/1000 XR FDC tablet to healthy subjects in the fed state, (b) to assess the effect of a meal (light-fat) on the single-dose PK of dapagliflozin and metformin administered in the 10/1000 XR FDC tablet in healthy subjects, and (c) to assess, in healthy subjects, the safety and tolerability of the individual component tablets administered in the fed state, and that of single doses (administered in the fed and fasted states) and multiple doses (administered in the fed state) of the 10/1000 XR FDC tablet</p>	<p>Open-label, randomized, 4-period, 4-treatment, crossover study in healthy fasted and fed subjects.</p>  <p>S = Screening — up to 21 days R = Randomization D = Discharge W = Washout period of at least 4 days after dosing in the previous period. Subjects in Period 4 were dosed approximately 48.5 hours after dosing in Period 3</p> <ul style="list-style-type: none"> • Treatment A: A single oral dose of IC tablets (one 10-mg dapagliflozin tablet and two 500-mg metformin XR tablets) administered in the fed state (bioequivalence reference treatment). • Treatment B: A single oral dose of the 10/1000 XR FDC tablet administered in the fed state (bioequivalence test treatment). • Treatment C: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state (food-effect assessment). • Treatment D: Once-daily oral doses of the 10/1000 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment).
<p>Phase I Fed-state Bioequivalence Study</p>	<p>Primary: To demonstrate the bioequivalence of dapagliflozin and metformin</p>	<p>Open-label, randomized, 4-period, 4-treatment, crossover study in healthy fasted and fed subjects.</p>

/ MB102100
Section 5.3.1.2

administered as a 5-mg dapagliflozin/500-mg extended-release (XR) metformin FDC tablet and a 5-mg dapagliflozin tablet coadministered with one 500-mg Glucophage XR tablet to healthy subjects in the fed state.

Secondary: (a) to characterize the single-dose and steady-state PK of dapagliflozin and metformin following administration of the 5/500 XR FDC tablet to healthy subjects in the fed state., (b) to assess the effect of a meal (light-fat) on the single-dose PK of dapagliflozin and metformin administered in the 5/500 XR FDC tablet in healthy subjects, and (c) to assess, in healthy subjects, the safety and tolerability of the individual component tablets administered in the fed state, and that of single doses (administered in the fed and fasted states) and multiple doses (administered in the fed state) of the 5/500 XR FDC tablet.



S = screening — up to 21 days; R = randomization; D = discharge; W = washout

- Treatment A: A single oral dose of IC tablets (one 5-mg dapagliflozin tablet and one 500-mg metformin XR tablet) administered in the fed state (bioequivalence reference treatment).
- Treatment B: A single oral dose of the 5/500 XR FDC tablet administered in the fed state (bioequivalence test treatment).
- Treatment C: A single oral dose of the 5/500 XR FDC tablet administered in the fasted state (food-effect assessment).
- Treatment D: Once-daily oral doses of the 5/500 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment).

NDA 20-5649 [505 (b)(1)] Dapagliflozin/ Metformin XR FDC Bristol-Myers Squibb

Clinical Pharmacology Review Team:

Sury Sista
Lokesh Jain (TL)

Overview: FDC Formulation

- Dapagliflozin/metformin XR FDC tablets are compressed in a (b) (4) tablet configuration using (b) (4) dapagliflozin and metformin (b) (4). The dapagliflozin (b) (4) formulated for immediate release, whereas the metformin (b) (4) formulated to provide extended release.

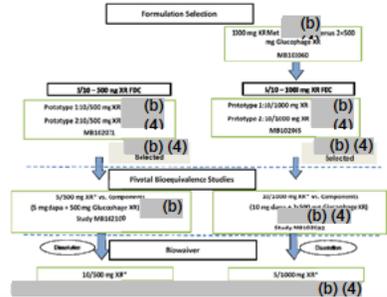


(b) (4)

Overview: Clinical Pharmacology Program

- Clinical Pharmacology program:** 5 Phase 1 studies; (12 Phase 3 studies were submitted earlier to the dapagliflozin NDA 20-2293)
 - Relative Bioavailability studies (n = 3)
 - Bioequivalence Studies (n = 2)

Figure 1: Links between Pilot (Relative Bioavailability), Bioequivalence Studies, In Vitro Dissolution Studies and the To-Be-Marketed Dapagliflozin/Metformin XR FDC Tablet.



Sponsor's Product Development Rationale

- The need for multiple daily antidiabetic medications to achieve and sustain adequate glycosylated hemoglobin A1c (HbA_{1c}) control often leads to poor adherence.
- A new therapeutic combination of dapagliflozin and metformin, available as one tablet, would provide an important treatment option for patients with T2DM, and could improve patient compliance.
- Dapagliflozin is a competitive, reversible, orally active inhibitor of sodium glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption.
- Metformin, a biguanide, is a well-characterized medicine that has been in widespread use for decades. It is the first line agent of choice for T2DM.
- Dapagliflozin's mechanism of action (MOA) is different from, and complementary to, the mechanisms of action of Metformin, resulting in the direct and insulin-independent elimination of glucose by the kidney.
- The two drugs with complementary MOAs, and with clinically important effects on HbA_{1c}, FPG, PPG and weight loss are expected to maintain glycemic control in patients who have difficulty with maintaining glycemic control on metformin alone, or in combination with other oral antidiabetic drugs or insulin.
- The sponsors have developed dapagliflozin/metformin XR FDC tablets with the following dose strengths: (i) 5 mg dapagliflozin/500 mg metformin XR, (ii) 5 mg dapagliflozin/1000 mg metformin XR, (iii) 10 mg dapagliflozin/500 mg metformin XR, (iv) and 10 mg dapagliflozin/1000 mg metformin XR.

Sponsor's Product Development Rationale

Available Combinations Matrix:

Approved Daily Doses of Individual Components of Dapagliflozin and Metformin IR and XR*		Suggested Dapagliflozin/Metformin XR FDC Dosing
Dapagliflozin	Metformin IR or XR	
5 mg	500 mg	5/500 FDC
	750 mg	5/500 FDC or 5/1000 FDC**
	850 mg	5/500 FDC or 5/1000 FDC**
	1000 mg	5/1000 FDC
	1500 mg	5/1000 FDC + Met XR 500
	1700 mg (2 tabs of 850 mg)	5/1000 FDC + Met XR 500 or 5/1000 FDC + 2 tabs of Met XR 500**
10 mg	2000 mg	5/1000 FDC + 2 tabs of Met XR 500
	500 mg	10/500 FDC
	750 mg	10/500 FDC or 10/1000 FDC**
	850 mg	10/500 FDC or 10/1000 FDC**
	1000 mg	10/1000 FDC
	1500 mg	10/1000 FDC + Met XR 500
	1700 mg (2 tabs of 850 mg)	10/1000 FDC + Met XR 500 or 2 tabs of 5/1000 FDC**
	2000 mg	2 tabs of 5/1000 FDC

*Available doses for metformin IR are: 500 mg, 850 mg, or 1000 mg.
Available doses for metformin XR are: 500 mg or 750 mg.
**Depending on desired glycemic goal.

5

Overview: Bioequivalence

Pivotal BE Study MB102092

Protocol	Study Description	Treatments	Number of Subjects	Bioequivalence Criteria Met? [Treatment B/A]			
				Dapagliflozin		Metformin	
				C _{max}	AUC	C _{max}	AUC
MB102092	Bioequivalence Study of a Fixed-Dose Combination Tablet of 10-mg Dapagliflozin/1000-mg Metformin XR Relative to a Single 10-mg Dapagliflozin Tablet and Two 500-mg Metformin XR Tablets administered in the fed state (bioequivalence reference treatment). Treatment A: A single oral dose of 10/1000 XR FDC tablet administered in the fed state (bioequivalence test treatment). Treatment B: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state (bioequivalence test treatment). Treatment C: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state (food-effect assessment). Treatment D: Once-daily oral doses of the 10/1000 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment).	4 period x 4 treatment: Treatment A: A single oral dose of 10 tablets (one 10-mg dapagliflozin tablet and two 500-mg metformin XR tablets) administered in the fed state (bioequivalence reference treatment). Treatment B: A single oral dose of the 10/1000 XR FDC tablet administered in the fed state (bioequivalence test treatment). Treatment C: A single oral dose of the 10/1000 XR FDC tablet administered in the fasted state (bioequivalence test treatment). Treatment D: Once-daily oral doses of the 10/1000 XR FDC tablet administered in the fasted state for 4 days (steady-state PK assessment).	36 (fasting)	Yes	Yes	Yes	Yes
				Food Effect [Treatment B/C] PE (90%CI) are provided if comparability criteria not met			
				Dapagliflozin		Metformin	
				C _{max}	AUC	C _{max}	AUC
			36	0.656 (0.605, 0.711)	Yes	Yes	Yes

6

Overview: Bioequivalence

Pivotal BE Study MB102100

Protocol	Study Description	Treatments	Number of Subjects	Bioequivalence Criteria Met? [Treatment B/A]			
				Dapagliflozin		Metformin	
				C _{max}	AUC	C _{max}	AUC
MB102100	Bioequivalence Study of a Fixed-Dose Combination Tablet of 5-mg Dapagliflozin/500-mg Metformin XR Relative to a Single 5-mg Dapagliflozin Tablet and a Single 500-mg GLUCOPHAGE XR Tablet Co-administered to Healthy Subjects in the Fed and Fasted States and Steady-State Pharmacokinetic Assessment of the Fixed-Dose Combination of 5-mg Dapagliflozin/500-mg Metformin XR.	4 period x 4 treatment: Treatment A: A single oral dose of 10 tablets (one 5-mg dapagliflozin tablet and a 500-mg metformin XR tablet) administered in the fed state (bioequivalence reference treatment). Treatment B: A single oral dose of the 5/500 XR FDC tablet administered in the fed state (bioequivalence test treatment). Treatment C: A single oral dose of the 5/500 XR FDC tablet administered in the fasted state (bioequivalence test treatment). Treatment D: Once-daily oral doses of the 5/500 XR FDC tablet administered in the fed state for 4 days (steady-state PK assessment).	36 (fasting)	Yes	Yes	Yes	Yes
				Food Effect [Treatment B/C] PE (90%CI) provided if comparability criteria not met			
				Dapagliflozin		Metformin	
				C _{max}	AUC	C _{max}	AUC
			36	0.659 (0.614, 0.706)	Yes	Yes	Yes

Compared to the fasted state, a light-fat meal decreased the C_{max} of dapagliflozin by 35% when administered as the FDC tablet and did not have an effect on AUC₀₋₄ and AUC_∞ of dapagliflozin in the FDC. As the daily amount of glucose excreted in the urine is dependent upon dapagliflozin AUC and not the peak concentration, changes in dapagliflozin C_{max} is not expected to influence dapagliflozin's safety, tolerability and efficacy hence dapagliflozin may be taken without regard to meals.

7

Pediatric Plan

Sponsor Request

- The sponsors are currently evaluating the PK/PD of dapagliflozin in pediatric patients aged 10 to 17 years old with T2DM (Study MB102091).

(b) (4)

Key Questions: Mid Cycle Deliverables

- Was bioequivalence between the individual components and the FDC established?

Conclusions

- This NDA is filable from OCP perspective
- OSI inspection will be requested for the pivotal BE studies

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Data in original NDA for dapagliflozin (20-2293)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	Data in original NDA for dapagliflozin (20-2293)
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	Rationale for dapagliflozin in NDA 20-2293. Rationale for available FDC strengths submitted with current application.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	Data in original dapagliflozin NDA (20-2293).
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	Data in original dapagliflozin NDA (20-2293).
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	Data in original dapagliflozin NDA (20-2293).
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	Data in original dapagliflozin NDA (20-2293).
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comment to Sponsor:
None

Suryanarayana M. Sista	09 Dec, 2013
Reviewing Clinical Pharmacologist	Date
Lokesh Jain	09 Dec, 2013
Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURYNARAYANA M SISTA
12/26/2013

LOKESH JAIN
12/26/2013