

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**200678Orig1s000**

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

## Addendum to the Clinical Pharmacology Review Dated October 15, 2010

NDA: 200678	Submission Date(s): 12/29/2009
Brand Name	Kombiglyze XR
Generic Name	saxagliptin/metformin HCl extended release fixed dose combination (FDC) tablets
Reviewer	Ritesh Jain, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology- II
OND division	Metabolism and Endocrinology Products
Sponsor	Bristol Myers Squibb
Submission Type; Code	Original NDA 505(b)(1); Standard
Formulation; Strength(s)	FDC product of saxagliptin/metformin XR at dose strengths 5 mg/500 mg, 2.5 mg/1000 mg, and 5 mg/1000 mg
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

### **BACKGROUND:**

NDA 200678 was submitted to seek a marketing approval for Kombiglyze XR (FDC) 5 mg/500 mg, 2.5 mg/1000 mg, and 5 mg/1000 mg of saxagliptin/metformin hydrochloride extended-release tablets. The Clinical Pharmacology review for this NDA was DARRTed on October 15, 2010. In this review, under the Summary of Important Clinical Pharmacology Findings section, this reviewer mentioned that the proposed FDC product was not studied in the Phase 3 trials. Thus, pivotal BE studies provided the link between the formulations utilized in Phase 3 trials and the proposed to-be-marketed formulation. This addendum to Clinical Pharmacology review dated October 15, 2010 clarifies the link between the Kombiglyze XR and the formulations used in Phase 3 clinical trials. There were no long term clinical efficacy or safety studies conducted with either Kombiglyze XR or metformin hydrochloride XR co-administered with saxagliptin with this NDA. The following studies were submitted in support of this NDA:

- Long term Phase 3 safety and efficacy trials conducted (typically 24-52 week long) with metformin hydrochloride immediate-release formulation (Glucophage IR) co-administered with saxagliptin under NDA 22350.
- 4-week, multi-center, randomized, double-blind, placebo-controlled, Phase 3b trial (CV181066) conducted with metformin hydrochloride extended-release formulation (Glucophage XR) co-administered with saxagliptin under this NDA.
- Bioequivalence study, CV181111 and CV181112 comparing the rate and extent of absorption of saxagliptin and metformin hydrochloride when administered as Kombiglyze XR or saxagliptin and metformin hydrochloride XR tablets administered together.

The duration of 4-week trial (CV181066) mentioned above is not sufficient to evaluate the efficacy and safety of metformin hydrochloride extended-release formulation (Glucophage XR) co-administered with saxagliptin.

**Reviewer's Findings on Pharmacokinetic Link between Glucophage IR vs. Glucophage XR:**

Glucophage XR is approved under NDA 21202. In NDA 21202, the steady state pharmacokinetics of 4 doses of Glucophage XR was evaluated in study CV138-028. In this study, sixteen healthy volunteers were dosed with 500 mg Glucophage XR (referred as biphasic in Table 1) as single dose and PK samples were taken. Subjects then received nightly doses of 500 mg Glucophage XR for a week and PK samples were again obtained after a week of dosing. The 500 mg dose of Glucophage XR increments continued each week up to 2000 mg QD. In this study, subjects also received 2 x 500 mg BID Glucophage IR tablets for one week to provide comparative PK parameters between Glucophage XR and Glucophage IR. The results of the study are summarized in Table 1.

At steady state, the peak plasma concentrations for Glucophage XR (1000 mg QD biphasic) were approximately 20% lower compared to the same dose of Glucophage IR (1000 mg BID Glucophage). However, the extent of absorption of Glucophage XR (2000 mg QD biphasic, as measured by AUC) is similar to Glucophage IR (1000 mg BID Glucophage) (Table 1).

**Table 1: Steady State Pharmacokinetics of Glucophage XR \***

Treatment	N	Cmax (ng/ml)	Tmax <sup>§</sup> (hr)	AUC (ng.hr/ml)*
500 mg biphasic single dose	16	645(115)	7(4,8)	6456(1751)
500 mg QD biphasic	16	603(166)	6(4,8)	6316(1996)
1000 mg QD biphasic	16	1080(259)	7(4,8)	12387(3164)
1500 mg QD biphasic	15	1441(362)	7(5,8)	16820(4160)
2000 mg QD biphasic	14	1780(288)	7(4,9)	20451(4114)
1000 mg BID Glucophage®	15	1321(234)	3(1.5,6)	20544(4445)

§ Median (range)

\* AUC(INF) for 500 mg single dose; all others AUC(0-24).

CMAX and TMAX for the Glucophage® treatment are from the PM dose.

\* Source: NDA 21202 review by Dr Robert M. Shore

The formal PK comparison between the Glucophage XR 2000 mg QD and Glucophage IR 1000 mg BID is shown in Table 2. Results from the comparison demonstrated that the extent of absorption of Glucophage XR (as measured by AUC) is similar to that of Glucophage IR (Table 2).

**Table 2: Pharmacokinetic Comparison of Glucophage XR 2000 mg QD and Glucophage IR 1000 mg BID\*.**

Parameter	Adjusted geometric means		Ratio of geometric means	
	2000 mg Biphasic QD	1000 mg Glucophage® BID	Point estimate	90% CI
C <sub>MAX</sub> (ng/ml)	1763	1297	1.36	(1.29, 1.44)
AUC(TAU) (ng.hr/ml)	19986	20053	1.00	(0.93, 1.07)

\* Source: NDA 21202 review by Dr Robert M. Shore

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**Reviewer’s Findings on Safety and Efficacy Link between Glucophage IR vs. Glucophage XR:**

Phase 3 clinical trials in NDA 21202 demonstrated the safety and efficacy of Glucophage XR. The efficacy and safety of Glucophage XR was established in a 12-week, double-blind, randomized, placebo-controlled trial (CV138010) (Table 3).

**Table 3:** Change in HbA1C at week 12 and 24 week following administration of Glucophage XR\*.

Change in HbA1c at 12 and 24 weeks (or last available measurement)				
	12 weeks		24 weeks	
HbA1c	Placebo n=79	Met XR n=155	Placebo n=79	Met XR n=156
Baseline	7.88	8.04	7.88	8.04
Week 12/24	8.00	7.47	8.09	7.42
Adj Mean chng	+0.09	-0.56	+0.19	-0.62
Diff		-0.65		-0.79

From table 11.1.1.4.1

\* Source: NDA 21202 review by Dr Robert Misbin

The results from another Phase 3 trial (Study 138036) under NDA 21202, a 16-week, double-blind, placebo-controlled, dose-response study of Glucophage XR, taken once daily with the evening meal or twice daily with meals, in patients with type 2 diabetes clearly demonstrated a dose response with increasing dose of Glucophage XR (Table 4).

**Table 4:** Summary of Mean Changes from Baseline in HbA1c, Fasting Plasma Glucose, and Body Weight at Final Visit (16 week study)\*

	GLUCOPHAGE XR					Placebo
	500 mg Once Daily	1000 mg Once Daily	1500 mg Once Daily	2000 mg Once Daily	1000 mg Twice Daily	
<b>Hemoglobin A<sub>1c</sub> (%)</b>	(n=115)	(n=115)	(n=111)	(n=125)	(n=112)	(n=111)
Baseline	8.2	8.4	8.3	8.4	8.4	8.4
Change at FINAL VISIT	-0.4	-0.6	-0.9	-0.8	-1.1	0.1
p-value <sup>a</sup>	<0.001	<0.001	<0.001	<0.001	<0.001	-
<b>FPG (mg/dL)</b>	(n=126)	(n=118)	(n=120)	(n=132)	(n=122)	(n=113)
Baseline	182.7	183.7	178.9	181.0	181.6	179.6
Change at FINAL VISIT	-15.2	-19.3	-28.5	-29.9	-33.6	7.6
p-value <sup>a</sup>	<0.001	<0.001	<0.001	<0.001	<0.001	-
<b>Body Weight (lbs)</b>	(n=125)	(n=119)	(n=117)	(n=131)	(n=119)	(n=113)
Baseline	192.9	191.8	188.3	195.4	192.5	194.3
Change at FINAL VISIT	-1.3	-1.3	-0.7	-1.5	-2.2	-1.8
p-value <sup>a</sup>	NS**	NS**	NS**	NS**	NS**	-

\* All patients on diet therapy at Baseline

<sup>a</sup> All comparisons versus Placebo

\*\* Not statistically significant

\* Source: Glucophage XR product label

In NDA 21202, the sponsor had a Phase 3 trial (Study 138012) comparing metformin Glucophage IR to metformin Glucophage XR. The study was a double blind trial to compare two doses of Glucophage XR (1000 mg and 1500 mg) given once daily to Glucophage IR 500 mg BID in patients who had already been taking Glucophage IR 500 mg twice daily for at least 8 weeks. The results from the trial are shown in Table 5.

**Table 5:** Summary of Mean Changes from Baseline\* in HbA1c, Fasting Plasma Glucose, and Body Weight at Week 12 and at Final Visit (24-week study) †

	GLUCOPHAGE 500 mg Twice Daily	GLUCOPHAGE XR	
		1000 mg Once Daily	1500 mg Once Daily
<b>Hemoglobin A<sub>1c</sub> (%)</b>	<b>(n=67)</b>	<b>(n=72)</b>	<b>(n=66)</b>
Baseline	7.06	6.99	7.02
Change at 12 Weeks	0.14	0.23	0.04
(95% CI)	(-0.03, 0.31)	(0.10, 0.36)	(-0.08, 0.15)
Change at FINAL VISIT	0.14 <sup>a</sup>	0.27	0.13
(95% CI)	(-0.04, 0.31)	(0.11, 0.43)	(-0.02, 0.28)
<b>FPG (mg/dL)</b>	<b>(n=69)</b>	<b>(n=72)</b>	<b>(n=70)</b>
Baseline	127.2	131.0	131.4
Change at 12 Weeks	12.9	9.5	3.7
(95% CI)	(6.5, 19.4)	(4.4, 14.6)	(-0.4, 7.8)
Change at FINAL VISIT	14.0	11.5	7.6
(95% CI)	(7.0, 21.0)	(4.4, 18.6)	(1.0, 14.2)
<b>Body Weight (lbs)</b>	<b>(n=71)</b>	<b>(n=74)</b>	<b>(n=71)</b>
Baseline	210.3	202.8	192.7
Change at 12 Weeks	0.4	0.9	0.7
(95% CI)	(-0.4, 1.5)	(0.0, 2.0)	(-0.4, 1.8)
Change at FINAL VISIT	0.9	1.1	0.9
(95% CI)	(-0.4, 2.2)	(-0.2, 2.4)	(-0.4, 2.0)

\* All patients on GLUCOPHAGE 500 mg twice daily at Baseline

<sup>a</sup> n=68

† *Source: Glucophage XR product label*

Thus, NDA 21202 demonstrated the comparable bioavailability between Glucophage XR and Glucophage IR. The differences in C<sub>max</sub> between the two formulations did not appear to result marked differences in efficacy based on a clinical trial in which patients with T2DM receiving Glucophage IR were either maintained on this regimen or switched to Glucophage XR.

**Reviewer’s Findings on pivotal BE studies CV181111 and CV181112 submitted under NDA 200678:**

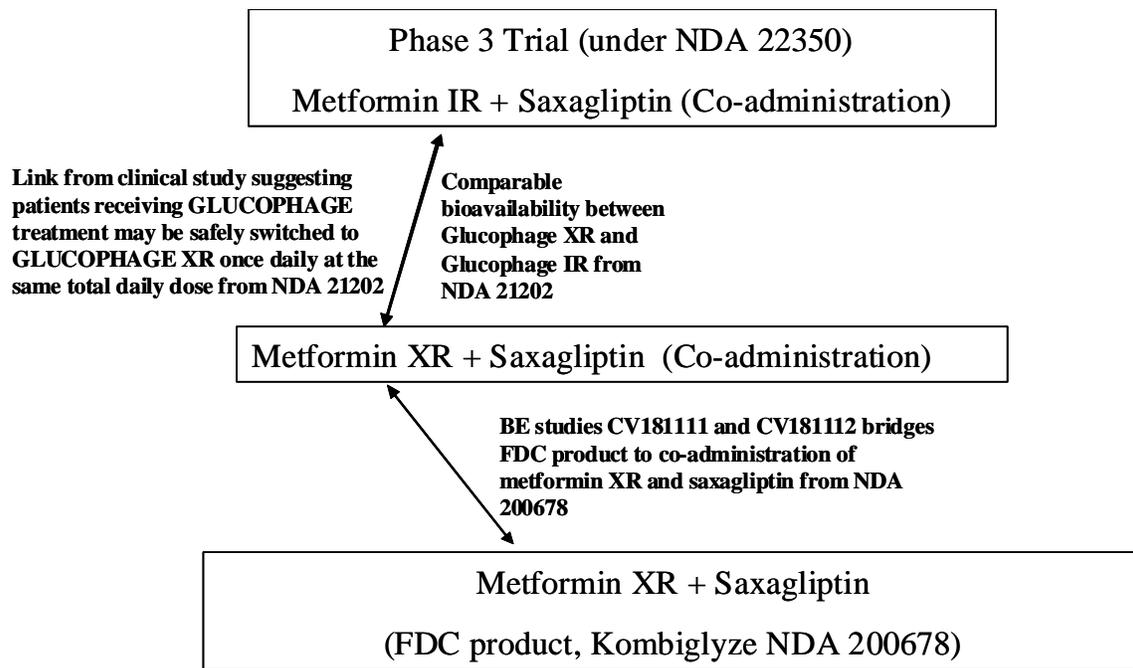
Bioequivalence trials, CV181111 and CV181112, comparing Kombiglyze XR to the individual components metformin hydrochloride XR and saxagliptin co-administered together demonstrated that there is no formulation effect.

**CONCLUSIONS:**

NDA 21202 demonstrated the comparable bioavailability between Glucophage XR and Glucophage IR. The differences in  $C_{max}$  between the two formulations did not appear to result marked differences in efficacy based on a clinical trial in which patients with T2DM receiving Glucophage IR were either maintained on this regimen or switched to Glucophage XR. Also, the current product label of GLUCOPHAGE XR states that **“In a randomized trial, patients currently treated with GLUCOPHAGE were switched to GLUCOPHAGE XR. Results of this trial suggest that patients receiving GLUCOPHAGE treatment may be safely switched to GLUCOPHAGE XR once daily at the same total daily dose, up to 2000 mg once daily”**

Figure 1 summarizes the bridging between the metformin extended-release and the metformin IR, which was co-administered with saxagliptin in the long term Phase 3 safety and efficacy trials in support of NDA 200678. In addition, the sponsor conducted BE studies comparing metformin XR and saxagliptin co-administered together to the FDC combination product and demonstrated that there was no formulation effect bridging the individual saxagliptin and metformin extended-release to Kombiglyze XR.

**Figure 1:** Link between FDC product (Kombiglyze XR) and metformin IR and saxagliptin co-administration used in the Phase 3 trials.



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**Office of New Drugs Quality Assessment  
BIOPHARMACEUTICS REVIEW**

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<b>NDA</b>	200-678
<b>Drugs</b>	Saxagliptin/Metformin
<b>Formulation</b>	Fixed dose Combination (FDC) Extended Release Tablets
<b>Strengths</b>	5 mg/500 mg, 2.5 mg/1000 mg, and 5 mg/1000 mg
<b>Sponsor</b>	Bristol Myers Squibb
<b>Letter Date</b>	December 29, 2009
<b>Review Type</b>	Justification for batch size used in the BE studies
<b>Reviewer/Team Leader</b>	Patrick J. Marroum, Ph.D.

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**Background:**

The Pivotal Phase 3 clinical studies used metformin XR (500 mg) manufactured in Evansville or metformin IR formulation; however, the proposed to-be-marketed FDC tablets are being manufactured at Mt. Vernon, Indiana. The following figure describes the studies conducted to link the currently approved products used in the clinical studies to the proposed to-be-marketed formulation.



Both saxagliptin and metformin are approved products and are marketed by Bristol Myers Squibb. Saxagliptin (Onglyza™) was approved in 2009 under NDA 22-350. Metformin hydrochloride XR is an extended-release (XR) tablet formulation of metformin hydrochloride approved under NDA 21-202 and is currently marketed by Bristol-Myers Squibb under the brand name Glucophage® XR (extended release tablets of metformin hydrochloride).

Bristol Myers Squibb conducted two pivotal bioequivalence studies to provide a direct link for the to-be-marketed FDC product manufactured at Mt Vernon, Indiana, to the marketed Glucophage® XR tablets manufactured at Evansville, Indiana. Bioequivalence study No. CV181111 was conducted to link the to-be-marketed 5 mg saxagliptin/500 mg metformin XR FDC to the marketed component 500 mg Glucophage® XR. The batch size for this study was (b) (4), which size is considerably less than 100,000 or 10% of the commercial batch size typically expected in pivotal bioequivalence studies. Bioequivalence study No. CV181112 provided the link for the 5 mg saxagliptin/1000 mg metformin XR FDC to the to-be-marketed 5 mg saxagliptin/1000 mg metformin XR FDC to 2 x 500 mg tablets of marketed Glucophage® XR tablets. The batch size for this study was (b) (4).

It should be noted that on February 13, 2009 under IND 76500 responses to the questions included in the...end of phase 2 (EOP2) meeting package were communicated to the sponsor.. Bristol Myers Squibb was informed that they were not required to repeat bioequivalence studies conducted with smaller batch sizes, as long as the recommendations given in the SUPAC MR guidance for batch-scale up were met.

### **Justification for Acceptance of a smaller batch size**

- 1- The new saxagliptin/metformin extended release fixed dose combination formulation has exactly the same (b) (4) as the approved extended release formulation of metformin with the only difference being the (b) (4).
- 2- The new manufacturing site for the (b) (4) as well as the fixed dose combination Mt. Vernon, Indiana has been qualified via a bioequivalence study for the metformin (b) (4).
- 3- The requirements described in the SUPAC MR guidance in terms of batch-scale up were met. The sponsor provided the supportive in vitro comparative dissolution profile data showing that the release characteristics of a pilot small scale batch are similar to the release characteristics of a full scale batch in three media (0.1 N HCl and phosphate buffer pH4.5 and 6.8).
- 4- The batch size requirement of 100,000 units or 10 % of the production batch size (whichever is greater), is not a CFR regulatory requirement but it is only a recommendation cited in a regulatory guidance to avoid issues that can arise from using smaller size batches. It is recommended to increase the probability of passing the confidence interval criteria for bioequivalence.
- 5- In general, the probability of a formulation to be bio-inequivalent when scaled to a full scale batch is very small when the pilot scale batch has shown to be bioequivalent to the reference formulation.

**Conclusion:**

For all the above reasons, the Biopharmaceutics group within ONDQA considers that the recommendation given to Bristol Myers Squibb during the EOP2 meeting of not to repeat bioequivalence studies conducted with the small scale batches is adequate and justified.

\_\_\_\_\_  
Patrick Marroum, Ph. D.  
Office of New Drug Quality Assessment

Date \_\_\_\_\_

cc: NDA 200-678, A Dorantes, A Al Hakim, Choe, Mahayni, Chikhale

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PATRICK J MARROUM  
10/20/2010

## CLINICAL PHARMACOLOGY REVIEW

NDA: 200678	Submission Date(s): 12/29/2009
Brand Name	Kombiglyze
Generic Name	saxagliptin/metformin HCl extended release fixed dose combination (FDC) tablets
Reviewer	Ritesh Jain, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology- II
OND division	Metabolism and Endocrinology Products
Sponsor	Bristol Myers Squibb
Submission Type; Code	Original NDA 505(b)(1); Standard
Formulation; Strength(s)	FDC product of saxagliptin/metformin XR at dose strengths 5 mg/500 mg, 2.5 mg/1000 mg, and 5 mg/1000 mg
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

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## 1 Executive Summary

### 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the clinical pharmacology data submitted under NDA 200678, dated 12/29/2009, and finds it not acceptable because of the following deficiency:

- 1) The batch sizes of the formulation that were utilized in the pivotal bioequivalence (BE) studies, CV181111 and CV181112, do not meet the biobatch size criteria of 10% or greater than that of the proposed commercial production batch or at least 100,000 units, whichever is greater.

**Comments to the Clinical Division:** These findings on the batch sizes used in the pivotal BE studies have been communicated to the Office of New Drug Quality Assessment (ONDQA) Biopharmaceutics and Chemistry Manufacturing and Controls (CMC) groups. They are in the process of evaluating these findings and will be finalizing their reviews on assessing the impact of using batch sizes lower than SUPAC-MR guidance and general criteria used by FDA.

### 1.2 Phase IV Commitments

None

### 1.3 Summary of Important Clinical Pharmacology Findings

The purpose of this application (NDA 200678) by Bristol Myers Squibb is to seek a marketing approval for the Fixed Dose Combination (FDC) 5 mg/500 mg, 2.5 mg/1000 mg, and 5 mg/1000 mg of saxagliptin/metformin hydrochloride extended-release tablets. The FDC product is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) when treatment with both saxagliptin and metformin is appropriate.

Both saxagliptin and metformin are approved products and are marketed by Bristol Myers Squibb. Saxagliptin (Onglyza™) has been approved in the United States in 2009 under NDA 22350. Saxagliptin is currently indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, both as monotherapy and as combination therapy with other anti-diabetic agents, including metformin. Saxagliptin is a highly potent, selective, reversible, competitive, dipeptidyl peptidase-4 (DPP4) inhibitor and is currently marketed as immediate-release tablets of 2.5 mg and 5 mg dose strengths.

Metformin hydrochloride is an oral anti-hyperglycemic agent also used in the treatment of T2DM. Metformin hydrochloride XR is an extended-release (XR) tablet formulation of metformin hydrochloride approved under NDA 21202 and is currently marketed by Bristol-Myers Squibb under the brand name Glucophage® XR (extended release tablets of metformin hydrochloride). In the United States, Glucophage® XR is marketed in the 500 and 750 mg dose strengths and is approved for doses up to 2000 mg to be taken once daily with the evening meal.

The safety and efficacy of the FDC product is supported by Phase 3 trials that were submitted under saxagliptin NDA (NDA 22350). In the Phase 3 trials the saxagliptin and metformin IR was found to be safe and efficacious when they were co-administered together.

FDC tablets of saxagliptin with metformin XR have been developed in the following 3 different dose strengths to allow once-daily dosing of saxagliptin with metformin at total daily doses up to 5 mg saxagliptin and 2000 mg metformin (i.e., the highest recommended once-daily doses of saxagliptin and metformin):

- ✓ 5 mg saxagliptin/500 mg metformin XR
- ✓ 5 mg saxagliptin/1000 mg metformin XR
- ✓ 2.5 mg saxagliptin/1000 mg metformin XR

The clinical pharmacology program for the FDC product consists of two pivotal and five supporting clinical pharmacology studies. Two pivotal clinical pharmacology studies evaluated the bioequivalence (BE) between the FDC product and saxagliptin and metformin XR tablets when administered together. The BE was assessed at two different dose strengths of FDC product (5/500mg, 5/1000mg as saxagliptin/metformin FDC) and individual components co-administered together (5 mg saxagliptin + 500 mg metformin and 5 mg saxagliptin + 1000 mg metformin). These pivotal studies also evaluated the effect of food and steady state pharmacokinetics of saxagliptin and metformin when administered as FDC product.

The proposed FDC product was not studied in the Phase 3 trials. Thus, pivotal BE studies provided the link between the formulations utilized in Phase 3 trials and the proposed to-be-marketed formulation. This review will focus on the following two pivotal Clinical Pharmacology studies.

- ❖ Study CV181111: Bioequivalence study of the fixed-dose combination of 5 mg saxagliptin and 500 mg metformin XR Tablet (manufactured in Mt Vernon, IN) relative to equivalent dose strengths of the currently marketed individual component formulations of 5 mg saxagliptin tablet and 500 mg metformin XR tablet co-administered to healthy subjects in a fed condition. The study also evaluated the effect of food on the FDC product. This study was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects.
- ❖ Study CV181112: Bioequivalence study of the fixed-dose combination of 5 mg saxagliptin and 1000 mg metformin XR (manufactured in Mt Vernon, IN) relative to 5 mg of saxagliptin and 2 × 500 mg metformin XR co-administered to healthy subjects in the fed state. This study also evaluated the single dose and steady state pharmacokinetics of saxagliptin and metformin when administered as FDC tablets. This study was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects.

Bioequivalence studies were conducted with the FDC product containing 5 mg saxagliptin. No clinical bioequivalence study was conducted for the 2.5 mg saxagliptin/1000 mg metformin XR FDC (b) (4)

The batch sizes of the formulation that were utilized in bioequivalence studies, CV181111 and CV181112, do not meet the biobatch size criteria of 10% or greater than that of the proposed commercial production batch or at least 100,000 units, whichever is greater. In this NDA, the proposed commercial batch size is (b) (4) tablets and the sponsor used batch sizes of (b) (4) in trials CV181111 and CV181112, respectively. These batch sizes do not meet the criteria of biobatch, (b) (4), for the pivotal BE studies.

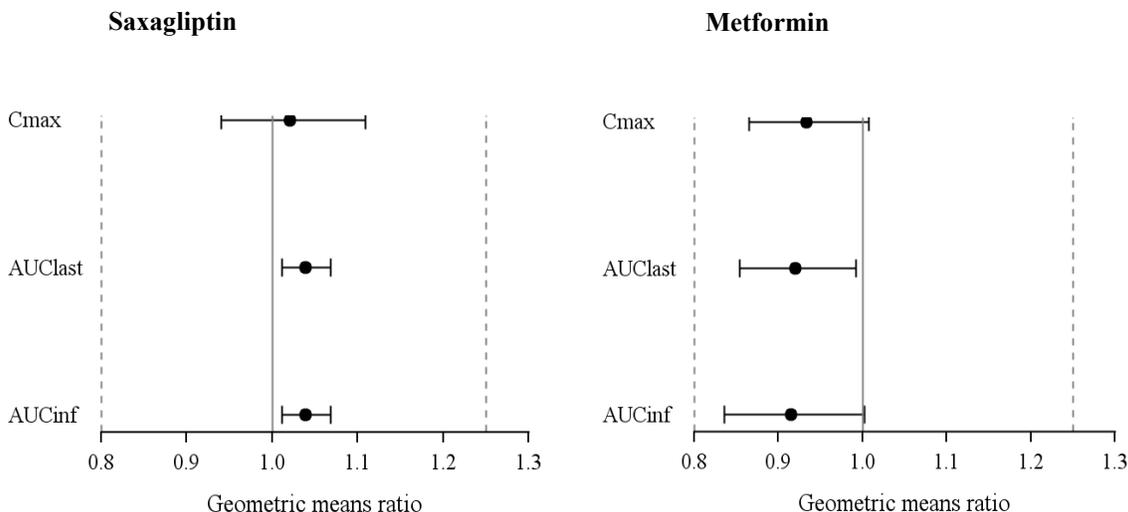
**Fixed-Dose Combination vs. Individual Component Bioequivalence**

Two pivotal bioequivalence studies (CV181111 and CV181112) were conducted to compare the rate and extent of absorption of saxagliptin and metformin when administered as FDC product or saxagliptin and metformin XR tablets administered together.

Study CV181111 evaluated the rate and extent of absorption of saxagliptin and metformin from the to-be-marketed 5 mg saxagliptin/500 mg metformin XR FDC formulation relative to the equivalent dose strengths of the currently marketed individual component formulations (5 mg saxagliptin and 500 mg metformin XR) under low fat meal condition (324 kcal).

The 90% confidence intervals (CIs) of the ratios of geometric least square (LS) means for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  were entirely contained within 0.80 to 1.25 for both saxagliptin and metformin (Figure 1). Therefore, the FDC tablet, which was manufactured at Mt Vernon was bioequivalent to the co-administered 5 mg saxagliptin and 500 mg metformin XR tablets, which were manufactured at Evansville when administered under low fed conditions.

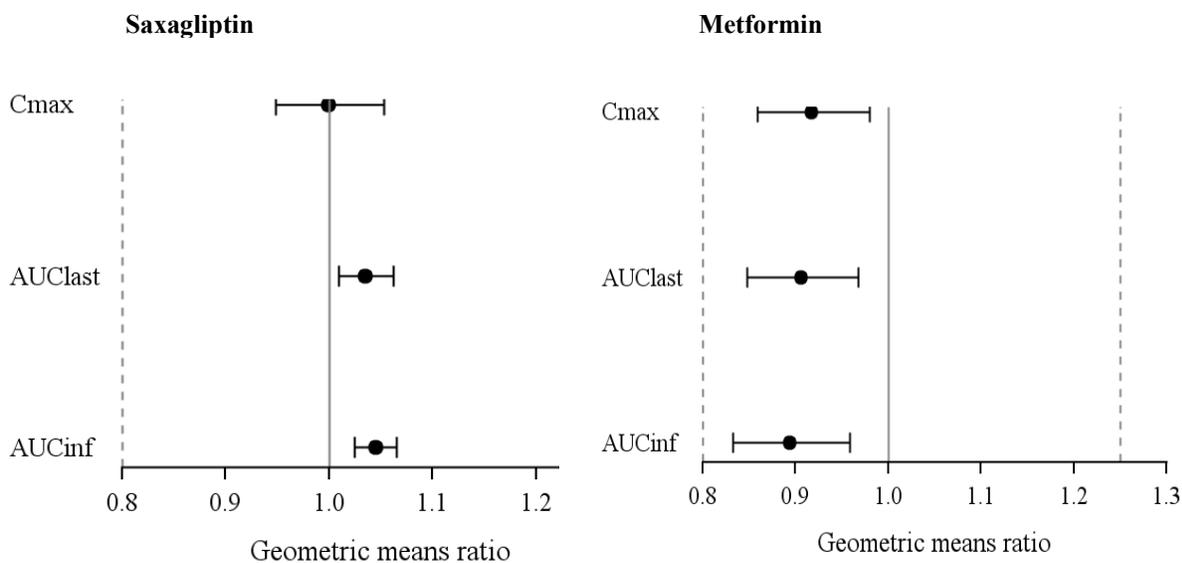
**Figure 1: Ratios of Geometric Means (Treatment B/ Treatment A) and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Saxagliptin and Metformin Following Co-administration of Saxagliptin 5 mg and Metformin XR 500 mg (Treatment A) and FDC Product (Treatment B) under Low Fat Meal Condition.**



Study CV181112 evaluated the rate and extent of absorption of saxagliptin and metformin from the to-be-marketed 5 mg saxagliptin/1000 mg metformin XR FDC tablet relative to the equivalent dose strengths of the currently marketed individual component formulations (5 mg saxagliptin plus two 500 mg metformin XR) administered under low fat meal (324 kcal).

The 90% CIs of the ratios of geometric LS means for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  of saxagliptin and metformin were all entirely contained within 0.80 to 1.25 (Figure 2). Therefore, the FDC tablet was bioequivalent to the co-administered 5 mg saxagliptin plus two of 500 mg metformin XR tablets when administered under fed conditions.

**Figure 2: Ratios of Geometric Means (Treatment B/ Treatment A) and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Saxagliptin and Metformin Following Co-administration of Saxagliptin 5 mg and Metformin XR 2 x 500 mg (Treatment A) and FDC Product (Treatment B) under Low Fat Meal Condition.**



Thus, the bioequivalence study with low fat meal bridges the use of FDC product to that to Phase 3 clinical program.

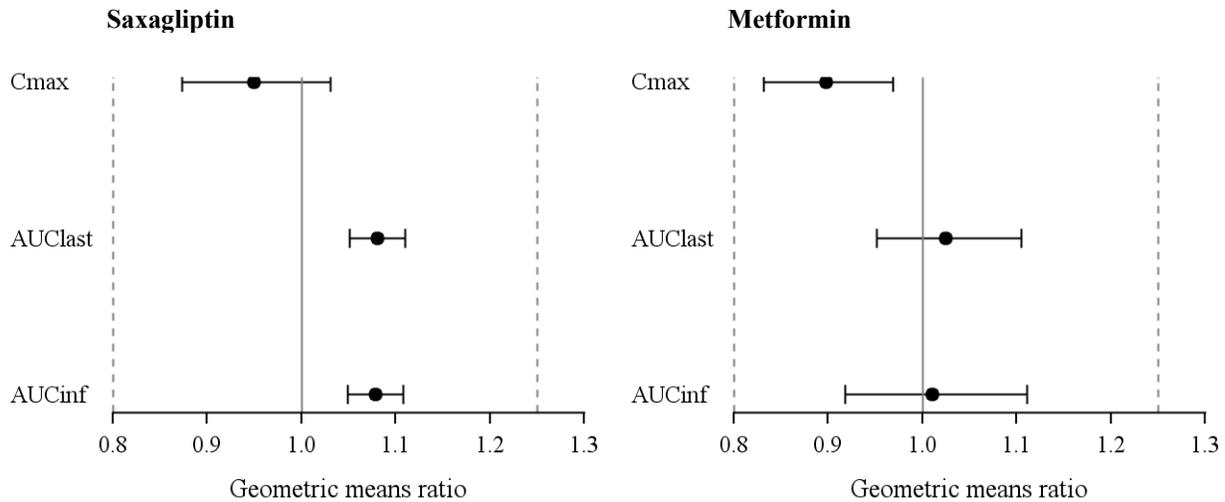
### **Drug –Drug Interaction**

No drug-drug interaction study between metformin and saxagliptin has been conducted under this NDA. However, in saxagliptin NDA 22350 it has been demonstrated that there is no significant drug-drug interaction between saxagliptin and metformin (Study CV181017). In this drug-drug interaction study, saxagliptin did not have any effect on the pharmacokinetics of metformin. Metformin decreased the  $C_{max}$  of saxagliptin by 21%, but did not alter the overall exposure  $AUC_{0-t}$  or  $AUC_{0-inf}$ . The decrease in metformin  $C_{max}$  was not considered to be clinically meaningful.

### **Food-Effect**

Study CV181111 evaluated the effect of food when 5 mg saxagliptin/500 mg metformin XR FDC was administered under fed (low fat meal 324 kcal) and fasted state. No significant food effect on the pharmacokinetics of saxagliptin or metformin was observed when the FDC tablet was administered under fed versus fasted conditions. The 90% CIs of the ratios of geometric LS means for the saxagliptin and metformin components of the FDC tablet were entirely contained within 0.80 to 1.25 (Figure 3).

**Figure 3: Ratios of Geometric Means (Treatment B/ Treatment A) and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Saxagliptin and Metformin Following administration of FDC product (5/500 mg saxagliptin/metformin) under fasted (Treatment A) and fed (Treatment B)**



### **Dose Dumping**

The influence of ethanol on the release of metformin from FDC product was assessed in *in vitro* dissolution studies with 5 mg saxagliptin/500 mg metformin XR and 5 mg saxagliptin/1000 mg metformin XR FDC tablets. The range of alcohol concentrations in the dissolution medium ranged from 5 to 25%. The sponsor claimed that for both strengths, 5 mg saxagliptin/500 mg metformin XR and 5 mg saxagliptin/1000 mg metformin XR, the dissolution release profile of extended release metformin did not result in dose dumping or accelerated release of metformin in the presence of alcohol. For further details please refer to Biopharmaceutics review by Dr. Houda Mahayni.

In conclusion, from clinical pharmacology aspect this NDA application is not acceptable because of the following deficiency:

- 1) The batch sizes of the formulation that were utilized in pivotal bioequivalence (BE) studies, CV181111 and CV181112, do not meet the biobatch size criteria of 10% or greater than that of the proposed commercial production batch or at least

100,000 units, whichever is greater. In this NDA, the proposed commercial batch size is (b) (4) and the sponsor used batch size of (b) (4) and (b) (4) in trials CV181111 and CV181112, respectively. These batch sizes do not meet the criteria of biobatch, in this case 100,000 tablets, for the pivotal BE studies and thus this application is not acceptable (Please refer to section 2.5.2 of this review for further information).

These findings on the batch sizes used in the pivotal BE studies have been communicated to the Office of New Drug Quality Assessment (ONDQA) Biopharmaceutics and Chemistry Manufacturing and Controls (CMC) groups. They are in the process of evaluating these findings and will be finalizing their reviews on assessing the impact of using batch sizes lower than SUPAC-MR guidance and general criteria used by FDA.

## 2 Question-Based Review (QBR)

### 2.1 General Attributes of the Drug and Drug Product

Both saxagliptin and metformin are approved products and are marketed by Bristol Myers Squibb. Saxagliptin (Onglyza™) has been approved in the United States in 2009 under NDA 22350. Saxagliptin is a highly potent, selective, reversible, competitive, dipeptidyl peptidase-4 (DPP4) inhibitor and is currently marketed as immediate release tablets of 2.5 mg and 5 mg dose strengths.

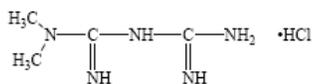
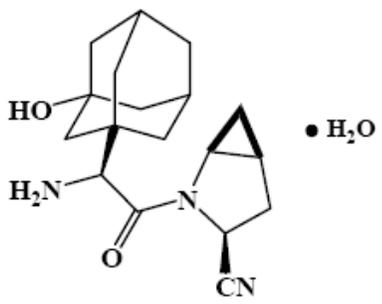
Metformin hydrochloride is an oral anti-hyperglycemic agent used in the treatment of type-2 diabetes mellitus (T2DM). Metformin hydrochloride XR is an extended release (XR) tablet formulation of metformin hydrochloride approved under NDA 21202 and is currently marketed by Bristol-Myers Squibb under the brand name Glucophage® XR (extended release tablets of metformin hydrochloride). In the United States, Glucophage® XR is marketed in the 500 and 750 mg dose strengths and is approved for doses up to 2000 mg to be taken once daily with the evening meal.

Saxagliptin and metformin fixed dose combination tablet (b) (4). Fixed dose combination (FDC) tablets of saxagliptin with metformin XR have been developed in the following 3 different dose strengths to allow once-daily dosing of saxagliptin with metformin at total daily doses up to 5 mg saxagliptin and 2000 mg metformin (i.e., the highest recommended once-daily doses of saxagliptin and metformin):

- ✓ 5 mg saxagliptin/500 mg metformin XR
- ✓ 5 mg saxagliptin/1000 mg metformin XR
- ✓ 2.5 mg saxagliptin/1000 mg metformin XR

#### 2.1.1 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

	Metformin HCl	Saxagliptin
<b>Description</b>	White or almost white crystals	White to light yellow or light brown powder
<b>Chemical Name</b>	<i>N,N</i> -Dimethylimidodicarbonimidic diamide hydrochloride	(1 <i>S</i> ,3 <i>S</i> ,5 <i>S</i> )-2-((2 <i>S</i> )-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate
<b>Molecular Formula</b>	C <sub>4</sub> H <sub>12</sub> ClN <sub>5</sub>	C <sub>18</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub> • H <sub>2</sub> O

<b>Molecular Weight</b>	165.6	333.43
<b>Structural Formula</b>		
<b>Solubility</b>	Freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.	Saxagliptin is sparingly soluble in water, soluble in acetone, methanol, isopropyl alcohol.

**Formulation:**



(b) (4)



(b) (4)

separate bioequivalence studies were conducted for the 500 mg and 1000 mg metformin XR FDCs. The composition of the formulations for the fixed dose combination tablets is shown in Appendix 4.1:

**2.1.2 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and Biopharmaceutics of the drug?**

The clinical Phase 3 studies used metformin XR (500 mg) manufactured in Evansville or metformin immediate release (IR) formulation, but the proposed to-be-market products for FDC tablets are manufactured in Mt. Vernon. As shown in Figure 5, sponsor conducted five BE studies (green line and red lines in the figure) to bridge the proposed to-be-marketed formulation to the formulations used in the clinical trials.

**Figure 5: Sponsor development program linking the proposed to-be-marketed formulation to the currently approved formulation.**

However, during the pre-NDA meeting, the Agency identified that there was no direct bridging between the proposed market formulation (5 mg/500 mg FDC manufactured in Mt. Vernon) and metformin XR formulation (500 mg manufactured in Evansville), which was used in clinical trials and previously found to be safe and efficacious (blue dotted lines in the Figure 5). Therefore, Agency then asked the Sponsor to conduct two pivotal bioequivalence studies study in order to provide a direct link for the to-be-marketed FDC product (manufactured in Mt Vernon, IN) to the marketed Glucophage<sup>®</sup> XR (Evansville, IN) tablets.

Sponsor conducted and submitted two additional bioequivalence studies:

- 1) CV181111 to link for the to-be-marketed 5 mg saxagliptin/500 mg metformin XR FDC to the marketed component 500 mg Glucophage<sup>®</sup> XR
- 2) CV181112, a single dose BE evaluation of the 5 mg saxagliptin/1000 mg metformin XR FDC to provide a direct link for the to-be-marketed 5 mg saxagliptin/1000 mg metformin XR FDC to 2 x 500 mg tablets of marketed Glucophage<sup>®</sup> XR

**Reviewers Comment:** *The long term Phase 3 safety and efficacy trials were conducted with metformin IR co-administered with saxagliptin. Clinical study CV181066, a four week trial, was the only clinical trial submitted which was conducted using metformin XR co-administered with saxagliptin. To support the approval of FDC product, sponsor conducted BE studies comparing metformin XR and saxagliptin co-administered together to the FDC combination product. Metformin XR is acceptable to bridge the clinical program (which was conducted with metformin IR) because the safety and efficacy bridging of metformin XR and metformin IR is well established.*

### **2.1.3 What is the proposed therapeutic indication and route of administration?**

Fixed dose combination tablets of saxagliptin and metformin are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

FDC product is intended to be administered orally once daily with evening meal.

### **2.1.4 Is any DSI (Division of Scientific Investigation) inspection requested for any of the clinical studies?**

Yes. The DSI inspection was requested for one pivotal BE study (Study CV181112). DSI inspection found no major issues upon the audit of the clinical and analytical portion of the BE study. Please refer to DSI memo DARRTS dated 10/08/2010 for further details.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The safety and efficacy of the FDC product, is supported by Phase 3 trials that were submitted under saxagliptin NDA (NDA 22350). In the Phase 3 trials the saxagliptin and metformin was found to be safe and efficacious when they were co-administered together.

FDC tablets of saxagliptin with metformin XR have been developed in the following 3 different dose strengths to allow once-daily dosing of saxagliptin with metformin at total daily doses up to 5 mg saxagliptin and 2000 mg metformin (i.e., the highest recommended once-daily doses of saxagliptin and metformin):

- ✓ 5 mg saxagliptin/500 mg metformin XR
- ✓ 5 mg saxagliptin/1000 mg metformin XR
- ✓ 2.5 mg saxagliptin/1000 mg metformin XR

The clinical pharmacology program for the FDC product consists of two pivotal and five supporting clinical pharmacology studies. Two pivotal clinical pharmacology studies evaluated the bioequivalence (BE) between the FDC product and saxagliptin and metformin XR tablets when administered together. The BE was assessed at two different dose strengths of FDC product (5/500mg, 500/1000mg as saxagliptin/metformin FDC) and individual components co-administered together (5 mg saxagliptin + 500 mg metformin and 5 mg saxagliptin + 1000 mg metformin).

The pivotal studies also evaluated the effect of food and steady state pharmacokinetics of saxagliptin and metformin when administered as FDC product. The proposed FDC product was not studied in the Phase 3 trials. Thus, pivotal BE studies provided the link between the formulations utilized in Phase 3 trials and the proposed to-be-marketed formulation. This review will focus on the following two pivotal Clinical Pharmacology studies.

- ❖ Study CV181111: Bioequivalence study of the fixed-dose combination of 5 mg saxagliptin and 500 mg metformin XR Tablet (manufactured in Mt Vernon, IN) relative to equivalent dose strengths of the currently marketed individual component formulations of 5 mg saxagliptin tablet and 500 mg metformin XR tablet co-administered to healthy subjects in a fed condition. The study also evaluated the effect of food on the FDC product. This study was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects.
- ❖ Study CV181112: Bioequivalence study of the fixed-dose combination of 5 mg saxagliptin and 1000 mg metformin XR (manufactured in Mt Vernon, IN) relative to 5 mg of saxagliptin and 2 × 500 mg metformin XR co-administered to healthy subjects in the fed state. This study also evaluated the single dose and steady state pharmacokinetics of saxagliptin and metformin when administered as FDC

tablets. This study was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects.

Five supporting clinical pharmacology studies that were submitted with this NDA are shown in Table 1 and the synopsis of these studies can be found in APPENDIX 4.3.

**Table 1: Supporting Clinical Pharmacology Studies of Saxagliptin/Metformin XR FDC Tablets Submitted Under this NDA**

Study Number	Type of Study
CV181074	Fed Dose Strength Equivalence - 2 x 500 mg metformin XR vs. 1 x 1000 mg metformin XR
CV181060	Fed Bioequivalence and Food Effect - 5 mg saxagliptin/500 mg metformin XR FDC
CV181076	Fed Bioequivalence and Food Effect - 5 mg saxagliptin/1000 mg metformin XR FDC
CV138098	Fasted and Fed Bioequivalence - Manufacturing site change for 500 mg metformin XR tablet core
CV138100	Fasted and Fed Bioequivalence - Manufacturing site change for 1000 mg metformin XR tablet core

**2.2.2 Are the active moieties in the plasma appropriately identified and measured?**

Yes. Please refer to the section 2.6 for details of the bioanalytical method.

**2.2.3 What is the steady-state pharmacokinetics of the new 5 mg/1000 mg strength tablets?**

Pivotal BE study (CV181112) characterized the single dose and steady state pharmacokinetics of saxagliptin and metformin following the administration of the 5 mg saxagliptin/1000 mg metformin XR FDC tablet (manufactured in Mt Vernon, Indiana) in the fed state in healthy subjects. For steady state assessment FDC tablet consisting of 5 mg saxagliptin and 1000 mg metformin XR (Mt Vernon, Indiana) administered orally once daily for 4 days under fed conditions.

Peak and total exposures of saxagliptin after QD dosing for 4 days with the FDC tablet were unchanged from the exposures observed after single dosing. Peak exposure of metformin, saxagliptin and its metabolite BMS 510849 after QD dosing for 4 days was similar to the peak exposure observed after a single dose.

**Table 2: Geometric Means (CV) for the Pharmacokinetic Parameter of Saxagliptin, Metformin and Saxagliptin Metabolite (BMS 510849) Following Single and Multiple Dose Administration of FDC Product Under Low Fat Meal Condition.**

Pharmacokinetic Parameters	Geometric Mean (CV)	
	Single Dose	Multiple Dose (Day =4)
<b>Saxagliptin</b>		
<b>C<sub>max</sub> (ng/mL)</b>	24.9 (27)	24.7 (28)
<b>AUC<sub>last</sub> (hr*ng/mL)</b>	101.2 (22)	-
<b>AUC<sub>0-inf</sub> (hr*ng/mL)</b>	103.1 (22)	-
<b>AUC<sub>0-τ</sub> (hr*ng/mL)</b>	-	97.2 (21)
<b>T<sub>max</sub>(hr)</b>	1.50 (0.50, 3.00)	1.29 (0.50, 2.00)
<b>T<sub>1/2</sub> (hr)</b>	8.85 (4.47)	-
<b>C<sub>min</sub> (ng/mL)</b>	-	0.28 (0.10)
<b>Metformin</b>		
<b>C<sub>max</sub> (ng/mL)</b>	1056 (21)	943 (27)
<b>AUC<sub>last</sub> (hr*ng/mL)</b>	8378 (37)	-
<b>AUC<sub>0-inf</sub> (hr*ng/mL)</b>	8735 (37)	-
<b>AUC<sub>0-τ</sub> (hr*ng/mL)</b>	-	8792 (42)
<b>T<sub>max</sub>(hr)</b>	5.00 (3.00, 8.00)	5.00 (4.00, 9.00)
<b>T<sub>1/2</sub> (hr)</b>	12.94 (6.74)	-
<b>C<sub>min</sub> (ng/mL)</b>	-	105.04 (88.09)
<b>Saxagliptin Metabolite (BMS 510849)</b>		
<b>C<sub>max</sub> (ng/mL)</b>	48.9 (32)	58.4 (23)
<b>AUC<sub>last</sub> (hr*ng/mL)</b>	281.5 (24)	-
<b>AUC<sub>0-inf</sub> (hr*ng/mL)</b>	289.3 (23)	-
<b>AUC<sub>0-τ</sub> (hr*ng/mL)</b>	-	313.9 (17)
<b>T<sub>max</sub>(hr)</b>	2.00 (1.50, 5.03)	2.00 (1.50, 3.00)
<b>T<sub>1/2</sub> (hr)</b>	13.82 (2.52)	-
<b>C<sub>min</sub> (ng/mL)</b>	-	1.51 (0.22)

**Reviewers Comment:** Mean total exposures ( $AUC_{0-\tau}$ ) of saxagliptin and its metabolite BMS-510849 over the dosing interval once daily at steady state were comparable to the total exposures ( $AUC_{0-inf}$ ) after single dosing. This is consistent with the saxagliptin NDA 22350 where multiple dose administration of saxagliptin showed no drug accumulation. Also, mean peak exposure of metformin for the FDC tablet at steady state was approximately 90% of the mean peak exposure of the FDC tablet after single dosing. This is also consistent with the currently approved Glucophage<sup>®</sup> XR tablet which has no accumulation following multiple dosing.

## 2.3 Intrinsic Factors

### 2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No intrinsic factors were evaluated in this NDA. The clinical pharmacology information in the proposed FDC product label is coming from the product label of the approved individual drug moieties of saxagliptin and metformin.

## 2.4 Extrinsic Factors

### 2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

#### 2.4.1.1 Drug-Drug Interaction

No drug-drug interaction study between metformin and saxagliptin has been conducted under this NDA. However, in saxagliptin NDA 22350 it has been demonstrated that there is no drug-drug interaction between saxagliptin and metformin (Study CV181017). In drug-drug interaction study saxagliptin 100 mg dose had no significant effect on the pharmacokinetic of metformin. However, metformin at 1000 mg dose decreased the  $C_{max}$  of saxagliptin by 21%, but did not alter the overall exposure  $AUC_{0-t}$  or  $AUC_{0-inf}$ . The decrease in metformin  $C_{max}$  was not considered to be clinically meaningful (For further details, refer to Clinical Pharmacology Review of NDA 22350 by Dr. Jayabharathi Vaidyanathan DAARTS date 05/06/2009).

**Reviewer's Comment:** Based on their respective absorption, disposition, metabolism, and elimination properties, no drug-drug interaction is expected when saxagliptin and metformin are co-administered. This is supported by the study results conducted under NDA 22350 where when saxagliptin and metformin are co-administered no clinical significant changes in the PK of either drugs was observed.

**2.4.1.2 What is the effect of Food on the FDC product?**

The effect of food on the FDC product was evaluated in the Study CV181111. The study was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects to evaluate the rate and extent of absorption of 5 mg saxagliptin/500 mg metformin XR FDC under fed (low fat meal 324 kcal) and fasted state. No food effect on the pharmacokinetics of saxagliptin or metformin was observed when the FDC tablet was administered under fed versus fasted conditions (**Table 3**). The 90% CIs of the ratios of geometric LS means for the saxagliptin and metformin components of the FDC tablet were entirely contained within 0.80 to 1.25 (**Table 4**).

**Table 3: Geometric Means for the Pharmacokinetic Parameter of Saxagliptin and Metformin following administration of FDC product in Fed (Low Fat Meal) and Fasted Conditions.**

Pharmacokinetic Parameters	Geometric Mean (CV)	
	Test (Fed)	Reference (Fasted)
<b>Saxagliptin</b>		
C <sub>max</sub> (ng/mL)	26.2 (29)	27.6 (30)
AUC <sub>last</sub> (hr*ng/mL)	106.9 (24)	99.0 (23)
AUC <sub>inf</sub> (hr*ng/mL)	108.7 (24)	100.8 (22)
T <sub>max</sub> (hr)	1.50 (0.50, 4.00)	0.50 (0.17, 3.00)
T <sub>1/2</sub> (hr)	8.6 (3.04)	9.2 (3.91)
<b>Metformin</b>		
C <sub>max</sub> (ng/mL)	567.9 (26)	632.4 (29)
AUC <sub>last</sub> (hr*ng/mL)	4866 (42)	4747 (27)
AUC <sub>inf</sub> (hr*ng/mL)	5114 (44)	4918 (28)
T <sub>max</sub> (hr)	5.00 (3.00, 8.00)	4.00 (3.00, 6.00)
T <sub>1/2</sub> (hr)	12.6 (7.05)	14.9 (7.40)
<b>Saxagliptin Metabolite (BMS 510849)</b>		
C <sub>max</sub> (ng/mL)	47.0 (30)	46.9 (31)
AUC <sub>last</sub> (hr*ng/mL)	278.5 (26)	273.7 (23)
AUC <sub>inf</sub> (hr*ng/mL)	285.6 (25)	280.9 (23)
T <sub>max</sub> (hr)	2.00 (1.50, 5.00)	1.50 (0.75, 4.00)
T <sub>1/2</sub> (hr)	13.7 (1.72)	14.0 (1.33)

**Table 4: Geometric Means, Ratios of Geometric Means and Their 90% Confidence Intervals for the Pharmacokinetic Parameter of Saxagliptin and Metformin following administration of FDC product in Fed (Low Fat Meal) and Fasted Conditions.**

Pharmacokinetic Parameters	Geometric Mean		Ratio (%) (Test/Reference)	(90% Confidence Interval)	
	Test (Fed)	Reference (Fasted)		Lower	Upper
<b>Saxagliptin</b>					
$C_{max}$ (ng/mL)	26.21	27.63	0.95	0.87	1.03
$AUC_{last}$ (hr*ng/mL)	106.89	98.99	1.08	1.05	1.11
$AUC_{inf}$ (hr*ng/mL)	108.74	100.84	1.08	1.05	1.10
<b>Metformin</b>					
$C_{max}$ (ng/mL)	567.85	632.39	0.89	0.83	0.96
$AUC_{last}$ (hr*ng/mL)	4866.2	4746.8	1.02	0.95	1.10
$AUC_{inf}$ (hr*ng/mL)	5072.3	5023.3	1.01	0.91	1.11

*Reviewers Comments: No effect of food was seen when FDC product was administered under low fat meal condition. The meal condition used in the study was a low fat low calorie diet which consists of standard breakfast of 324 total kcal (11.1% protein, 10.5% fat, and 78.4% carbohydrate).*

*The effect of high fat meal was not evaluated in this NDA. The sponsor's rationale for using low fat meal is that the target diabetic patient population is usually on diet and calorie control and thus low fat low calorie meal represents the actual clinical scenario.*

*Although the sponsor did not evaluate the impact of high fat meal on the FDC product, this reviewer is not recommending any additional study with high fat meal because of the following reasons:*

1) *The FDC product employs the same manufacturing technology as used in the single component.*

a. *The FDC product consists*

(b) (4)



- 2) *The effect of high fat meal on saxagliptin and metformin XR has been studied in saxagliptin and metformin NDA's, respectively. High fat meal resulted in increase in exposure for both metformin XR and saxagliptin, however no dose adjustment is recommended with food.*
  - a. *In case of metformin, exposure from Glucophage® XR tablets increased by approximately 50% when given with high fat food. High fat meal and low fat meal had a similar effect. The current dosing recommendation for Glucophage® XR is once daily with evening meal.*
  - b. *In case of saxagliptin, exposure from Onglyza tablet increased by 27% when given with a high fat meal as compared to fasted conditions. The current dosing recommendation is with or without food.*
- 3) *In the current food interaction study, the impact of low fat meal on FDC tablet is lower than those observed in individual component product of FDC tablet. So, the impact of high fat meal is not expected to be higher than the individual component product of FDC tablet.*

## 2.5 General Biopharmaceutics

### 2.5.1 What is the impact of fixed dose combination formulation, containing saxagliptin and metformin XR as a tablet, on systemic exposures of saxagliptin and metformin?

The formulation effect of FDC product was assessed in two pivotal bioequivalence studies (CV181111 and CV181112) comparing the rate and extent of absorption of saxagliptin and metformin when administered as FDC product or saxagliptin and metformin XR tablets administered together.

Study CV181111 was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects. This study evaluated the rate and extent of absorption of saxagliptin and metformin from the to-be-marketed 5 mg saxagliptin/500 mg metformin XR FDC formulation manufactured at the BMS facilities at Mt Vernon, Indiana, relative to the equivalent dose strengths of the currently marketed individual component formulations (5 mg saxagliptin and 500 mg metformin XR) under low fat meal condition (324 kcal).

The 90% CIs of the ratios of geometric LS means for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  were entirely contained within 0.80 to 1.25 for both saxagliptin and metformin (Table 5). Therefore, the FDC tablet (Mt Vernon) was bioequivalent to the co-administered 5 mg saxagliptin and 500 mg metformin XR tablets (Evansville) when administered under low fed conditions.

**Table 5: Geometric Mean, Ratios of Geometric Means (Treatment B/ Treatment A) and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Saxagliptin and Metformin Following Co-administration of Saxagliptin 5 mg and Metformin XR 500 mg (Treatment A) and FDC Product (Treatment B) under Low Fat Meal Condition.**

Pharmacokinetic Parameters	Geometric Mean		Ratio (%) (Test/Reference)	(90% Confidence Interval)	
	Treatment A	Treatment B		Lower	Upper
<b>Saxagliptin</b>					
$C_{max}$ (ng/mL)	25.68	26.21	1.021	0.940	1.109
$AUC_{last}$ (hr*ng/mL)	102.84	106.89	1.039	1.011	1.068
$AUC_{inf}$ (hr*ng/mL)	104.65	108.74	1.039	1.011	1.068
<b>Metformin</b>					
$C_{max}$ (ng/mL)	608.41	567.85	0.933	0.865	1.007
$AUC_{last}$ (hr*ng/mL)	5287.1	4866.2	0.920	0.854	0.992
$AUC_{inf}$ (hr*ng/mL)	5542.2	5072.9	0.915	0.836	1.002

CV181112 was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects. This study evaluated the rate and extent of absorption of saxagliptin and metformin from the to-be-marketed 5 mg saxagliptin/1000 mg metformin XR FDC tablet relative to the equivalent dose strengths of the currently marketed individual component formulations (5 mg saxagliptin plus two 500 mg metformin XR) administered under low fat meal (324 kcal).

The 90% CIs of the ratios of geometric least squares (LS) means for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  of saxagliptin and metformin were all entirely contained within 0.800 to 1.250 (Table 6). Therefore, the FDC tablet was bioequivalent to the co-administered 5 mg saxagliptin plus two 500 mg metformin XR tablets with respect to total and peak exposures of saxagliptin and metformin when administered under fed conditions.

**Table 6: Geometric Mean, Ratios of Geometric Means (Treatment B/ Treatment A) and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Saxagliptin and Metformin Following Co-administration of Saxagliptin 5 mg and Metformin XR 2x500 mg (Treatment A) and FDC Product (Treatment B) under Low Fat Meal Condition.**

Pharmacokinetic Parameters	Geometric Mean		Ratio (%) (Test/Reference)	(90% Confidence Interval)	
	Treatment A	Treatment B		Lower	Upper
<b>Saxagliptin</b>					
$C_{max}$ (ng/mL)	24.88	24.85	0.999	0.948	1.053
$AUC_{last}$ (hr*ng/mL)	97.72	101.16	1.035	1.009	1.062
$AUC_{inf}$ (hr*ng/mL)	98.61	103.05	1.045	1.025	1.065
<b>Metformin</b>					
$C_{max}$ (ng/mL)	1151.2	1055.9	0.917	0.859	0.980
$AUC_{last}$ (hr*ng/mL)	9246.8	8377.8	0.906	0.848	0.968
$AUC_{inf}$ (hr*ng/mL)	9746.3	8713.4	0.894	0.833	0.959

Thus, the bioequivalence study with low fat meal bridges the use of FDC product to that to Phase 3 clinical program

**Reviewers Comment:** *When administered under fed conditions, the 5 mg saxagliptin/1000 mg metformin XR FDC tablet (Mt Vernon, Indiana) was bioequivalent to the co-administered 5 mg saxagliptin (Mt Vernon, Indiana) plus two 500 mg metformin XR tablets (Evansville, Indiana). In this NDA FDC tablets of saxagliptin with metformin XR have been developed in the following 3 different dose strengths*

- ✓ 5 mg saxagliptin/500 mg metformin XR
- ✓ 5 mg saxagliptin/1000 mg metformin XR
- ✓ 2.5 mg saxagliptin/1000 mg metformin XR

*Bioequivalence studies were conducted with the FDC product containing 5 mg saxagliptin. No clinical bioequivalence study was conducted for the 2.5 mg saxagliptin/1000 mg metformin XR FDC* (b) (4)

**2.5.2 What is the batch size of the FDC formulation used in the pivotal BE studies CV181111 and CV181112?**

Table 7 shows the tablet batch sizes used in the pivotal BE studies CV181111 and CV181112. The batch sizes used for the FDC tablets are 12,705 and 9,100 for studies CV181111 and CV181112, respectively.

**Table 7: Batch size of the tablets used in pivotal BE studies**

Study No.	Product Identification No.	Drug Product Batch No.	Dosage Form, Strength	Date of Manufacture	Batch Size (Tablets)
CV181-111	0003-4215-21	9D4707B	BMS-477118-11 Film coated tablet, 5mg	6-April-2009	(b) (4)
	0087-6063-13	8L3022A	Glucophage®XR, 500 mg	11-Nov-2008	
	477118-K999-142	9L50239	Saxagliptin/metformin hydrochloride extended release, 5 mg/500 mg tablet	30-Oct-2009	
CV181-112	0003-4215-21	9D4707B	BMS-477118-11 Film coated tablet, 5mg	6-April-2009	
	0087-6063-13	8L3022A	Glucophage®XR, 500 mg	11-Nov-2008	
	477118-K999-140	9L51087	Saxagliptin/metformin hydrochloride extended release, 5 mg/1000 mg tablet	23-Nov-2009	

**Reviewer’s Comment:** The batch sizes of the formulation that were utilized in pivotal bioequivalence studies, CV181111 and CV181112, do not meet the biobatch size criteria of 10% or greater than that of the proposed commercial production batch or at least 100,000 units, whichever is greater. These criteria are stated in guidance for industry on 1) scale-up and post approval changes: chemistry, manufacturing, and controls; *In vitro* dissolution testing and *in vivo* bioequivalence documentation (SUPAC MR) and 2) guidance for industry on clozapine tablets: *in vivo* bioequivalence and *in vitro* dissolution testing. In this NDA, the proposed commercial batch size is (b) (4) tablets and the sponsor used batch sizes of (b) (4) in trials CV181111 and CV181112, respectively. These batch sizes do not meet the biobatch criteria for the pivotal BE studies, (b) (4).

Sponsor was also aware of this requirement of the batch size, which is evident from their October 24, 2008, submission under IND 76,500 where the sponsor stated:

*“BMS recognizes that the clinical batch size for Saxa 5/Met XR 500 did not meet the 10% of commercial scale or 100,000 units rule. In section IV.1 of the briefing package, a justification for waiver to repeat the BE study on a Saxa 5/Met XR 500 batch, manufactured at commercial scale or 10% of the commercial scale, is provided.”*

This reviewer is also aware of the Agency’s communication dated Feb 19, 2009, with the Sponsor in which Agency agreed on not repeating the BE study with 5/500 XR

manufactured at commercial scale size. The Agency's response to the Sponsor is stated below:

*Question 3: Does the Agency concur with BMS justification and that repeating the BE study with 5/500 XR manufactured at commercial scale or 10% of the commercial scale is not needed?*

*FDA Response: You do not need to repeat the BE study as long as you meet the Scale-up and Post-Approval Changes for Modified Release Solid Orals (SUPAC MR) requirement for Scale up and show that the dissolution profiles of the reduced size batch are similar to the full size commercial batch. Refer to the Guidance for Industry titled "SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (<http://www.fda.gov/cder/guidance/1214fnl.pdf>) for the required data to be submitted.*

This reviewer also considered whether the response from the Agency to the question 3 above impacts the current recommendation from clinical pharmacology on this NDA. In IND meeting response dated February 19, 2009, Agency agreed with the sponsor in not repeating BE studies, even though they did not meet the biobatch size criteria, as long as they meet the SUPAC MR guidance requirements. In this reviewer's opinion, this response, however, may not be applicable to the biobatch size concerns on the pivotal BE studies, CV181111 and CV181112, for the following reasons:

- 1) In the current submission, the pivotal BE studies, CV181111 and CV181112, are the only studies that provide the bridge to the efficacy and the safety results of this new FDC product to the approved products.
- 2) The Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In vitro Dissolution Testing and In Vivo Bioequivalence Documentation (SUPAC-MR) guidance states the following for the changes in the batch size: "***Postapproval changes in the size of a batch from pivotal/pilot scale biobatch material to larger or smaller production batches call for submission .....***.....***the application.***" Thus, based on the above paragraph on changes in batch size, this reviewer believes that the SUPAC guidance with respect to batch size changes is applicable to pivotal/pilot scale biobatch material, which according to guidance is a minimum of one tenth of full production of 100,000 tablets, whichever is larger.

These findings on the batch sizes used in the pivotal BE studies have been communicated to the ONDQA Biopharmaceutics and CMC groups. They are in the process of evaluating these findings and will be finalizing their reviews on assessing the impact of using batch sizes lower than SUPAC-MR guidance and general criteria used by FDA.

### **2.5.3 What is the dose dumping potential of FDC product?**

The influence of ethanol on the release of metformin from FDC product was assessed in *in vitro* dissolution studies with 5 mg saxagliptin/500 mg metformin XR and 5 mg saxagliptin/1000 mg metformin XR FDC tablets. The range of alcohol concentrations in the dissolution medium ranged from 5 to 25%. The sponsor claimed that for both strengths, 5 mg saxagliptin/500 mg metformin XR and 5 mg saxagliptin/1000 mg metformin XR, the dissolution release profile of extended release metformin did not result in dose dumping or accelerated release of metformin in the presence of alcohol. For further details, refer to Biopharmaceutics review by Dr. Houda Mahayni.

## **2.6 Analytical**

### **2.6.1 How are the active moieties identified and measured in the plasma/serum?**

Concentrations of saxagliptin, its metabolite BMS 510849 and metformin in human plasma were measured using validated high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS).

### **2.6.2 What bioanalytical methods are used to assess concentrations?**

Concentrations of metformin in human plasma were analyzed according to (b) (4) LCMS 153.5 V 1.02, entitled “Quantitation of Metformin in Human Plasma via HPLC with MS/MS Detection,” which was validated under Project Code “RQT2. Plasma samples, standards, or quality control (QC) samples were isolated through solid phase extraction prior to being analyzed via HPLC with MS/MS detection. An aliquot was injected onto Micro Mass Quattro Micro LC/MS/MS equipped with an HPLC column. The peak of m/z 130.25→71 metformin product ion was measured against the peak area of the m/z 136.40→77.10 product ion of the internal standard. The validated linear range for the assay for metformin in plasma was 2 ng/mL to 1,000 ng/mL.

Concentrations of saxagliptin and its metabolite BMS 510849 in human plasma were analyzed according to (b) (4) method validation report TNJR08-296. Plasma samples, standards, or quality control (QC) samples were isolated through solid phase extraction prior to being analyzed via HPLC with MS/MS detection. An aliquot was injected onto API 4000LC/MS/MS equipped with an HPLC column. The peak of m/z 316.3→180.3 saxagliptin product ion was measured against the peak area of the m/z 319.3→180.3 product ion of the internal standard. The validated linear range for the assay for saxagliptin in plasma was 1ng/mL to 100 ng/mL. For saxagliptin metabolite, BMS 510849, the peak of m/z 332.3→196.3 product ion was measured against the peak area of the m/z 335.3→196.3 product ion of the internal standard. The validated linear range for the assay for saxagliptin in plasma was 2 ng/mL to 200 ng/mL

A brief summary of the different bioanalytical methods used is shown in the Table 8 below. Accepted validation indicates that method met the FDA guidance “Bioanalytical Method Validation” recommendations, and was therefore acceptable.

**Table 8: Assay Validation Results for Saxagliptin and Metformin**

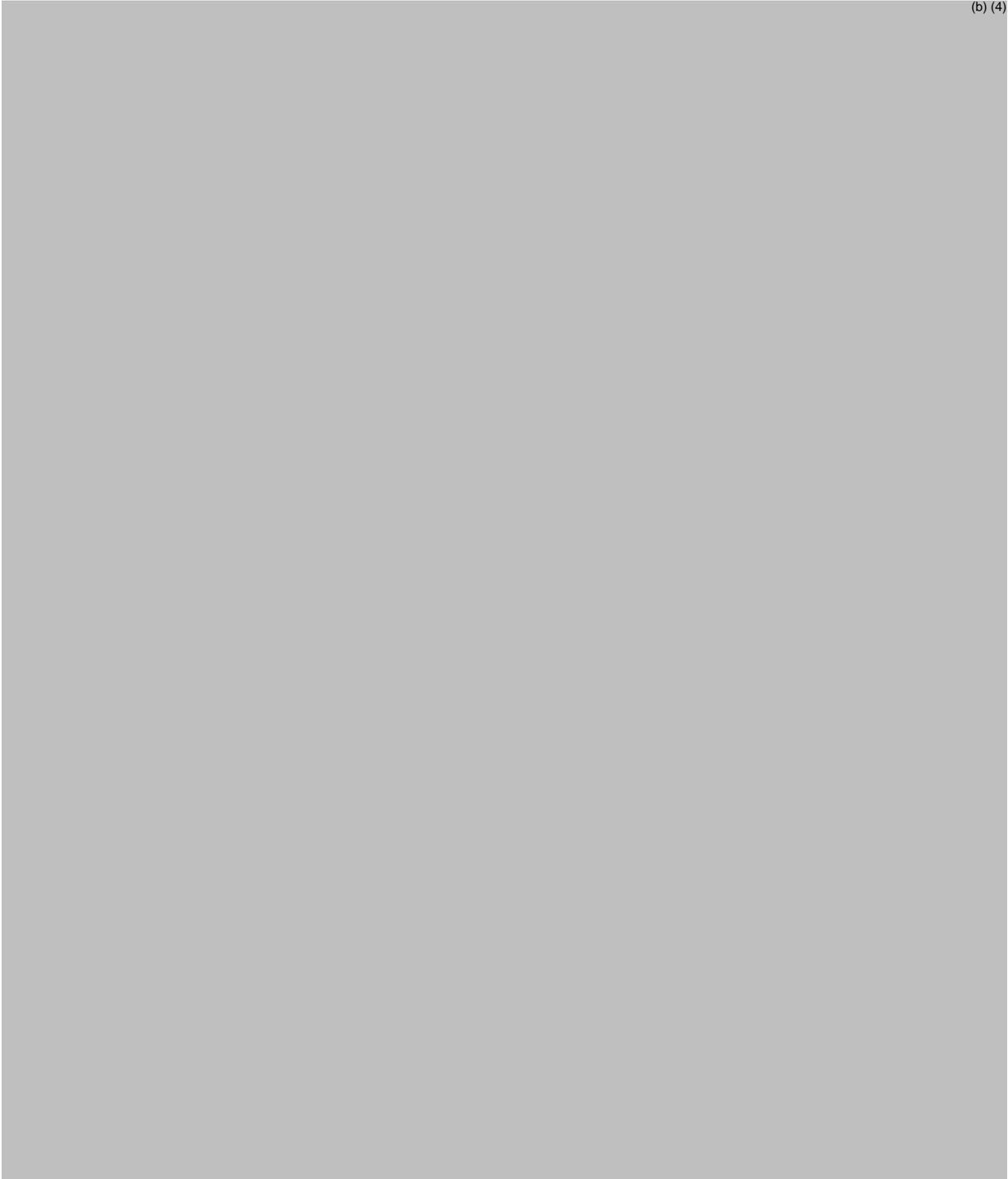
	<b>Metformin</b>	<b>Saxagliptin</b>
Standard Curve Range	2 ng/mL- 1000 ng/mL	1ng/mL-100 ng/mL
QC Sample Concentrations	2,6,12,60,200,750 ng/mL	1,3,10,40,80 ng/mL
Precision (%CV)	Intra-Assay: 0.975% to 5.85 % Inter-Assay: 3.03% to 6.02%	Intra-Assay: 2.7% to 4.6 % Inter-Assay: 0% to 6.1%
Accuracy (%)	Intra-Assay: 93.09% to 105.1% Inter-Assay: 96.63% to 102.47%	Intra-Assay: 102% to 111.7% Inter-Assay: 95.3% to 104%
Internal Standard	<b>Metformin-d<sub>6</sub></b> Lot No: V283P6	<b>BMS-477118-13CD<sub>2</sub></b>
Specificity	No Interference	No Interference
Recovery	~89.1-97.8% (Drug) ~86.9-95.2% (Internal Standard)	~68.3-74.6% (Drug) ~69.9-74.3 % (Internal Standard)
Stability	Benchtop Stability: 24 hours room temperature Freeze/ Thaw Stability: 3/5 FT Cycle Long Term Matrix Stability: 328 Days at -20°C	Benchtop Stability: 24 hours Freeze/ Thaw Stability: 3 FT Cycle Long Term Matrix Stability: 578 days -20°C

<sup>y</sup>Note: Data presented is based on the original validation report.

### 3 DETAILED LABELING RECOMMENDATION

The following are the labeling recommendations relevant to clinical pharmacology for NDA 200678. 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.

(b) (4)



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

4 APPENDIX

4.1 Composition of To-Be-Marketed Formulation at Different Dose Strengths

Bristol-Myers Squibb Company

BMS-477118

saxagliptin

**Table 3.2.P.1.T02: Tablet Composition of Saxagliptin/Extended-Release Metformin Hydrochloride Film-Coated Tablet, 5 mg/500 mg (Saxa 5/Met XR 500)**

	Component	Quality Standard	Function	Quantity per Unit Dose (mg/tablet)
(b) (4) Tablet	Metformin Hydrochloride (b) (4)	In-house	Active	502.5
	Carboxymethylcellulose Sodium (b) (4)	USP	(b) (4)	(b) (4)
	Hypromellose 2208	USP, Ph.Eur.		
	Hypromellose 2910	USP, Ph.Eur.		
	Microcrystalline Cellulose	NF, Ph.Eur.		
	Magnesium Stearate	NF, Ph.Eur.		

Bristol-Myers Squibb Company

BMS-477118

saxagliptin

**Table 3.2.P.1.T02: Tablet Composition of Saxagliptin/Extended-Release Metformin Hydrochloride Film-Coated Tablet, 5 mg/500 mg (Saxa 5/Met XR 500)**

Component	Quality Standard	Function	Quantity per Unit Dose (mg/tablet)
(b) (4)			
Total Tablet Weight			Ca. 1180.5
q.s. = quantity sufficient	NA = not applicable	Ca. = Calculated average	(b) (4)

**Table 3.2.P.1.T03: Tablet Composition of Saxagliptin/Extended-Release Metformin Hydrochloride Film-Coated Tablet, 5 mg/1000 mg (Saxa 5/Met XR 1000)**

	Component	Quality Standard	Function	Quantity per Unit Dose (mg/tablet)
(b) (4) Tablet	Metformin Hydrochloride (b) (4)	In-house	Active	1005.0
	Carboxymethylcellulose Sodium (b) (4)	USP	(b) (4)	(b) (4)
	Hypromellose 2208	USP, Ph.Eur.		
	Magnesium Stearate	NF, Ph.Eur.		
	(b) (4)	(b) (4)		
Total Tablet Weight				Ca. 1653.5

Bristol-Myers Squibb Company

BMS-477118

Saxa/Met XR

q.s. = quantity sufficient

NA = not applicable

Ca. = Calculated average

(b) (4)



Bristol-Myers Squibb Company

BMS-477118

Saxa/Met XR

**Table 3.2.P.1.T04: Tablet Composition of Saxagliptin/Extended-Release Metformin Hydrochloride Film-Coated Tablet, 2.5 mg/1000 mg (Saxa 2.5/Met XR 1000)**

	Component	Quality Standard	Function	Quantity per Unit Dose (mg/tablet)
(b) (4) Tablet	Metformin Hydrochloride (b) (4)	In-house	Active	1005.0
	Carboxymethylcellulose Sodium (b) (4)	USP	(b) (4)	(b) (4)
	(b) (4)	USP, Ph.Eur.		
	Hypromellose 2208	USP, Ph.Eur.		
	Magnesium Stearate	NF, Ph.Eur.		
(b) (4)				
Total Tablet Weight				Ca. 1651.0

q.s. = quantity sufficient

NA = not applicable

Ca. = Calculated average

Bristol-Myers Squibb Company

BMS-477118

Saxa/Met XR

(b) (4)



## 4.2 OCP FILING MEMO

### CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200678

NDA Number: 200678

Applicant: Bristol-Myers Squibb Stamp Date: December 29, 2010

Drug Name: Saxagliptin/Metformin NDA Type: Standard Hydrochloride

On initial overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
<b>Criteria for Refusal to File (RTF)</b>				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	Yes		The sponsor has submitted reports of two pivotal bioequivalence studies within 90 days of the NDA submission
2	Has the applicant provided metabolism and drug-drug interaction information?			The sponsor indicates that the relevant information was included in Onglyza NDA (22350)
<b>Criteria for Assessing Quality of an NDA</b>				
<b>Data</b>				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	Yes		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA
<b>Studies and Analyses</b>				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	Yes		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			NA
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			NA
8	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?			The sponsor stated in the proposed labeling that the dose of saxagliptin should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor, and it is the same as stated by labeling of Onglyza NDA 22350 (drug-drug interaction studies were conducted in NDA 22350).
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			(b) (4)

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR NDA 200678**

				(b) (4)
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		No	
11	Is the appropriate pharmacokinetic information submitted?	Yes		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes		
<b>General</b>				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	Yes		Reports of two pivotal bioequivalence studies have been submitted within 90 days of the NDA submission.
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	Yes		See comments above as 13
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	Yes		See comments above as 13
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes		See comments above as 13
17	Was the translation from another language important or needed for publication?		No	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Since the sponsor has submitted the reports of two pivotal bioequivalence studies within 90 days of the NDA submission, it is considered fileable.**

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.

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR NDA 200678**

Weili Huang, Ph.D.

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Reviewing Pharmacologist

Date

Sally Y. Choe, Ph.D.

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Team Leader/Supervisor

Date

The 7 page NDA Filing And Review Form that has been Withheld in Full immediately following this page can be seen by going to the document dated 3-31-10 of this ClinPharm section.

3

### 4.3 INDIVIDUAL STUDY REVIEW

#### 4.3.1 Bioequivalence Study CV181111

**Title:** Bioequivalence Study of the Fixed-Dose Combination of 5-mg Saxagliptin and 500-mg Metformin XR Tablet (Manufactured in Mt Vernon, IN) Relative to 5-mg Saxagliptin Tablet and 500-mg Metformin XR Tablet (Manufactured in Evansville, IN) Coadministered to Healthy Subjects in a Fed Condition

**Investigator and Study Center(s):**

Matthew Medlock, MD, at the PPD Phase I  
Clinic, 7551 Metro Center Drive, Suite 200, Austin, TX 78744

**Study Sponsor:**

Bristol-Myers Squibb  
Research and Development  
Route 206 & Province Line Road  
Princeton, NJ 08543

**Bioanalytical Analysis:**

(b) (4)

(b) (4)

Study Initiation Date: 03 December 2009  
Study Completion Date: 11 December 2009

<b>Name of Sponsor/Company:</b> Bristol-Myers Squibb	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b> Saxagliptin		
<b>Title of study:</b> Bioequivalence Study of the Fixed-Dose Combination of 5-mg Saxagliptin and 500-mg Metformin XR Tablet (Manufactured in Mt Vernon, IN) Relative to 5-mg Saxagliptin Tablet and 500-mg Metformin XR Tablet (Manufactured in Evansville, IN) Coadministered to Healthy Subjects in a Fed Condition		
<b>Investigator:</b> Matthew Medlock, MD		
<b>Study site:</b> PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin TX 78744		
<b>Publication (reference):</b> None		
<b>Studied period (years):</b> 03 December 2009 to 11 December 2009		<b>Phase of development:</b> 1
<p><b>Objective:</b> The primary objectives were to demonstrate bioequivalence (BE) of a 5-mg saxagliptin/500-mg metformin extended-release (XR) fixed-dose combination (FDC) tablet (manufactured in Mt Vernon, Indiana) to coadministered 5-mg saxagliptin and 500-mg metformin XR tablet (manufactured in Evansville, Indiana) in fed healthy subjects, and to assess the effect of a standard meal on the single-dose pharmacokinetics of an FDC tablet of 5-mg saxagliptin/500-mg metformin XR in healthy subjects.</p> <p>The secondary objectives were:</p> <ul style="list-style-type: none"> <li>to estimate the pharmacokinetics of the active metabolite of saxagliptin, BMS-510849, when saxagliptin was coadministered with a metformin XR tablet (manufactured in Evansville, Indiana) under the fed condition or in an FDC tablet with metformin XR (manufactured in Mt Vernon, Indiana) under the fasted or fed condition in healthy subjects; and</li> <li>to assess the safety and tolerability of 5-mg saxagliptin when coadministered with a 500-mg metformin XR tablet (manufactured in Evansville, Indiana) under the fed condition or in a FDC tablet with metformin XR (manufactured in Mt Vernon, Indiana) under the fasted or fed condition in healthy subjects.</li> </ul>		

<b>Name of Sponsor/Company:</b> Bristol-Myers Squibb	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b> Saxagliptin		

**Methodology:** This was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects. Subjects underwent screening evaluations to determine eligibility within 21 days before dosing. Subjects were admitted to the clinical facility the evening before dosing (Day -1). On Day 1 of Period 1, a total of 30 subjects who met all of the inclusion and none of the exclusion criteria were randomly assigned to 1 of 6 treatment sequences as follows:

Sequence	Period 1	Period 2	Period 3
ABC	A	B	C
ACB	A	C	B
BAC	B	A	C
BCA	B	C	A
CAB	C	A	B
CBA	C	B	A

Treatment A: single 5-mg saxagliptin tablet plus a single 500-mg metformin XR tablet (Evansville) administered orally under fed conditions.  
Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fed conditions.  
Treatment C: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fasted conditions.

On Day 1 of each period, each subject received 1 of 3 treatments according to the sequence determined by the randomization scheme. Treatments A and B were administered to subjects within 5 minutes of completing a standard meal (breakfast) in the morning. Treatment C was administered to subjects under fasted conditions in the morning. Subjects underwent at least a 3-day (72-hour) washout period before receiving the next scheduled dose. Subjects were discharged from the clinical facility on Day 3 of Period 3 after the pharmacokinetic sampling and all safety evaluations were completed.

**Number of subjects (planned and analyzed):** A total of 30 subjects were planned, enrolled, and completed the study. All 30 subjects were included in the pharmacokinetic and safety analyses.

<b>Name of Sponsor/Company:</b> Bristol-Myers Squibb	<b>Individual Study Table Referring to Part of the Dossier</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Saxagliptin	<b>Page:</b>	
<b>Diagnosis and main criteria for inclusion:</b> Healthy male and female subjects as determined by medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory tests, were eligible to participate in the study. Women of childbearing potential could not have been nursing or pregnant and must have been using an acceptable method of contraception. All women were required to have a negative pregnancy test within 24 hours before dosing.		
<b>Test product, dose, and mode of administration, batch number:</b> Saxagliptin/metformin XR FDC tablet (Mt Vernon, Indiana) consisting of 5-mg saxagliptin and 500-mg metformin XR, single dose administered orally under fed conditions, label batch number 9L45836; product batch number 9L50239.		
<b>Duration of treatment:</b> On Day 1 of Periods 1 through 3, subjects received either Treatment A (single 5-mg saxagliptin tablet plus a single 500-mg metformin XR tablet [Evansville] administered orally under fed conditions), Treatment B (single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR [Mt Vernon] administered orally under fed conditions), or Treatment C (single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR [Mt Vernon] administered orally under fasted conditions).		
<b>Reference therapy, dose, and mode of administration, batch number:</b> Saxagliptin 5-mg tablet (Mt Vernon, Indiana), single dose coadministered orally with metformin XR under fed conditions, label batch number 9K57859; product batch number 9D4707B. Metformin XR 500-mg tablet (Evansville, Indiana), single dose coadministered orally with saxagliptin under fed conditions, label batch number 9K57861; product batch number 8L3022A. Saxagliptin/metformin XR FDC tablet (Mt Vernon, Indiana) consisting of 5-mg saxagliptin and 500-mg metformin XR, single dose administered orally under fasted conditions, label batch number 9L45836; product batch number 9L50239.		
<b>Criteria for evaluation:</b> <u>Pharmacokinetics:</u> Blood samples for the determination of plasma concentrations of saxagliptin, its active metabolite BMS-510849, and metformin were collected before dosing, and at 0.167, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, and 48 hours after dosing.		

<b>Name of Sponsor/Company:</b> Bristol-Myers Squibb	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b>  Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b>  Saxagliptin		
<p>The following plasma pharmacokinetic parameters were calculated:</p> <p><math>AUC_{0-t}</math>            area under the plasma concentration versus time curve from time 0 to the time of the last quantifiable concentration (<math>C_t</math>)</p> <p><math>AUC_{0-inf}</math>            area under the plasma concentration versus time curve from time 0 extrapolated to infinity</p> <p><math>C_{max}</math>                observed maximum plasma concentration</p> <p><math>T_{max}</math>                time to achieve the observed maximum plasma concentration</p> <p><math>t_{1/2}</math>                 terminal half-life</p> <p><u>Safety:</u> Safety assessments included adverse events (AEs), clinical laboratory results, vital sign measurements, 12-lead ECG results, and physical examination findings.</p> <p><b>Statistical methods:</b> If there was no difference between the bioavailabilities of saxagliptin from the FDC tablet versus saxagliptin from coadministration of a saxagliptin tablet and a metformin XR tablet under fed conditions, then 24 subjects would have provided 99% power to conclude BE with respect to <math>C_{max}</math> and <math>AUC_{0-inf}</math>. If there was a 5% difference, then 24 subjects would have provided 94% and 99% power to conclude BE with respect to <math>C_{max}</math> and <math>AUC_{0-inf}</math>, respectively. If there was no difference between the bioavailabilities of metformin from the FDC tablet versus metformin from coadministration of a saxagliptin tablet and a metformin XR tablet under fed conditions, then 24 subjects would have provided 99% power to conclude BE with respect to <math>C_{max}</math> and <math>AUC_{0-inf}</math>. If there was a 5% difference, then 24 subjects would have provided 96% and 97% power to conclude BE with respect to <math>C_{max}</math> and <math>AUC_{0-inf}</math>, respectively.</p> <p><u>Pharmacokinetics:</u> Plasma concentration and pharmacokinetic parameter data were presented in data listings and summarized. Mean and individual plasma concentration versus scheduled time profiles were presented in figures on both linear and semilogarithmic scales.</p> <p>A linear mixed model with fixed factors for period and treatment and measurements within each subject as repeated measurements was performed on the natural logarithms of <math>AUC_{0-t}</math>, <math>AUC_{0-inf}</math>, and <math>C_{max}</math> to assess the differences between the test product (FDC tablet, fed [Treatment B]) and the reference product (coadministration of a separate 5-mg saxagliptin tablet and a 500-mg metformin XR tablet, fed [Treatment A]). Likewise, the differences were assessed between the FDC tablet, fed (Treatment B) and the FDC tablet, fasting (Treatment C). The geometric mean ratio of the</p>		

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<b>Name of Finished Product:</b>  Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b>  Saxagliptin		
<p>2 treatments for <math>AUC_{0-t}</math>, <math>AUC_{0-inf}</math>, and <math>C_{max}</math> was calculated by the antilog of the mean difference of the log-transformed values. A 90% confidence interval (CI) for the ratio was constructed as the antilog of the confidence limits of the mean difference. In addition, the geometric least squares (LS) means were computed for <math>AUC_{0-t}</math>, <math>AUC_{0-inf}</math>, and <math>C_{max}</math> by taking the antilog of the LS means from the analysis of variance on the natural logarithm of the corresponding pharmacokinetic parameters. The <i>P</i> values for treatment and period were presented.</p> <p>Bioequivalence was concluded if the 90% CIs for the test-to-reference (B/A) ratios of geometric means were entirely contained within 0.80 to 1.25 for both <math>AUC_{0-inf}</math> and <math>C_{max}</math>. The absence of food effect (<math>AUC_{0-inf}</math> and <math>C_{max}</math>) was concluded if the 90% CIs for the test-to-reference (B/C) ratios of geometric means were entirely contained within 0.80 to 1.25.</p> <p>The AUC ratio and <math>C_{max}</math> ratio estimates and their CIs were corrected for measured content using the method specified in the Canadian guidance for industry on conduct and analysis of bioavailability and BE studies. The potency-corrected results were presented in a summary table.</p> <p><b>Safety:</b> Subject disposition, demographics, and baseline characteristics were presented in data listings and summarized. All AE data were presented in data listings and treatment-emergent AE data were summarized by overall incidence, relationship to study drug, severity, serious AEs, and AEs leading to study drug discontinuation. Clinical laboratory results and vital sign measurements were presented in data listings and summarized. Change from Baseline in hematology and serum chemistry results were summarized and shifts from Baseline in urinalysis results were presented. Clinical laboratory results outside the reference range were flagged in the data listings and evaluated for clinical significance by the investigator. Physical examination findings, 12-lead ECG results, medical history, medical or surgical treatment procedures, admission criteria data, prior and concomitant medications, study drug administration, and meal records were presented in data listings.</p>		

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<b>Name of Finished Product:</b>  Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b>  Saxagliptin		

**SUMMARY - CONCLUSIONS**

**Pharmacokinetics:** The 90% CIs of the ratios of geometric LS means for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for both saxagliptin and metformin were all entirely contained within 0.80 to 1.25 for both the fed BE (Treatments B/A) and the food effect (Treatments B/C) assessments as shown in the following tables:

**Statistical Analysis of Plasma Pharmacokinetic Parameters of Saxagliptin**

<b>Parameter (unit)</b>	<b>Treatment<sup>a</sup></b>	<b>N</b>	<b>Geometric LS Mean</b>	<b>Ratio of Geometric LS Means and 90% CI of the Ratio (Treatments B/A or B/C)</b>
$AUC_{0-t}$ (ng·h/mL)	A	30	102.84	B/A: 1.039 (1.011, 1.068)
	B	30	106.89	
	C	30	98.99	B/C: 1.080 (1.051, 1.110)
$AUC_{0-inf}$ (ng·h/mL)	A	30	104.65	B/A: 1.039 (1.011, 1.068)
	B	30	108.74	
	C	30	100.84	B/C: 1.078 (1.049, 1.108)
$C_{max}$ (ng/mL)	A	30	25.68	B/A: 1.021 (0.940, 1.109)
	B	30	26.21	
	C	30	27.63	B/C: 0.949 (0.873, 1.031)

Abbreviations: CI, confidence interval; FDC, fixed-dose combination; LS, least squares; XR, extended release.

Note: An analysis of variance model was performed on the natural logarithms of AUCs and  $C_{max}$  with period and treatment as fixed effects and measurements within each subject as repeated measurements.

- <sup>a</sup> Treatment A: single 5-mg saxagliptin tablet plus a single 500-mg metformin XR tablet (Evansville) administered orally under fed conditions.  
 Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fed conditions.  
 Treatment C: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fasted conditions.

<b>Name of Sponsor/Company:</b> Bristol-Myers Squibb	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b> Saxagliptin		

Statistical Analysis of Plasma Pharmacokinetic Parameters of Metformin				
Parameter (unit)	Treatment <sup>a</sup>	N	Geometric LS Mean	Ratio of Geometric LS Means and 90% CI of the Ratio (Treatments B/A or B/C)
AUC <sub>0-t</sub> (ng·h/mL)	A	30	5287.1	B/A: 0.920 (0.854, 0.992)
	B	30	4866.2	B/C: 1.025 (0.951, 1.105)
	C	30	4746.8	
AUC <sub>0-inf</sub> (ng·h/mL)	A	25 <sup>b</sup>	5542.2	B/A: 0.915 (0.836, 1.002)
	B	24 <sup>b</sup>	5072.9	B/C: 1.010 (0.918, 1.111)
	C	23 <sup>b</sup>	5023.3	
C <sub>max</sub> (ng/mL)	A	30	608.41	B/A: 0.933 (0.865, 1.007)
	B	30	567.85	B/C: 0.898 (0.832, 0.969)
	C	30	632.39	

Abbreviations: CI, confidence interval; FDC, fixed-dose combination; LS, least squares; XR, extended release.  
Note: An analysis of variance model was performed on the natural logarithms of AUCs and C<sub>max</sub> with period and treatment as fixed effects and measurements within each subject as repeated measurements.

<sup>a</sup> Treatment A: single 5-mg saxagliptin tablet plus a single 500-mg metformin XR tablet (Evansville) administered orally under fed conditions.  
Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fed conditions.  
Treatment C: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fasted conditions.

<sup>b</sup> The smaller sample size for AUC<sub>0-inf</sub> was due to the inability to estimate K<sub>el</sub> for some of the subjects.  
Source: [End-of-Text Table 14.2.8](#).

The 90% CIs of the potency-corrected ratios of geometric LS means for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> showed similar results to the nominal strength analysis. Therefore, the FDC tablet was bioequivalent to the coadministered 5-mg saxagliptin and 500-mg metformin XR tablets (Treatments B/A) with respect to total and peak exposures of saxagliptin and metformin when administered under fed conditions. Likewise, no food effect on the pharmacokinetics of saxagliptin or metformin was observed when the FDC tablet was administered under fed versus fasted conditions (Treatments B/C).

<b>Name of Sponsor/Company:</b> Bristol-Myers Squibb	<b>Individual Study Table Referring to Part of the Dossier</b>	<b>(For National Authority Use Only)</b>	
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<b>Geometric Mean (CV) Plasma Pharmacokinetic Parameters of BMS-510849</b>			
	<b>Treatment<sup>a</sup></b>		
<b>Parameter (unit)</b>	<b>A (N=30)</b>	<b>B (N=30)</b>	<b>C (N=30)</b>
AUC <sub>0-t</sub> (ng·h/mL)	272.9 (28)	278.5 (26)	273.7 (23)
AUC <sub>0-mf</sub> (ng·h/mL)	280.2 (27)	285.6 (25)	280.9 (23)
C <sub>max</sub> (ng/mL)	46.9 (34)	47.0 (30)	46.9 (31)
T <sub>max</sub> (h) <sup>b</sup>	2.00 (1.00, 4.00)	2.00 (1.50, 5.00)	1.50 (0.75, 4.00)
t <sub>1/2</sub> (h)	13.9 (1.53)	13.7 (1.72)	14.0 (1.33)
Abbreviations: CV, coefficient of variation; h, hours.			
Note: Geometric mean (arithmetic mean CV) is presented for AUC <sub>0-t</sub> , AUC <sub>0-mf</sub> , and C <sub>max</sub> . Arithmetic mean (SD) is presented for t <sub>1/2</sub> .			
<sup>a</sup> Treatment A: single 5-mg saxagliptin tablet plus a single 500-mg metformin extended-release (XR) tablet (Evansville) administered orally under fed conditions.			
Treatment B: single fixed-dose combination (FDC) tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fed conditions.			
Treatment C: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fasted conditions.			
<sup>b</sup> For T <sub>max</sub> , the median (minimum, maximum) values are presented.			
Source: <a href="#">End-of-Text Table 14.2.5</a>			
When the 2 formulations (coadministered 5-mg saxagliptin and 500-mg metformin XR tablets versus single FDC tablet) were compared, exposures of the saxagliptin metabolite (BMS-510849) were similar. Peak and total exposures of BMS-510849 were also similar under fasted versus fed conditions for the FDC tablet.			

<b>Name of Sponsor/Company:</b> Bristol-Myers Squibb	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b> Saxagliptin		

**Safety:**

Subject disposition is summarized in the following table:

No. of subjects (%)	Treatment Sequence <sup>a</sup>						Overall (N=30)
	ABC (N=5)	ACB (N=5)	BAC (N=5)	BCA (N=5)	CAB (N=5)	CBA (N=5)	
Pharmacokinetic population	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	30 (100.0)
Safety population	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	30 (100.0)
Completed	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	30 (100.0)
Discontinued	0	0	0	0	0	0	0

Abbreviations: FDC, fixed-dose combination; XR, extended release.

Note: Percentages were based on the number of subjects randomly assigned in each sequence and overall.

<sup>a</sup> Treatment A: single 5-mg saxagliptin tablet plus a single 500-mg metformin XR tablet (Evansville) administered orally under fed conditions.

Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fed conditions.

Treatment C: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fasted conditions.

Subject demographics and baseline characteristics are summarized in the following table:

	Overall (N=30)
Age (years)	
Mean (SD)	29.1 (8.0)
Median	27.0
Minimum, Maximum	19, 43
Sex, No. (%)	
Male	16 (53.3)
Female	14 (46.7)
Race, No. (%)	
White	17 (56.7)
Black or African American	12 (40.0)
Asian	1 (3.3)
Ethnicity, No. (%)	
Hispanic or Latino	9 (30.0)
Not Hispanic or Latino	21 (70.0)

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<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet																														
<b>Name of Active Ingredient:</b> Saxagliptin																														
<table border="1"> <tr> <td colspan="2"><b>Height (cm)</b></td> </tr> <tr> <td>Mean (SD)</td> <td>170.00 (9.22)</td> </tr> <tr> <td>Median</td> <td>168.25</td> </tr> <tr> <td>Minimum, Maximum</td> <td>155.5, 194.0</td> </tr> <tr> <td colspan="2"><b>Weight (kg)</b></td> </tr> <tr> <td>Mean (SD)</td> <td>78.31 (13.74)</td> </tr> <tr> <td>Median</td> <td>76.85</td> </tr> <tr> <td>Minimum, Maximum</td> <td>56.2, 120.2</td> </tr> <tr> <td colspan="2"><b>Body Mass Index (kg/m<sup>2</sup>)</b></td> </tr> <tr> <td>Mean (SD)</td> <td>26.97 (3.07)</td> </tr> <tr> <td>Median</td> <td>27.80</td> </tr> <tr> <td>Minimum, Maximum</td> <td>21.4, 31.9</td> </tr> </table>			<b>Height (cm)</b>		Mean (SD)	170.00 (9.22)	Median	168.25	Minimum, Maximum	155.5, 194.0	<b>Weight (kg)</b>		Mean (SD)	78.31 (13.74)	Median	76.85	Minimum, Maximum	56.2, 120.2	<b>Body Mass Index (kg/m<sup>2</sup>)</b>		Mean (SD)	26.97 (3.07)	Median	27.80	Minimum, Maximum	21.4, 31.9				
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<p>Note: Percentages were calculated based on the number of subjects in the safety population who received the specified treatment and overall.</p> <p>Overall AEs are summarized in the following table:</p> <table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="3">Treatment<sup>a</sup></th> <th rowspan="2">Overall (N=30)</th> </tr> <tr> <th>A (N=30)</th> <th>B (N=30)</th> <th>C (N=30)</th> </tr> </thead> <tbody> <tr> <td>Number of subjects with at least 1 AE</td> <td>3 (10.0)</td> <td>2 (6.7)</td> <td>4 (13.3)</td> <td>8 (26.7)</td> </tr> <tr> <td>Discontinuation because of an AE</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Deaths</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Serious AEs</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> </tbody> </table>				Treatment <sup>a</sup>			Overall (N=30)	A (N=30)	B (N=30)	C (N=30)	Number of subjects with at least 1 AE	3 (10.0)	2 (6.7)	4 (13.3)	8 (26.7)	Discontinuation because of an AE	0	0	0	0	Deaths	0	0	0	0	Serious AEs	0	0	0	0
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<p>Abbreviations: AE, adverse event; FDC, fixed-dose combination; XR, extended release.</p> <p><sup>a</sup> Treatment A: single 5-mg saxagliptin tablet plus a single 500-mg metformin XR tablet (Evansville) administered orally under fed conditions.  Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fed conditions.  Treatment C: single FDC tablet consisting of 5-mg saxagliptin and 500-mg metformin XR (Mt Vernon) administered orally under fasted conditions.</p> <p>The highest percentage of subjects (13.3%) reported AEs after receiving a single FDC tablet (Mt Vernon) administered under fasted conditions. Two subjects (6.7%) reported at least 1 AE that was considered related to the study drug (diarrhea, constipation, flatulence, and headache) after</p>																														

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<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b> Saxagliptin		
receiving a single FDC tablet (Mt Vernon) under fed conditions. All AEs were mild in severity, and there were no deaths, serious AEs, or AEs that led to study drug discontinuation. All AEs resolved by the end of the study. No treatment-related trends were observed in AEs, clinical laboratory results, vital sign measurements, 12-lead ECG results, or physical examination findings.		
<b>CONCLUSIONS:</b>		
<u>Pharmacokinetics</u>		
<ul style="list-style-type: none"> <li>• When administered under fed conditions, the FDC tablet (Mt Vernon) was bioequivalent to the coadministered 5-mg saxagliptin and 500-mg metformin XR tablets (Evansville).</li> <li>• No food effect on the pharmacokinetics of saxagliptin or metformin was observed when the FDC tablet (Mt Vernon) was administered under fed versus fasted conditions.</li> <li>• For the saxagliptin metabolite (BMS-510849), the 2 formulations (coadministered 5-mg saxagliptin and 500-mg metformin XR tablets versus single FDC tablet) showed similar exposures. Peak and total exposures of BMS-510849 were also similar under fasted versus fed conditions for the FDC tablet.</li> </ul>		
<u>Safety</u>		
<ul style="list-style-type: none"> <li>• A single oral dose of 5-mg saxagliptin and 500-mg metformin XR was safe and well tolerated by the healthy male and female subjects in this study when administered together as separate tablets under fed conditions or in an FDC tablet under fed or fasted conditions.</li> <li>• No treatment-related trends were observed in AEs, clinical laboratory results, vital sign measurements, 12-lead ECG results, or physical examination findings.</li> </ul>		
<b>Date of report:</b> 19 February 2010 (Version 3.0)		

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**Conclusions from the study**

- When administered under low fat meal conditions, the FDC tablet (Mt Vernon) was bioequivalent to the co-administered 5 mg saxagliptin and 500 mg metformin XR tablets (Evansville). This Reviewer conducted reanalysis of the data and agree with the sponsor's results.

- No food effect on the pharmacokinetics of saxagliptin or metformin was observed when the FDC tablet (Mt Vernon) was administered under low fat versus fasted conditions.
- For the saxagliptin metabolite (BMS-510849), the 2 formulations (coadministered 5-mg saxagliptin and 500-mg metformin XR tablets versus single FDC tablet) showed similar exposures. Peak and total exposures of BMS-510849 were also similar under fasted versus fed conditions for the FDC tablet.

**Bioanalysis:**

**Metformin:** Quantitative assessment of metformin in plasma was done using validated LC/MS/MS method. The lower limit of the quantification of the assay was 2.0 ng/mL. The calibration curves for alogliptin were analysed at concentration range of 2 ng/mL to 1000 ng/mL. Between-run precision (%CV) as determined from analysis of quality control (QC) samples ranged between 3.30 and 8.30%. Within run precision (%CV) as determined from analysis of quality control (QC) samples ranged between 5.63 and 11.1%. The mean accuracy (% Bias) ranged between -1.5% to 0.72%.

**Saxagliptin:**

Quantitative assessment of saxagliptin in plasma was done using validated LC/MS/MS method. The lower limit of the quantification of the assay was 0.1 ng/mL. The calibration curves for alogliptin were analysed at concentration range of 0.1 ng/mL to 50 ng/mL. Between-run precision (%CV) as determined from analysis of quality control (QC) samples ranged between 0.4 to 2.5%. Within run precision (%CV) as determined from analysis of quality control (QC) samples ranged between 2.3 and 6.1%. The mean accuracy (% Bias) ranged between -5% to 2%.

**Reviewer's Comments:**

- *Bioanalytical method for saxagliptin was modified and the lower limit of the quantification was set to 0.1 ng/mL. Although the sponsor mentioned in their reports that this low LOQ was validated, no validation reports for this lower LOQ were submitted with this NDA. This reviewer is aware of the fact that the DSI inspection is requested for study CV 181112 which used the similar bioanalytical method and this reviewer is relying on the DSI findings for the lower LOQ validation.*
- *The long term Phase 3 safety and efficacy trials were conducted with metformin IR co-administered with saxagliptin. Clinical study CV181066, a four week trial, was the only submitted which was conducted using metformin XR co-administered with saxagliptin. To support the approval of FDC product, sponsor conducted BE studies comparing metformin XR and saxagliptin co-administered together to the FDC combination product. Metformin XR is acceptable to bridge the clinical program (which was conducted with metformin IR) because the safety and efficacy bridging of metformin XR and metformin IR is well established.*

- *No effect of food was seen when FDC product was administered under low fat meal condition. The meal condition used in the study was a low fat low calorie diet which consists of standard breakfast of 324 total kcal (11.1% protein, 10.5% fat, and 78.4% carbohydrate).*
- *The effect of high fat meal was not evaluated in this NDA .The sponsor’s rationale for using low fat meal is that the target diabetic patient population is usually on diet and calorie control and thus low fat low calorie meal represents the actual clinical scenario.*
- *Although the sponsor did not evaluate the impact of high fat meal on the FDC product, this reviewer is not recommending any additional study with high fat meal because of the following reasons:*

- 1) *The FDC product employs the same manufacturing technology as used in the single component.*

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

(b) (4)

(b) (4)

(b) (4)

- 2) *The effect of high fat meal on saxagliptin and metformin XR has been studied in saxagliptin and metformin NDA’s, respectively. High fat meal resulted in increase in exposure for both metformin XR and saxagliptin, however no dose adjustment is recommended with food.*
  - b. *In case of metformin, exposure from Glucophage® XR tablets increased by approximately 50% when given with high fat food. High fat meal and low fat meal had a similar effect. The current dosing recommendation for Glucophage® XR is once daily with evening meal.*
  - c. *In case of saxagliptin, exposure from Onglyza tablet increased by 27% when given with a high fat meal as compared to fasted conditions. The current dosing recommendation is with or without food.*
- 3) *In the current food interaction study, the impact of low fat meal on FDC tablet is lower than those observed in individual component product of FDC tablet. So, the impact of high fat meal is not expected to be higher than the individual component product of FDC tablet.*

*The overall study design and data analysis seems reasonable and acceptable. However the batch sizes of the formulation that were utilized in pivotal bioequivalence (BE) studies, CV181111 and CV181112, do not meet the biobatch size criteria of 10% or greater than that of the proposed commercial production batch or at least 100,000 units, whichever is greater. In this NDA, the proposed commercial batch size is (b) (4) and the sponsor used batch size of (b) (4) in trials CV181111 and CV181112, respectively. These batch sizes do not meet the criteria of biobatch, in this case 100,000 tablets, for the pivotal BE studies and thus this application is not acceptable (Please refer to section 2.5.2 of this review for further information). These findings on the batch sizes used in the pivotal BE studies have been communicated to the*

*Office of New Drug Quality Assessment (ONDQA) biopharmaceutical and chemistry manufacturing and controls (CMC) group. They are in process of evaluating these findings and will be finalizing their reviews on assessing the impact of using batch size lower than SUPAC-MR guidance and general criteria used by FDA*

4.3.2 **Bioequivalence Study CV181112**

<b>Name of Sponsor/Company:</b> Bristol-Myers Squibb	<b>Individual Study Table Referring to Part of the Dossier</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Saxagliptin	<b>Page:</b>	
<b>Title of study:</b> Bioequivalence Study of the Fixed-Dose Combination of 5-mg Saxagliptin/1000-mg Metformin XR (Manufactured in Mt Vernon, IN) Relative to 5 mg of Onglyza and 2 × 500-mg Glucophage XR Coadministered to Healthy Subjects in the Fed State and Steady-State Pharmacokinetic Assessment of the Fixed-Dose Combination of 5-mg Saxagliptin/1000-mg Metformin XR		
<b>Investigator:</b> Matthew Medlock, MD		
<b>Study site:</b> PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin TX 78744		
<b>Publication (reference):</b> None		
<b>Studied period (years):</b> 09 December 2009 to 29 December 2009		<b>Phase of development:</b> 1
<p><b>Objective:</b> The primary objective was to demonstrate bioequivalence (BE) of a 5-mg saxagliptin/1000-mg metformin extended-release (XR) fixed-dose combination (FDC) tablet (manufactured in Mt Vernon, Indiana) relative to a coadministered 5-mg Onglyza tablet (saxagliptin, manufactured in Mt Vernon, Indiana) and two 500-mg Glucophage XR tablets (metformin XR, manufactured in Evansville, Indiana) in the fed state in healthy subjects.</p> <p>The secondary objectives were:</p> <ul style="list-style-type: none"> <li>to characterize the single-dose and steady-state pharmacokinetics of saxagliptin and metformin following the administration of the 5-mg saxagliptin/1000-mg metformin XR FDC tablet (manufactured in Mt Vernon, Indiana) in the fed state in healthy subjects;</li> <li>to characterize the pharmacokinetics of the active metabolite of saxagliptin, 5-hydroxy saxagliptin (BMS-510849) in healthy subjects when 5-mg Onglyza (saxagliptin, manufactured in Mt Vernon, Indiana) was coadministered with two 500-mg Glucophage XR tablets (metformin XR, manufactured in Evansville, Indiana) administered in the fed state (single dose only) or when a 5-mg saxagliptin/1000-mg metformin XR FDC tablet (manufactured in Mt Vernon, Indiana) was administered in the fed state (single dose and steady state); and</li> </ul>		

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- to assess the safety and tolerability in healthy subjects of 5-mg Onglyza (saxagliptin, manufactured in Mt Vernon, Indiana) coadministered with two 500-mg Glucophage XR tablets (metformin XR, manufactured in Evansville, Indiana) administered in the fed state or of single and multiple doses of 5-mg saxagliptin/1000-mg metformin XR FDC tablets (manufactured in Mt Vernon, Indiana) administered in the fed state.

**Methodology:** This was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects. Subjects underwent screening evaluations to determine eligibility within 21 days before dosing. Subjects were admitted to the clinical facility the evening before dosing (Day -1). On Day 1 of Period 1, a total of 30 subjects who met all of the inclusion and none of the exclusion criteria were randomly assigned to 1 of 2 treatment sequences as follows:

Sequence	Period 1	Period 2	Period 3
ABC	A	B	C
BA	B	A	-

Treatment A: single 5-mg Onglyza (saxagliptin) tablet (Mt Vernon, Indiana) plus two 500-mg Glucophage (metformin) XR tablets (Evansville, Indiana) administered orally under fed conditions.  
 Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally under fed conditions.  
 Treatment C: FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally once daily for 4 days under fed conditions.

On Day 1 of Periods 1 and 2, each subject received either Treatment A or Treatment B according to the randomization scheme. The 15 subjects randomly assigned to Treatment Sequence ABC received Treatment C (5-mg saxagliptin/1000-mg metformin XR FDC tablet administered once daily [QD] for 4 days instead of a single dose) in a third treatment period designed to assess the steady-state pharmacokinetics of the FDC tablet. All doses of study drug were administered to subjects within 5 minutes of completing a standard meal (breakfast) in the morning. Subjects underwent a 2-day washout period between Periods 1 and 2; there was also a 2-day washout between Periods 2 and 3. Subjects in Treatment Sequence BA were discharged from the clinical facility on Day 3 of Period 2, and subjects in Treatment Sequence ABC were discharged on Day 5 of Period 3, after the pharmacokinetic sampling and all safety evaluations were completed.

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<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b> Saxagliptin		
<b>Number of subjects (planned and analyzed):</b> A total of 30 subjects were planned and enrolled and 28 subjects completed the study. All 30 subjects were included in the pharmacokinetic and safety analyses.		
<b>Diagnosis and main criteria for inclusion:</b> Healthy male and female subjects as determined by medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory tests, were eligible to participate in the study. Women of childbearing potential could not have been nursing or pregnant and must have been using an acceptable method of contraception. All women were required to have a negative pregnancy test within 24 hours before dosing.		
<b>Test product, dose and mode of administration, batch number:</b> Fixed-dose combination tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (manufactured in Mt Vernon, Indiana), single dose administered orally under fed conditions, label batch number 9L45849; product batch number 9L51087.		
<b>Duration of treatment:</b> On Day 1 of Periods 1 and 2, each subject received either Treatment A (single 5-mg Onglyza [saxagliptin] tablet [Mt Vernon, Indiana] plus two 500-mg Glucophage [metformin] XR tablets [Evansville, Indiana]) or Treatment B (single FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR [Mt Vernon, Indiana]) administered orally under fed conditions. On Days 1 through 4 of Period 3, subjects in Treatment Sequence ABC received Treatment C (single FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR [Mt Vernon, Indiana]) administered orally under fed conditions.		
<b>Reference therapy, dose and mode of administration, batch number:</b> Onglyza (saxagliptin), 5-mg tablet (manufactured in Mt Vernon, Indiana), single dose coadministered orally with Glucophage (metformin) XR under fed conditions, label batch number 9K57859; product batch number 9D4707B. Glucophage (metformin) XR, two 500-mg tablets (manufactured in Evansville, Indiana), single dose coadministered orally with Onglyza under fed conditions, batch number 9K57861; label product batch number 8L3022A.		

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<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b> Saxagliptin		
<b>Criteria for evaluation:</b>		
<p><u>Pharmacokinetics:</u> In Periods 1 and 2, blood samples for the determination of plasma concentrations of saxagliptin, BMS-510849, and metformin were collected before dosing, and at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 36, and 48 hours after dosing. In Period 3, blood samples for the determination of plasma concentrations of saxagliptin, BMS-510849, and metformin were collected before dosing on Days 2 and 3, and before dosing and at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, and 24 hours after dosing on Day 4.</p> <p>In Periods 1 and 2, the following single-dose plasma pharmacokinetic parameters were calculated:</p> <p><math>AUC_{0-t}</math>            area under the plasma concentration versus time curve from time 0 to the time of the last quantifiable concentration (<math>C_t</math>)</p> <p><math>AUC_{0-inf}</math>            area under the plasma concentration versus time curve from time 0 extrapolated to infinity</p> <p><math>C_{max}</math>                observed maximum plasma concentration</p> <p><math>T_{max}</math>                time to achieve the observed maximum plasma concentration</p> <p><math>t_{1/2}</math>                 terminal half-life</p> <p>In Period 3, the following multiple-dose plasma pharmacokinetic parameters were calculated:</p> <p><math>AUC_{0-\tau}</math>            area under the plasma concentration versus time curve from time 0 to the end of the dose interval (24 hours)</p> <p><math>C_{max}</math>                observed maximum plasma concentration</p> <p><math>T_{max}</math>                time to achieve the observed maximum plasma concentration</p> <p><math>C_{min}</math>                trough (predose) plasma concentration</p> <p><u>Safety:</u> Safety assessments included adverse events (AEs), clinical laboratory results, vital sign measurements, 12-lead ECG results, and physical examination findings.</p> <p><b>Statistical methods:</b> If there was no difference between the bioavailabilities of saxagliptin from the FDC tablet versus saxagliptin from coadministration of a 5-mg saxagliptin tablet</p>		

Name of Sponsor/Company:	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Bristol-Myers Squibb		
Name of Finished Product:  Saxagliptin/metformin XR fixed-dose combination tablet	Volume:	
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<p>plus two 500-mg metformin XR tablets under fed conditions, then 24 subjects would have provided 99% power to conclude BE with respect to <math>C_{max}</math> and <math>AUC_{0-inf}</math>. If there was a 5% difference, then 24 subjects would have provided 94% and 99% power to conclude BE with respect to <math>C_{max}</math> and <math>AUC_{0-inf}</math>. If there was no difference between the bioavailabilities of metformin from the FDC tablet versus metformin from coadministration of a 5-mg saxagliptin tablet plus two 500-mg metformin XR tablets under fed conditions, then 24 subjects would have provided 99% power to conclude BE with respect to <math>C_{max}</math> and <math>AUC_{0-inf}</math>. If there was a 5% difference, then 24 subjects would have provided at least 99% power to conclude BE with respect to <math>C_{max}</math> and <math>AUC_{0-inf}</math>.</p> <p><u>Pharmacokinetics:</u> Plasma concentration and pharmacokinetic parameter data were presented in data listings and summarized. Mean and individual plasma concentration versus scheduled time profiles were presented in figures on both linear and semilogarithmic scales.</p> <p>To assess the effect of formulation (FDC tablet versus coadministration of separate saxagliptin and metformin XR tablets) on the bioavailabilities of saxagliptin and metformin, a linear mixed model with fixed factors for period and treatment and measurements within each subject as repeated measurements was performed on <math>\log(C_{max})</math>, <math>\log(AUC_{0-t})</math>, and <math>\log(AUC_{0-inf})</math> of saxagliptin and metformin, respectively, to assess the differences between the test product (FDC tablet, fed [Treatment B]) and the reference product (coadministration of a separate 5-mg saxagliptin tablet plus two 500-mg metformin XR tablets, fed [Treatment A]). Point estimates and 90% confidence intervals (CIs) were calculated for the Treatment B to Treatment A ratios of geometric means for <math>C_{max}</math>, <math>AUC_{0-t}</math>, and <math>AUC_{0-inf}</math> on the original scale of measurement. Bioequivalence was concluded if the 90% CIs for the test-to-reference ratios of geometric means were entirely contained within 0.800 to 1.250 for both <math>C_{max}</math> and <math>AUC_{0-inf}</math> of saxagliptin and metformin.</p> <p>The <math>AUC</math> ratio and <math>C_{max}</math> ratio estimates and their CIs were corrected for measured content using the method specified in the Canadian guidance for industry on conduct and analysis of bioavailability and BE studies. Potency-corrected results were presented in a summary table.</p> <p><u>Safety:</u> Subject disposition, demographics, and baseline characteristics were presented in data listings and summarized. All AE data were presented in data listings and treatment-emergent AE data were summarized by overall incidence, relationship to study drug, severity, serious</p>		

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<b>Name of Active Ingredient:</b> Saxagliptin		

AEs, and AEs leading to discontinuation of the study drug. Clinical laboratory results and vital sign measurements were presented in data listings and summarized. Change from Baseline in hematology and serum chemistry results were summarized and shifts from Baseline in urinalysis results were presented. Clinical laboratory results outside the reference range were flagged in the data listings and evaluated for clinical significance by the investigator. Physical examination findings, 12-lead ECG results, medical history, medical or surgical treatment procedures, admission criteria data, prior and concomitant medications, study drug administration, and meal records were presented in data listings.

#### SUMMARY - CONCLUSIONS

**Pharmacokinetics:** The 90% CIs of the ratios of geometric least squares means for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  of saxagliptin and metformin were all entirely contained within 0.800 to 1.250 as shown in the following tables:

**Statistical Analysis of Plasma Pharmacokinetic Parameters of Saxagliptin**

Parameter (unit)	Treatment <sup>a</sup>	N	Geometric LS Mean	Ratio of Geometric LS Means and 90% CI of the Ratio (Treatments B/A)
$AUC_{0-t}$ (ng·h/mL)	A	29	97.72	1.035 (1.009, 1.062)
	B	30	101.16	
$AUC_{0-inf}$ (ng·h/mL)	A	28	98.61	1.045 (1.025, 1.065)
	B	30	103.05	
$C_{max}$ (ng/mL)	A	29	24.88	0.999 (0.948, 1.053)
	B	30	24.85	

Abbreviations: CI, confidence interval; FDC, fixed-dose combination; LS, least squares; XR, extended release.

Note: An analysis of variance model was performed on the natural logarithms of  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  with period and treatment as fixed effects and measurements within each subject as repeated measurements.

<sup>a</sup> Treatment A: single 5-mg Onglyza (saxagliptin) tablet (Mt Vernon, Indiana) plus two 500-mg Glucophage (metformin) XR tablets (Evansville, Indiana) administered orally under fed conditions.

Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally under fed conditions.

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<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet				
<b>Name of Active Ingredient:</b> Saxagliptin				
<b>Statistical Analysis of Plasma Pharmacokinetic Parameters of Metformin</b>				
<b>Parameter (unit)</b>	<b>Treatment<sup>a</sup></b>	<b>N</b>	<b>Geometric LS Mean</b>	<b>Ratio of Geometric LS Means and 90% CI of the Ratio (Treatments B/A)</b>
AUC <sub>0-t</sub> (ng·h/mL)	A	29	9246.8	0.906 (0.848, 0.968)
	B	30	8377.8	
AUC <sub>0-inf</sub> (ng·h/mL)	A	27	9746.3	0.894 (0.833, 0.959)
	B	29	8713.4	
C <sub>max</sub> (ng/mL)	A	29	1151.2	0.917 (0.859, 0.980)
	B	30	1055.9	
<p>Abbreviations: CI, confidence interval; FDC, fixed-dose combination; LS, least squares; XR, extended release.          Note: An analysis of variance model was performed on the natural logarithms of AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> with period and treatment as fixed effects and measurements within each subject as repeated measurements.  <sup>a</sup> Treatment A: single 5-mg Onglyza (saxagliptin) tablet (Mt Vernon, Indiana) plus two 500-mg Glucophage (metformin) XR tablets (Evansville, Indiana) administered orally under fed conditions.          Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally under fed conditions.</p> <p>The 90% CIs of the potency-corrected ratios of geometric least squares means for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> showed similar results to the nominal strength analysis. Therefore, the FDC tablet was bioequivalent to the coadministered 5-mg saxagliptin plus two 500-mg metformin XR tablets with respect to total and peak exposures of saxagliptin and metformin when administered under fed conditions.</p>				

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The plasma pharmacokinetic parameters of BMS-510849 are summarized in the following table:

**Geometric Mean (CV) Plasma Pharmacokinetic Parameters of BMS-510849**

Parameter (unit)	Treatment <sup>a</sup>		
	A (N=29)	B (N=30)	C (N=14)
AUC <sub>0-t</sub> (ng·h/mL)	285.6 (23)	281.5 (24)	–
AUC <sub>0-inf</sub> (ng·h/mL) <sup>b</sup>	291.3 (23)	289.3 (23)	–
AUC <sub>0-τ</sub> (ng·h/mL)	–	–	313.9 (17)
C <sub>max</sub> (ng/mL)	52.1 (31)	48.9 (32)	58.4 (23)
T <sub>max</sub> (h) <sup>c</sup>	3.00 (1.50, 4.00)	2.00 (1.50, 5.03)	2.00 (1.50, 3.00)
t <sub>1/2</sub> (h) <sup>b</sup>	13.48 (1.78)	13.82 (2.52)	–
C <sub>min</sub> (ng/mL) <sup>d</sup>	–	–	1.51 (0.22)

Abbreviations: CV, coefficient of variation; FDC, fixed-dose combination; h, hours; XR, extended release.

Note: Geometric mean (CV) is presented for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, AUC<sub>0-τ</sub>, and C<sub>max</sub>. Arithmetic mean (SD) is presented for t<sub>1/2</sub> and C<sub>min</sub>.

<sup>a</sup> Treatment A: single 5-mg Onglyza (saxagliptin) tablet (Mt Vernon, Indiana) plus two 500-mg Glucophage (metformin) XR tablets (Evansville, Indiana) administered orally under fed conditions.

Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally under fed conditions.

Treatment C: FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally once daily for 4 days under fed conditions.

<sup>b</sup> For AUC<sub>0-inf</sub> and t<sub>1/2</sub>, N=28 (Treatment A).

<sup>c</sup> For T<sub>max</sub>, the median (minimum, maximum) values are presented.

<sup>d</sup> C<sub>min</sub> was based on Day 4 predose concentrations. Predose for Days 2 and 3 are presented in End-of-Text Table 14.2.2.

Mean total and peak exposures of the saxagliptin metabolite (BMS-510849) were similar when the 2 formulations (single FDC tablet versus coadministered 5-mg saxagliptin plus two 500-mg metformin XR tablets) were compared.

Mean peak exposure of saxagliptin at steady state was similar (99%) to the mean peak exposure after single dosing. Mean total exposures (AUC<sub>0-τ</sub>) of saxagliptin and BMS-510849 over the dosing interval at steady state were comparable to the total exposures (AUC<sub>0-inf</sub>) after single dosing, 94% and 109%, respectively. Mean peak exposure of metformin for the FDC

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tablet at steady state was approximately 90% of the mean peak exposure of the FDC tablet after single dosing. Mean total exposures ( $AUC_{0-\tau}$ ) of metformin over the dosing interval at steady state were nearly identical (101%) to the total exposure ( $AUC_{0-\infty}$ ) after single dosing

**Safety:**

Subject disposition is summarized in the following table:

No. of subjects (%)	Treatment Sequence <sup>a</sup>		Overall (N=30)
	ABC (N=15)	BA (N=15)	
Pharmacokinetic population	15 (100.0)	15 (100.0)	30 (100.0)
Safety population	15 (100.0)	15 (100.0)	30 (100.0)
Completed	14 (93.3)	14 (93.3)	28 (93.3)
Discontinued	1 (6.7)	1 (6.7)	2 (6.7)
Reason for discontinuation			
Other	1 (6.7)	1 (6.7)	2 (6.7)

Abbreviations: FDC, fixed-dose combination; XR, extended release.

Note: Percentages were based on the number of subjects randomly assigned in each sequence and overall.

<sup>a</sup> Treatment A: single 5-mg Onglyza (saxagliptin) tablet (Mt Vernon, Indiana) plus two 500-mg Glucophage (metformin) XR tablets (Evansville, Indiana) administered orally under fed conditions.

Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally under fed conditions.

Treatment C: FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally once daily for 4 days under fed conditions.

Subject demographics and baseline characteristics are summarized in the following table:

	Treatment <sup>a</sup>			Overall (N=30)
	A (N=29)	B (N=30)	C (N=14)	
Age (years)				
Mean (SD)	31.9 (7.68)	31.6 (7.76)	33.4 (8.69)	31.6 (7.76)
Median	30.0	30.0	34.5	30.0
Min, Max	20, 44	20, 44	21, 44	20, 44
Sex, No. (%)				
Male	13 (44.8)	13 (43.3)	9 (64.3)	13 (43.3)
Female	16 (55.2)	17 (56.7)	5 (35.7)	17 (56.7)

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Race, No. (%)				
White	22 (75.9)	22 (73.3)	10 (71.4)	22 (73.3)
Black or African American	7 (24.1)	8 (26.7)	4 (28.6)	8 (26.7)
Ethnicity, No. (%)				
Hispanic or Latino	13 (44.8)	13 (43.3)	4 (28.6)	13 (43.3)
Not Hispanic or Latino	16 (55.2)	17 (56.7)	10 (71.4)	17 (56.7)
Height (cm)				
Mean (SD)	167.12 (9.06)	166.85 (9.02)	169.36 (8.07)	166.85 (9.02)
Median	169.00	168.50	170.75	168.50
Min, Max	152.0, 180.5	152.0, 180.5	153.5, 180.5	152.0, 180.5
Weight (kg)				
Mean (SD)	71.99 (9.24)	71.56 (9.39)	74.19 (9.35)	71.56 (9.39)
Median	73.80	73.45	72.95	73.45
Min, Max	55.9, 94.2	55.9, 94.2	59.4, 94.2	55.9, 94.2
BMI (kg/m <sup>2</sup> )				
Mean (SD)	25.77 (2.71)	25.69 (2.70)	25.89 (2.96)	25.69 (2.70)
Median	25.80	25.60	26.60	25.60
Min, Max	21.8, 31.5	21.8, 31.5	21.8, 31.3	21.8, 31.5
Abbreviations: BMI, body mass index; FDC, fixed-dose combination; Max, maximum; Min, minimum; XR, extended release.				
Note: Percentages were calculated based on the number of subjects in the safety population who received the specified treatment and overall.				
<sup>a</sup> Treatment A: single 5-mg Onglyza (saxagliptin) tablet (Mt Vernon, Indiana) plus two 500-mg Glucophage (metformin) XR tablets (Evansville, Indiana) administered orally under fed conditions.				
Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally under fed conditions.				
Treatment C: FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally once daily for 4 days under fed conditions.				

<b>Name of Sponsor/Company:</b> Bristol-Myers Squibb	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet		
<b>Name of Active Ingredient:</b> Saxagliptin		

Overall AEs are summarized in the following table:

	Treatment <sup>a</sup>			Overall (N=30)
	A (N=29)	B (N=30)	C (N=14)	
Number of subjects with at least 1 AE	3 (10.3)	3 (10.0)	4 (28.6)	9 (30.0)
Discontinuation because of an AE	0	0	0	0
Deaths	0	0	0	0
Serious AEs	0	0	0	0

Abbreviations: AE, adverse event; FDC, fixed-dose combination; XR, extended release.

<sup>a</sup> Treatment A: single 5-mg Onglyza (saxagliptin) tablet (Mt Vernon, Indiana) plus two 500-mg Glucophage (metformin) XR tablets (Evansville, Indiana) administered orally under fed conditions.

Treatment B: single FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally under fed conditions.

Treatment C: FDC tablet consisting of 5-mg saxagliptin and 1000-mg metformin XR (Mt Vernon, Indiana) administered orally once daily for 4 days under fed conditions.

Nine subjects (30.0%) reported at least 1 AE during the study, with similar numbers of subjects (3 to 4) reporting AEs after each treatment. Four subjects (13.3%) reported at least 1 AE that was considered related to the study drug (dry mouth, nausea, constipation, and headache). All AEs were mild or moderate in severity, and there were no deaths, serious AEs, or AEs that led to study drug discontinuation. All AEs resolved by the end of the study. No treatment-related trends were observed in AEs, clinical laboratory results, vital sign measurements, 12-lead ECG results, or physical examination findings.

## CONCLUSIONS:

### Pharmacokinetics

- When administered under fed conditions, the 5-mg saxagliptin/1000-mg metformin XR FDC tablet (Mt Vernon, Indiana) was bioequivalent to the coadministered 5-mg saxagliptin (Mt Vernon, Indiana) plus two 500-mg metformin XR tablets (Evansville, Indiana).

<b>Name of Sponsor/Company:</b> Bristol-Myers Squibb	<b>Individual Study Table Referring to Part of the Dossier</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> Saxagliptin/metformin XR fixed-dose combination tablet	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Saxagliptin	<b>Page:</b>	
<ul style="list-style-type: none"> <li>• Peak and total exposures of saxagliptin after QD dosing for 4 days with the FDC tablet were unchanged from the exposures observed after single dosing. Peak exposure of metformin after QD dosing for 4 days was similar to the peak exposure observed after a single dose, and there was no evidence of unexpectedly rapid release (dose dumping) of metformin from the 1000-mg metformin XR FDC tablet formulation.</li> <li>• Exposures of BMS-510849 were comparable between the 5-mg saxagliptin/1000-mg metformin XR FDC tablet (Mt Vernon, Indiana) and the coadministered 5-mg saxagliptin plus two 500-mg metformin XR tablets (Evansville, Indiana). Further, the steady-state PK of BMS-510849 was similar to the single-dose PK of BMS-510849 following single and repeated once-daily dosing of the 5-mg saxagliptin/1000-mg metformin XRFDC tablet.</li> </ul> <p><u>Safety</u></p> <ul style="list-style-type: none"> <li>• Single oral 5-mg saxagliptin and 1000-mg metformin XR tablets were safe and well tolerated by the healthy subjects in this study when administered together, either as separate tablets (5-mg saxagliptin [Mt Vernon, Indiana] plus two 500-mg metformin XR tablets [Evansville, Indiana]) or as a single FDC tablet (5-mg saxagliptin and 1000-mg metformin XR [Mt Vernon, Indiana]) under fed conditions. The FDC tablet (5-mg saxagliptin and 1000-mg metformin XR [Mt Vernon, Indiana]) administered under fed conditions was safe and well tolerated by the healthy subjects in this study when administered once daily for 4 days.</li> <li>• No treatment-related trends were observed in AEs, clinical laboratory results, vital sign measurements, 12-lead ECG results, or physical examination findings.</li> </ul>		
<b>Date of report:</b> 26 February 2010 (Version 3.0)		

## **Conclusions from the study**

- When administered under fed conditions, the 5 mg saxagliptin/1000 mg metformin XR FDC tablet (Mt Vernon, Indiana) was bioequivalent to the coadministered 5 mg saxagliptin (Mt Vernon, Indiana) plus two 500 mg metformin XR tablets (Evansville, Indiana).
- Peak and total exposures of saxagliptin after QD dosing for 4 days with the FDC tablet were unchanged from the exposures observed after single dosing. Peak exposure of metformin after QD dosing for 4 days was similar to the peak exposure observed after a single dose, and there was no evidence of unexpectedly rapid release (dose dumping) of metformin from the 1000 mg metformin XR FDC tablet formulation.
- Exposures of BMS-510849 were comparable between the 5 mg saxagliptin/1000 mg metformin XR FDC tablet (Mt Vernon, Indiana) and the co-administered 5 mg saxagliptin plus two 500 mg metformin XR tablets (Evansville, Indiana). Further, the steady-state PK of BMS-510849 was similar to the single-dose PK of BMS-510849 following single and repeated once-daily dosing of the 5 mg saxagliptin/1000 mg metformin XR FDC tablet.

## **Bioanalysis:**

**Metformin:** Quantitative assessment of metformin in plasma was done using validated LC/MS/MS method. The lower limit of the quantification of the assay was 2.0 ng/mL. The calibration curves for alogliptin were analysed at concentration range of 2 ng/mL to 1000 ng/mL. Between-run precision (%CV) as determined from analysis of quality control (QC) samples ranged between 2.85 and 4.80 %. Within run precision (%CV) as determined from analysis of quality control (QC) samples ranged between 3.48 and 12.8 %. The mean accuracy (% Bias) ranged between -1.46% to 0.913%.

## **Saxagliptin:**

Quantitative assessment of saxagliptin in plasma was done using validated LC/MS/MS method. The lower limit of the quantification of the assay was 0.1 ng/mL. The calibration curves for alogliptin were analysed at concentration range of 0.1 ng/mL to 50 ng/mL. Between-run precision (%CV) as determined from analysis of quality control (QC) samples ranged between 0.6 to 3.9 %. Within run precision (%CV) as determined from analysis of quality control (QC) samples ranged between 2.2 and 8.3 %. The mean accuracy (% Bias) ranged between -4.7% to -0.3%.

## **Reviewer's Comments:**

- *Bioanalytical method for saxagliptin was modified and the lower limit of the quantification was set to 0.1 ng/mL. Although the sponsor mentioned in their reports that this low LOQ was validated, no validation reports for this lower LOQ were submitted with this NDA. This reviewer is aware of the fact that the DSI inspection is requested for this study and this reviewer is relying on the DSI findings for the lower LOQ validation.*

- *Mean total exposures ( $AUC_{0-\tau}$ ) of saxagliptin and its metabolite BMS-510849 over the dosing interval at steady state were comparable to the total exposures ( $AUC_{0-inf}$ ) after single dosing. This is consistent with the saxagliptin NDA 22350 where multiple dose administration of saxagliptin showed no drug accumulation. Also, Mean peak exposure of metformin for the FDC tablet at steady state was approximately 90% of the mean peak exposure of the FDC tablet after single dosing.*
- *The long term Phase 3 safety and efficacy trials were conducted with metformin IR co-administered with saxagliptin. Clinical study CV181066, a four week trial, was the only submitted which was conducted using metformin XR co-administered with saxagliptin. To support the approval of FDC product, sponsor conducted BE studies comparing metformin XR and saxagliptin co-administered together to the FDC combination product. Metformin XR is acceptable to bridge the clinical program (which was conducted with metformin IR) because the safety and efficacy bridging of metformin XR and metformin IR is well established.*
- *No effect of food was seen when FDC product was administered under low fat meal condition. The meal condition used in the study was a low fat low calorie diet which consists of standard breakfast of 324 total kcal (11.1% protein, 10.5% fat, and 78.4% carbohydrate).*
- *The effect of high fat meal was not evaluated in this NDA. The sponsor's rationale for using low fat meal is that the target diabetic patient population is usually on diet and calorie control and thus low fat low calorie meal represents the actual clinical scenario.*
- *Although the sponsor did not evaluate the impact of high fat meal on the FDC product, this reviewer is not recommending any additional study with high fat meal because of the following reasons:*

- 1) *The FDC product employs the same manufacturing technology as used in the single component.*

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

(b) (4)

(b) (4)

- 2) *The effect of high fat meal on saxagliptin and metformin XR has been studied in saxagliptin and metformin NDA's, respectively. High fat meal resulted in increase in exposure for both metformin XR and saxagliptin, however no dose adjustment is recommended with food.*
  - b. *In case of metformin, exposure from Glucophage® XR tablets increased by approximately 50% when given with high fat food. High fat meal and low fat meal had a similar effect. The current dosing recommendation for Glucophage® XR is once daily with evening meal.*

- c. *In case of saxagliptin, exposure from Onglyza tablet increased by 27% when given with a high fat meal as compared to fasted conditions. The current dosing recommendation is with or without food.*
- 3) *In the current food interaction study, the impact of low fat meal on FDC tablet is lower than those observed in individual component product of FDC tablet. So, the impact of high fat meal is not expected to be higher than the individual component product of FDC tablet.*

*The overall study design and data analysis seems reasonable and acceptable. However the batch sizes of the formulation that were utilized in pivotal bioequivalence (BE) studies, CV181111 and CV181112, do not meet the biobatch size criteria of 10% or greater than that of the proposed commercial production batch or at least 100,000 units, whichever is greater. In this NDA, the proposed commercial batch size is (b) (4) ( ) and the sponsor used batch size of (b) (4) in trials CV181111 and CV181112, respectively. These batch sizes do not meet the criteria of biobatch, in this case 100,000 tablets, for the pivotal BE studies and thus this application is not acceptable (Please refer to section 2.5.2 of this review for further information). These findings on the batch sizes used in the pivotal BE studies have been communicated to the Office of New Drug Quality Assessment (ONDQA) biopharmaceutical and chemistry manufacturing and controls (CMC) group. They are in process of evaluating these findings and will be finalizing their reviews on assessing the impact of using batch size lower than SUPAC-MR guidance and general criteria used by FDA*

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RITESH JAIN  
10/15/2010

SALLY Y CHOE  
10/15/2010

CHANDRAHAS G G SAHAJWALLA  
10/15/2010

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 200-678 (000)	<b>Reviewer:</b> Houda Mahayni, Ph.D.	
<b>Submission Date:</b>	Dec 29, 2009; Sep 24, 2010		
<b>Division:</b>	DMEDP	<b>Team Leader:</b> Angelica Dorantes, Ph.D.	
<b>Sponsor:</b>	Bristol-Myers Squibb Company	<b>Supervisor:</b> Patrick J. Marroum, Ph.D.	
<b>Trade Name:</b>	(b) (4)	<b>Date Assigned:</b>	Jan 25, 2010
<b>Generic Name:</b>	Saxagliptin (BMS-477118)/metformin HCl	<b>Date of Review:</b>	Aug 30, 2010
<b>Indication:</b>	Type 2 Diabetes Mellitus	<b>Type of Submission:</b> Original NDA	
<b>Formulation/strengths</b>	Extended-Release Fixed Dose Combination Tablet/5mg saxa/500 mg met, 5 mg saxa/1000 mg met, 2.5 mg saxa/1000 mg met		
<b>Route of Administration</b>	Oral		

### **SUBMISSION:**

Saxagliptin (Trade name: Onglyza) is an inhibitor of dipeptidyl peptidase-4 (DPP-4) and was approved by the FDA as an anti-diabetic drug on July 31, 2009, under NDA 22-350. The approved usual clinical doses of saxagliptin in adults are 2.5 and 5 mg administered orally once daily.

Metformin (Trade name: Glucophage) XR is an anti-diabetic drug of the biguanide class and was approved by the FDA on October 13, 2000, under NDA 21-202. Glucophage XR is marketed in the 500 and 750 mg dose strengths and is approved for doses up to 2000 mg to be taken once daily with the evening meal. Both drug products are marketed by BMS.

This submission is for a Fixed Dose Combination (FDC) tablets of saxagliptin with metformin XR developed in the following 3 different dose strengths to allow once-daily dosing of saxagliptin with metformin at total daily doses up to 5 mg saxagliptin and 2000 mg metformin (i.e., the highest recommended once-daily doses of saxagliptin and metformin):

- 5 mg saxagliptin/500 mg metformin XR
- 5 mg saxagliptin/1000 mg metformin XR
- 2.5 mg saxagliptin/1000 mg metformin XR

The biopharmaceutics review will focus on the evaluation of the proposed dissolution method and specifications, the three biowaiver requests, and dose dumping (the effect of alcoholic concentrations on the in-vitro dissolution behavior of Saxa/Met XR FDC tablets).

Given that the sponsor performed the following bioequivalence (BE) studies in support of Saxa/Met XR FDCs, the sponsor is requesting three biowaivers:

1. Study CV181060 was conducted to demonstrate bioequivalence of Saxa 5/Met XR 500, and co-administered 5-mg saxagliptin film-coated tablet and a GLUCOPHAGE XR 500 tablet in fed healthy subjects.
2. Study CV181074 was conducted to demonstrate bioequivalence of metformin XR (1 x 1000-mg tablet), and metformin XR (2 x 500-mg tablets) in fed healthy subjects using tablets manufactured at the BMS Evansville, Indiana, facility.
3. Study CV181076 was conducted to establish bioequivalence of a Saxa 5/Met XR 1000 FDC tablet, and co-administered saxagliptin 5-mg tablet and metformin XR 1000-mg tablet in fed and fasted healthy subjects.
4. Study CV138098 was conducted to demonstrate bioequivalence of GLUCOPHAGE XR 500 manufactured in Mt. Vernon, Indiana, and GLUCOPHAGE XR 500 manufactured in Evansville, Indiana, in fasted and fed healthy subjects.
5. Study CV138100 was conducted to demonstrate bioequivalence of Met XR 1000 manufactured in Mt. Vernon, Indiana, and Met XR 1000 manufactured in Evansville, Indiana, in fasted and fed healthy subjects.

The above bioequivalence studies will be reviewed by the Office of Clinical Pharmacology.

The following are the three biowaiver requests:

1. **Biowaiver request for the 2.5 Saxa/1000 Met FDC tablet.** According to the sponsor, the data from the bioequivalence study which used the FDC tablet of 5 mg saxagliptin/1000 mg metformin XR are applicable to the lower strength FDC tablet of 2.5 mg saxagliptin/1000 mg metformin XR formulation, and no separate bioequivalence study is needed with the lower saxagliptin strength with 1000 mg metformin XR formulation. For this biowaiver request, the sponsor provided the following justifications:

(b) (4)

**Reviewer's Note:**

The biowaiver request for 2.5 Saxa/1000 Met is acceptable. The two FDC tablets (2.5/1000 and 5/1000) have comparable dissolution data and the only difference between them [REDACTED] (b) (4)

**2. Biowaiver request to waive the requirement to repeat the BE study using Saxa 5/Met XR 500 manufactured at the commercial scale.**

The sponsor used a batch size of [REDACTED] (b) (4) for a pivotal BE study which was less than the "10% of the commercial scale or 100,000 units, whichever is greater" criterion for a biobatch. The commercial scale [REDACTED] (b) (4) will be conducted at about [REDACTED] (b) (4)

. The sponsor provided the following rationale in support of a waiver repeat the BE study using Saxa 5/Met XR 500 manufactured at commercial scale:

[REDACTED] (b) (4)

**Reviewer's Note:**

The biowaiver request to waive the requirement to repeat the BE study using Saxa 5/Met XR 500 manufactured at the commercial scale is irrelevant because the sponsor agreed with FDA at the October 15, 2009 pre-NDA meeting and at the November 5, 2009 pre-NDA follow-up meeting to repeat the bioequivalence study. To provide a direct link using commercial scale batch, the bioequivalence study was repeated using the to-be-marketed FDC formulation manufactured at the BMS manufacturing facility at Mt Vernon, IN (test) versus 5 mg Onglyza and 500 mg Glucophage XR (Evansville, IN, clinical formulation).

It is noted that the Office of Clinical Pharmacology determined the BCS classification of saxagliptin during ONGLYZA NDA review to be considered as BCS Class 3 drug (high solubility, low permeability). (b) (4)

**3. Biowaiver request to waive any requirement to conduct a bioequivalence study of Saxa 5/Met XR 500, Saxa 5/Met XR 1000, and Saxa 2.5/Met XR 1000 manufactured using Mt. Vernon Met XR (b) (4) with the same Saxa/Met XR products manufactured using Evansville Met XR (b) (4)** The sponsor provided the following justifications in support for this biowaiver request:

The sponsor performed bioequivalence study to establish bioequivalence between GLUCOPHAGE XR 500 manufactured in Mt. Vernon compared to GLUCOPHAGE XR 500 manufactured in Evansville (Study CV138098). The sponsor also performed another bioequivalence study to establish bioequivalence between Met XR 1000 manufactured in Mt. Vernon and Met XR 1000 manufactured in Evansville (Study CV138100). The sponsor is requesting a biowaiver to conduct bioequivalence studies of Saxa 5/Met XR 500, Saxa 5/Met XR 1000, and Saxa 2.5/Met XR 1000 manufactured with Mt. Vernon Met XR (b) (4) tablets.

Saxagliptin dissolution data provided in Tables 24-26 shows that saxagliptin is rapidly dissolved irrespective of the pH of the dissolution medium in all strengths of Saxa/Met XR.



**Reviewer's Note:**

The biowaiver request to waive any requirement to conduct a bioequivalence study of Saxa 5/Met XR 500, Saxa 5/Met XR 1000, and Saxa 2.5/Met XR 1000 manufactured using Mt. Vernon Met XR (b) (4) with the same Saxa/Met XR products manufactured using Evansville Met XR (b) (4) is acceptable based on comparable dissolution data of saxagliptin and metformin in three pH media.

Based on the Office of Clinical Pharmacology review of ONGLYZA NDA, the BCS classification of saxagliptin is considered BCS Class 3 drug (high solubility, low permeability). (b) (4)



***Dose Dumping***



**In Vitro Dissolution Testing of 500 and 1000 mg Metformin XR in Ethanol Solutions**

The influence of ethanol on the release of metformin from the (b) (4) tablets was examined with dissolution methodology. Dissolution assessments of metformin, in saxagliptin/metformin XR FDC tablets, were performed on two strengths; 5 mg saxagliptin/500 mg metformin XR and 5 mg saxagliptin/1000 mg metformin XR, using NDA (21-202) approved method 249209 (USP Apparatus 1 at 100 rpm in 1000 mL of 50 mM potassium phosphate buffer, pH 6.8, at 37 °C) in the presence of 0, 5, 10, and 25% v/v ethanol solution. The sponsor stated that the range of alcohol concentrations in the dissolution medium mimics the levels that are likely to be reached in the fluid of the stomach, and proximal GI tract, following alcohol consumption.

Dissolution testing was performed over a 12-hour time period using an automated sampling device. Dissolution tests in each medium were performed on six dosage units of each of the following batches, as described in Table 30.

**Table 30: Dissolution Test Conditions for Metformin in 5 mg saxagliptin/500 mg metformin XR and 5 mg saxagliptin/1000 mg metformin XR FDC Tablets**

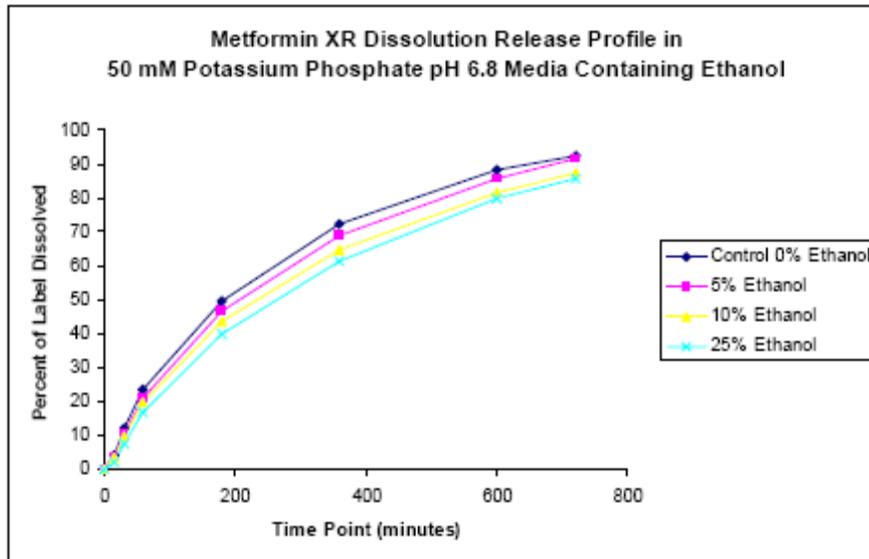
Dosage Strength	Batch Number	Registrational Method (USP Apparatus 1 at 100 rpm in 50mM Potassium Phosphate, pH 6.8, at 37 °C)			
		Control (0% Ethanol)	5% Ethanol	10% Ethanol	25% Ethanol
5 mg/ 500 mg	8A4326X	x	x	x	x
5 mg/ 1000 mg	8A4332X	x	x	x	x

Dissolution results are summarized in Table 31, and presented graphically in Figure and Figure 3.

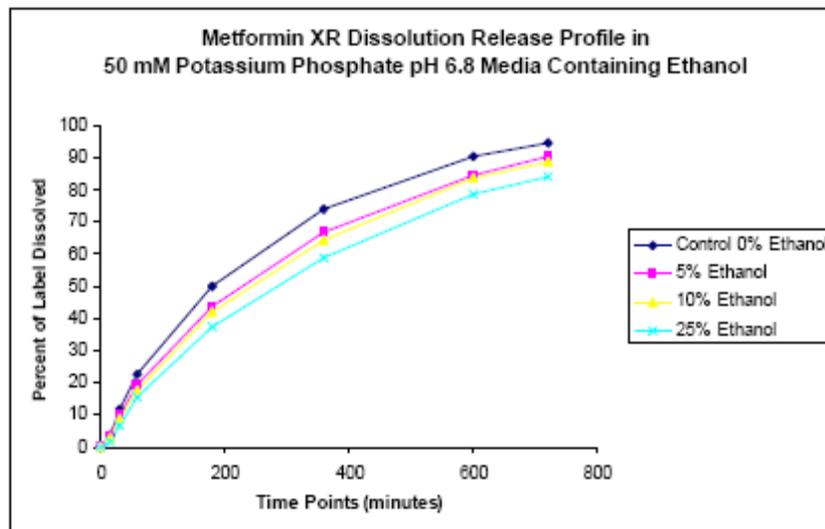
**Table 31: Summary of Metformin XR Dissolution Results in Saxagliptin/Metformin XR FDC Tablets in 1000 mL of pH 6.8, 50 mM Potassium Phosphate Buffer Containing 0, 5, 10 and 25% v/v Ethanol, Using USP Apparatus 1 at 100 rpm, at 37 °C**

Sample Description	Ethanol	Average Percent Dissolved (n=6)							Similarity Factor (f <sub>2</sub> )
		15 min	30 min	60 min	180 min	360 min	600 min	720 min	
5 mg/ 500 mg	0%	4	12	23	50	72	88	93	----
		range (4-5)	range (12-13)	range (23-24)	range (49-50)	range (71-73)	range (88-89)	range (92-94)	
	5%	4	11	21	47	69	86	92	81
		range (3-4)	range (11-10)	range (20-22)	range (44-49)	range (67-71)	range (84-88)	range (89-94)	
	10%	3	10	20	44	65	82	87	66
range (3-4)		range (9-10)	range (20-21)	range (43-44)	range (63-67)	range (80-85)	range (86-90)		
25%	2	8	17	40	61	80	86	57	
range (2-2)	range (7-8)	range (16-18)	range (38-41)	range (60-63)	range (78-81)	range (84-86)			
5 mg/ 1000 mg	0%	4	12	23	50	74	90	94	----
		range (3-4)	range (11-12)	range (22-24)	range (48-51)	range (72-77)	range (89-94)	range (93-96)	
	5%	4	10	20	44	67	84	90	67
		range (3-4)	range (12-13)	range (18-21)	range (42-45)	range (65-69)	range (82-87)	range (88-93)	
	10%	3	9	18	42	64	84	89	62
range (2-3)		range (8-9)	range (17-18)	range (41-44)	range (62-68)	range (80-87)	range (86-93)		
25%	2	7	16	38	59	79	84	51	
range (1-2)	range (6-8)	range (15-17)	range (35-42)	range (55-66)	range (74-88)	range (81-96)			

**Figure 2: Mean *In Vitro* Dissolution Profiles of Metformin from 5 mg Saxagliptin/500 mg Metformin XR in 1000 mL of pH 6.8, 50 mM Potassium Phosphate Buffer Containing 0, 5, 10, and 25% v/v Ethanol (n=6), Using USP Apparatus 1 at 100 rpm at 37 °C**



**Figure 3: Mean *In Vitro* Dissolution Profiles of Metformin from 5 mg Saxagliptin/1000 mg Metformin XR in 1000 mL of pH 6.8, 50 mM Potassium Phosphate Buffer Containing 0, 5, 10, and 25% v/v Ethanol (n=6), Using USP Apparatus 1 at 100 rpm at 37 °C**



The  $f_2$  values shown in Table 30 and the dissolution profiles of metformin from the 500 and 1000 mg metformin XR formulations shown in the Figure 2 and Figure 3, indicate similarity of the release profiles in the absence and presence of up to 25% ethanol in the proposed dissolution medium. The sponsor attributed the slight decrease in the release rates with increased ethanol content to decreased metformin drug solubility in ethanol compared to the registrational method media (50mM potassium phosphate buffer pH 6.8), and were not considered significant.

**Reviewer’s Note:**

For both strengths, 5 mg saxagliptin/500 mg metformin XR and 5 mg saxagliptin/1000 mg metformin XR, the dissolution profiles of extended release metformin in the proposed dissolution medium containing a range of alcohol concentrations did not result in a failure of the (b) (4) over 12 hours.

**RECOMMENDATIONS:**

**Dissolution Method:**

The following proposed dissolution method for Saxa/Met XR FDC tablets is acceptable.

Apparatus: USP Apparatus I (baskets)  
Speed: 100 rpm  
Medium: pH 6.8 Phosphate Buffer  
Volume: 1000 mL  
Temperature: 37 C  
Sampling Times: Saxagliptin 30 minutes  
Metformin 1,3, and 10 hours

**Dissolution Specifications:**

The dissolution specifications for Saxa/Met XR FDCs are as follows:

**Saxagliptin**

*NLT (b) (4) (Q) dissolved in 15 minutes*

**Metformin**

*1 hour: (b) (4)*  
*3 hours: (b) (4)*  
*10 hours: NLT (b) (4)*

**Biowaiver Requests:**

1. Biowaiver request for the 2.5 Saxa/1000 Met FDC tablet is acceptable.
2. The request to waive the requirement to repeat the in vivo BE study using Saxa 5/Met XR 500 manufactured at the commercial scale is not applicable, because the sponsor decided to repeat the study using the to-be-marketed FDC formulation manufactured at the BMS manufacturing facility

at Mt Vernon, IN (test) versus 5 mg Onglyza and 500 mg Glucophage XR (Evansville, IN, clinical formulation) using commercial scale batches.

3. The request to waive any requirement to conduct an in vivo bioequivalence study of Saxa 5/Met XR 500, Saxa 5/Met XR 1000, and Saxa 2.5/Met XR 1000 manufactured using Mt. Vernon Met XR (b) (4) with the same Saxa/Met XR products manufactured using Evansville Met XR (b) (4) is acceptable.

**Alcohol Induced Dose Dumping:**

The results from the in-vitro alcohol study showed that alcohol concentrations in the range of 5% to 25% do not induce the dumping of metformin from the (b) (4) tablets.

**Signature**

Houda Mahayni, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Signature**

Patrick J. Marroum, Ph.D.  
Biopharmaceutics Lead  
Office of New Drugs Quality Assessment

cc: NDA 200-678, MHai, ADorantes, EChikhale, Dhenry, STran

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HOUDA MAHAYNI  
09/27/2010

PATRICK J MARROUM  
09/28/2010

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200678

NDA Number: 200678

Applicant: Bristol-Myers Squibb Stamp Date: December 29, 2010

Drug Name: Saxagliptin/Metformin NDA Type: Standard Hydrochloride

On initial overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
<b>Criteria for Refusal to File (RTF)</b>				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	Yes		The sponsor has submitted reports of two pivotal bioequivalence studies within 90 days of the NDA submission
2	Has the applicant provided metabolism and drug-drug interaction information?			The sponsor indicates that the relevant information was included in Onglyza NDA (22350)
<b>Criteria for Assessing Quality of an NDA</b>				
<b>Data</b>				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	Yes		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA
<b>Studies and Analyses</b>				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	Yes		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			NA
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			NA
8	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?			The sponsor stated in the proposed labeling that the dose of saxagliptin should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor, and it is the same as stated by labeling of Onglyza NDA 22350 (drug-drug interaction studies were conducted in NDA 22350).
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			(b) (4)

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR NDA 200678**

				(b) (4)
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		No	
11	Is the appropriate pharmacokinetic information submitted?	Yes		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes		
<b>General</b>				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	Yes		Reports of two pivotal bioequivalence studies have been submitted within 90 days of the NDA submission.
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	Yes		See comments above as 13
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	Yes		See comments above as 13
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes		See comments above as 13
17	Was the translation from another language important or needed for publication?		No	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Since the sponsor has submitted the reports of two pivotal bioequivalence studies within 90 days of the NDA submission, it is considered fileable.**

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.

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR NDA 200678**

Weili Huang, Ph.D.

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Reviewing Pharmacologist

Date

Sally Y. Choe, Ph.D.

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Team Leader/Supervisor

Date

**Office of Clinical Pharmacology**  
***New Drug Application Filing and Review Form***

**General Information About the Submission**

	Information		Information
NDA	200678	Brand Name	(b) (4)
OCP Division	II	Generic Name	Saxagliptin/metformin hydrochloride
Medical Division	DMEP	Drug Class	DPP4 inhibitor and biguanide combination
OCP Reviewer	Weili Huang	Indication(s)	Treat adults with type 2 diabetes mellitus
OCP Team Leader	Sally Y. Choe	Dosage Form	5 mg/ 500 mg, 2.5 mg/1000 mg, and 5 mg/1000 mg extended-release tablet
Date of Submission	29-Dec-2009	Dosing Regimen	Once daily with the evening meal
Estimated Due Date of OCP Review	29-Aug-2009	Route of Administration	Oral
PDUFA Due Date	29-Oct-2009	Sponsor	Bristol-Myers Squibb
Division Due Date	29-Aug-2009	Priority Classification	Standard
		Submission Type	505 (b) (1)

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
In vivo mass balance:				
In vitro isozyme characterization:				
In vitro metabolite identity				
In vitro metabolism inhibition:				
In vitro mechanism of uptake in human liver				
In vitro plasma protein binding:				
Blood/plasma ratio:				
Pharmacokinetics (e.g., Phase I) -				
Dose proportionality, healthy volunteers – fasting & non-fasting single and multiple doses:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
pediatrics:				
gender & geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 1:				
Phase 3:				
<b>PK/PD:</b>				
Phase 2, dose ranging studies:				
Phase 3 clinical STUDIES (placebo controlled):	X	2		CV181038 and CV181066
Phase 3 clinical STUDIES (active controlled):				
Population Analyses -				
Meta-analysis:				
NONMEM:				
<b>II. Biopharmaceutics</b>				

<b>Absolute bioavailability:</b>				
Bioequivalence studies – traditional design	X	7		The submitted studies in the NDA include CV181060, CV138098, CV181074, CV181076 and CV138100. Two pivotal bioequivalence studies (CV181111 and CV181112) have been submitted within 90 days of the NDA submission
<b>Relative bioavailability alternate formulation as reference:</b>				
Food-drug interaction studies:	X	2		Pivotal bioequivalence and food effect study CV181111 have been submitted within 90 days of the NDA submission
<b>Absorption site</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Phenotype studies:</b>				
Chronopharmacodynamics				
Pediatric development plan				
Literature References				
QT prolongation assessment				
<b>Total Number of Studies</b>			9	
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable?	X	The NDA is fileable from the clinical pharmacology perspective.		
Comments to be sent to firm?				
QBR questions (key issues to be considered)	<p>Are the to-be-marketed FDC tablets (saxagliptin/metformin) manufactured in Mt. Vernon bioequivalent to metformin XR tablets (manufactured in Evansville) used in the pivotal clinical studies?</p> <p>What is the food effect on the FDC tablets?</p> <p>What is the steady-state pharmacokinetics of the new 5 mg/1000 mg strength tablets?</p>			

<p><b>Other comments or information not included above</b></p>	<p>Study CV181112 titled “Bioequivalence Study of the Fixed Dose Combination of 5 mg Saxagliptin/1000 mg Metformin XR (Manufactured in Mt. Vernon, In) Relative to 5 mg of Onglyza and 2x500 mg Glucophage XR Coadministered to Healthy Subjects in the Fed State and Steady-State Pharmacokinetic Assessment of the Fixed Dose Combination of 5 mg Saxagliptin/1000 mg Metformin XR” will link the Phase 3 clinically-tested formulation and the to-be-marketed formulation. Hence, a DSI inspection on this pivotal bioequivalence study is in order.</p> <p><b>Clinical Site:</b>  <b>Matthew M. Medlock, MD, Principal Investigator</b>  PPD Development, LP  7551 Metro Center Drive  Suite 200  Austin, TX 78744  Study CV181112</p> <p><b>Bioanalytical sites:</b></p> <p><b>Saxagliptin/BMS 510849 PK samples :</b>  <span style="background-color: #cccccc; display: inline-block; width: 300px; height: 1em;"></span> (b) (4)</p> <p><b>Metformin PK samples :</b>  <span style="background-color: #cccccc; display: inline-block; width: 300px; height: 1em;"></span> (b) (4)</p> <p><b>Note :</b> The above information and address have been provided and confirmed by the sponsor.</p>
<p><b>Primary reviewer Signature and Date</b></p>	<p>Weili Huang</p>
<p><b>Secondary reviewer Signature and Date</b></p>	<p>Sally Choe</p>

## Filing Memo

### Summary

The sponsor (Bristol-Myers Squibb Company) submitted the NDA to seek a marketing approval for the Fixed Dose Combination (FDC) 5 mg/500 mg, 2.5 mg/1000 mg, and 5 mg/1000 mg saxagliptin/metformin hydrochloride extended-release tablets. The drug product is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. The individual component drug products have been marketed by the same sponsor: saxagliptin immediate-release tablets (ONGLYZA, 5 mg and 2.5 mg) was approved by the Agency on July 31, 2009 under NDA 22350 and metformin hydrochloride extended-release tablets (GLUCOPHAGE XR, 500 mg and 750 mg) was approved by the Agency on Oct 13, 2000 under NDA 21202.

The submission type of this NDA is 505 (b) (1). NDA includes 5 Phase 1 bioequivalence studies in healthy volunteers and 2 clinical Phase 3 studies in patients with type 2 diabetes. The pivotal clinical Phase 3 study (CV181066) used metformin XR (500 mg) manufactured in Evansville, but the proposed market products for FDC tablets are manufactured in Mt. Vernon. In the Pre-NDA meeting, the Agency indicated that there was no direct bridging between the proposed market formulation (5 mg/500 mg FDC manufactured in Mt. Vernon) and metformin XR formulation (500 mg manufactured in Evansville) in pivotal clinical trials. Also the Agency requested the steady-state PK information of the FDC that contains 1000 mg XR metformin because it is the new highest strength of metformin XR formulation that has never been evaluated in a clinical setting beyond the single-dose PK trial. Therefore, the sponsor informed the Agency that they will conduct two pivotal bioequivalence studies (CV181111 and CV181112) and the clinical study reports have been submitted within 90 days of the NDA submission. The sponsor requests a biowaiver for 2.5 mg/1000 mg strength and it will be reviewed by ONDQA/Biopharm.

Two pivotal ongoing bioequivalence studies are shown as follows:

- **Fed bioequivalence and food effect, single dose study (CV181111)**

Test product: 5 mg /500 mg FDC tablet (Mt. Vernon, (b)(4) Mt. Vernon) given fasted and fed

Reference product: 5 mg saxagliptin tablet + 500 mg Glucophage XR tablet (Evansville) given fed

Results: The 5 mg/500 mg FDC table (Mt. Vernon, (b)(4) Mt. Vernon) is bioequivalent to the reference product under fed condition. There is no food effect on the pharmacokinetics of saxagliptin or metformin for the test product.

- **Fed bioequivalence and steady-state assessment (CV181112)**

Test product: 5 mg saxagliptin/1000 mg metformin FDC tablet (Mt. Vernon) given fed (single dose and QD for 4 days)

Reference product: 5 mg saxagliptin tablet + 2 x 500 mg Glucophage XR tablet (Evansville) given fed (single dose)

Results: The 5 mg/1000 mg FDC table (Mt. Vernon) is bioequivalent to the reference product under fed condition. Mean C<sub>max</sub> of saxagliptin for the FDC at steady state was similar (99%) to that after single dosing. Mean total exposures (AUC<sub>0-24 hr</sub>) of saxagliptin and its metabolite BMS-510849 over the dosing interval at steady state were comparable to the total exposures (AUC<sub>0-inf</sub>) after single dosing, 94% and 109%, respectively. Mean C<sub>max</sub> of metformin for the FDC was approximately 90% of that of the FDC tablet after single dose. Mean AUC<sub>0-24hr</sub> of metformin over the dosing interval at steady state were 101% of the AUC<sub>0-inf</sub> after single dosing.

A list of completed supporting bioequivalence studies are provided as follows:

**1. Fed bioequivalence and food effect (CV181060)**

Test product: 5 mg /500 mg FDC tablets (New Brunswick, (b) (4) Evansville) given fasted and fed  
Reference product: 5 mg saxagliptin tablet (New Brunswick) + 500 mg Glucophage XR tablet (Evansville) given fed

Results: The 5 mg/500 mg FDC is bioequivalent to the reference product under fed condition. Therefore, there is no formulation effect under fed condition. Given with food, saxagliptin C<sub>max</sub> decreased by 13.5% and there were no changes for metformin C<sub>max</sub>, AUC of saxagliptin and AUC of metformin.

**2. Fasted and fed bioequivalence – manufacturing site change (CV138098)**

Test product: 500 mg metformin XR (Mt. Vernon) tablet given fasted and fed  
Reference product: 500 mg Glucophage (Evansville) tablet given fasted and fed

Results: The 500 mg metformin XR (Mt. Vernon) tablet is bioequivalent to the 500 mg Glucophage (Evansville) tablet under fasted and fed conditions.

**3. Fed dose strength equivalence (CV181074)**

Test product: 1000 mg metformin XR (Evansville) tablet given fed  
Reference product: 2 x 500 mg Glucophage (Evansville) tablets given fed

Results: The 1000 mg metformin XR (Evansville) tablet is not bioequivalent to the 2x500 mg Glucophage (Evansville) tablets under fed condition (C<sub>max</sub> ratio: 1.171, CI: 1.037-1.323).

Reviewer's comments: The performance of bioanalytical assay for the analysis of metformin in human plasma in Study CV181074 is poor, based on the values of between-run %CV ≤31.35 and within-run %CV ≤62.38 for metformin.

**4. Fed bioequivalence and food effect (CV181076)**

Test product: 5 mg/1000 mg metformin XR tablet (Mt. Vernon, (b) (4) Evansville) given fasted and fed  
Reference product: 5 mg saxagliptin tablet + 1000 mg metformin (Evansville) tablet given fasted and fed

Results: The 5 mg/1000 mg metformin XR tablet is bioequivalent to the reference product under fasted and fed conditions. Food increased merformin C<sub>max</sub> by 21%, metformin AUC<sub>t</sub> by 13% and metformin AUC<sub>inf</sub> by 12%. There is no food effect on saxagliptin C<sub>max</sub> and AUC.

**5. Fasted and fed bioequivalence – manufacture site change (CV138100)**

Test product: 1000 mg metformin XR tablet (Mt. Vernon) given fasted and fed  
Reference: 1000 mg metformin XR tablet (Evansville) given fasted and fed

Results: The 1000 mg metformin XR tablet (Mt. Vernon) is bioequivalent to the 1000 mg metformin XR tablet (Evansville) under fed condition. But the 1000 mg metformin XR tablet (Mt. Vernon) is not bioequivalent to the 1000 mg metformin XR tablet (Evansville) under fasted condition (C<sub>max</sub> ratio: 0.888, CI: 0.773-1.019)

**Proposed labeling:** The reviewer checked the proposed labeling and the relevant clinical pharmacology information has been submitted in this NDA, Onglyza NDA 22350, or Glucophage XR NDA 21202.

**The reviewer's conclusion and comments:**

- The NDA is fileable from the clinical pharmacology perspective. Clinical study reports of two pivotal bioequivalence studies (CV181111 and CV181112) have been submitted within 90 days of the NDA submission as stated by the sponsor in the NDA submission.
- The performance of bioanalytical assay for the analysis of metformin in human plasma in Study CV181074 is poor, based on the values of between-run %CV  $\leq 31.35$  and within-run %CV  $\leq 62.38$  for metformin.
- DSI inspection is requested for the bioequivalence study CV181112. The information of clinical sites and bioanalytical sites have been provided and confirmed by the sponsor.

**Major review questions (key issues to be considered)**

- Are the to-be-marketed FDC tablets (saxagliptin/metformin) manufactured in Mt. Vernon bioequivalent to metformin XR tablets (manufactured in Evansville) used in the two pivotal clinical studies?
- What is the food effect on the FDC tablets?
- What is the steady-state pharmacokinetics of the new 5 mg/1000 mg strength tablets?

Attachment

Protocol	Study Description	Treatments [Manufacturing Site]	Number of Subjects	Bioequivalence Criteria Met? If not, the PE (90%CI) are provided			
				Fasted		Fed	
				Cmax	AUC	Cmax	AUC
CV181060 <sup>18</sup>	Fed Bioequivalence and Food Effect - 5 mg saxagliptin/500 mg metformin XR FDC vs individual components	3 period x 3 treatment: 5 mg saxagliptin/500 mg metformin XR FDC [New Brunswick] (test) given fed and fasted and 5 mg saxagliptin [New Brunswick] plus 500 mg Glucophage XR [Evansville] (reference) given together in the fed state	24	N/E	N/E	Yes	Yes
CV138098 <sup>16</sup>	Fasted and Fed Bioequivalence - Manufacturing site change from BMS Evansville, IN to BMS Mt Vernon, IN for the 500 mg metformin XR; (b) (4) tablet for the 5 mg saxagliptin/500 mg metformin XR FDC	4 period x 4 treatment: 500 mg Glucophage XR [Evansville] (reference) in the fed and fasted states and 500 mg metformin XR [Mt Vernon] (test) in the fed and fasted states	28	Yes	Yes	Yes	Yes
CV181111 <sup>4</sup>	Fed Bioequivalence and Food Effect - 5 mg saxagliptin/500 mg metformin XR FDC vs. individual components using to-be-marketed formulations	3 period x 3 treatment: 5 mg saxagliptin/500 mg metformin XR FDC [Mt Vernon] (test) given fed and fasted and 5 mg Onglyza [Mt Vernon] plus 500 mg Glucophage XR [Evansville] (reference) given together in the fed state	30	N/E	N/E	Yes	Yes

All studies were open label, randomized, crossover studies conducted in healthy subjects

Abbreviations: BMS = Bristol-Myers Squibb; CI = confidence interval FDC = fixed dose combination, mg = milligram; N/E = fasted bioequivalence not evaluated; PE = point estimate; saxa = saxagliptin; XR = extended release

Protocol	Study Description	Treatments [Manufacturing Site]	Number of Subjects	Bioequivalence Criteria Met? If not, the PE (90%CI) are provided			
				Fasted		Fed	
				Cmax	AUC	Cmax	AUC
CV181074 <sup>20</sup>	Fed Dose Strength Equivalence - 2 x 500 mg metformin XR vs 1 x 1000 mg metformin XR	2 period x 2 treatment: 1 x 1000 mg metformin XR [Evansville](test) and 2 x 500 mg Glucophage XR [Evansville] (reference), both in the fed condition	18	N/E	N/E	No 1.171, (1.037, 1.323)	Yes
CV181076 <sup>19</sup>	Fed Bioequivalence and Food Effect - 5 mg saxagliptin/1000 mg metformin XR FDC vs individual components	3 period x 3 treatment: 5 mg saxagliptin/1000 mg metformin XR FDC [Mt Vernon] (test) given fed and fasted and 5 mg saxagliptin [New Brunswick] plus 1000 mg metformin XR [Evansville] (reference) given together in the fed state	24	N/E	N/E	Yes	Yes
CV138100 <sup>17</sup>	Fasted and Fed Bioequivalence - Manufacturing site change from BMS Evansville, IN to BMS Mt Vernon, IN for the 1000 mg metformin XR: (b) (4) tablet for the 2.5 and 5 mg saxagliptin/1000 mg	4 period x 4 treatment: 1000 mg metformin XR manufactured at the BMS Evansville site (reference) in the fed and fasted states and 1000 mg metformin XR manufactured at the BMS Mt Vernon site (test) in the fed and fasted states	28	No 0.888 (0.773, 1.019)	Yes	Yes	Yes

Protocol	Study Description	Treatments [Manufacturing Site]	Number of Subjects	Bioequivalence Criteria Met? If not, the PE (90%CI) are provided			
				Fasted		Fed	
				Cmax	AUC	Cmax	AUC
CV181112 <sup>5</sup>	Fed Bioequivalence and Steady-State Assessment - Single dose fed BE of 5 mg saxagliptin/1000 mg metformin XR FDC vs individual components followed by a steady-state assessment of the 5 mg saxagliptin/1000 mg metformin XR FDC	3 period x 3 treatment. Periods 1 and 2: 5 mg saxagliptin/1000 mg metformin XR FDC [Mt Vernon] (test) given fed and 5 mg Onglyza [Mt. Vernon] plus 2 x 500 mg Glucophage XR [Evansville] (reference) given together in the fed state. Period 3 a steady-state PK assessment of QD 5 mg saxagliptin/1000 mg metformin XR FDC [Mt Vernon] on Day 4 in subjects randomized to 5 mg saxagliptin/1000 mg metformin XR FDC [Mt Vernon] in Period 2.	30	N/E	N/E	Yes	Yes

All studies were open label, randomized, crossover studies conducted in healthy subjects

Abbreviations: BMS = Bristol-Myers Squibb; CI = confidence interval FDC = fixed dose combination, QD = once daily; mg = milligram; N/E = fasted bioequivalence not evaluated; PE = point estimate; saxa = saxagliptin; XR = extended release

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-200678

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ORIG-1

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BRISTOL MYERS  
SQUIBB

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 (b) (4) (saxagliptin +  
metformin XR) Tablets

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WEILI HUANG  
03/31/2010

SALLY Y CHOE  
03/31/2010

<b>BIOPHARMACEUTICS REVIEW</b>			
<b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 200-678 (000)	<b>Reviewer:</b> Houda Mahayni, Ph.D.	
<b>Division:</b>	DMEDP		
<b>Sponsor:</b>	Bristol-Myers Squibb Company	<b>Team Leader:</b> Angelica Dorantes, Ph.D.	
<b>Trade Name:</b>	(b) (4)	<b>Supervisor:</b> Patrick J. Marroum, Ph.D.	
<b>Generic Name:</b>	Saxagliptin (BMS-477118)/metformin HCl	<b>Date Assigned:</b>	Jan 25, 2010
<b>Indication:</b>	Type 2 Diabetes Mellitus	<b>Date of Review:</b>	Feb 6, 2010
<b>Formulation</b>	Extended-Release Fixed Dose Combination Tablet		
<b>Route of Administration</b>	Oral		
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Dec 29, 2009	Dec 29, 2009	Jan 25, 2010	Oct 29, 2010
<b>Type of Submission:</b>	Original NDA		
<b>Type of Consult:</b>	Biowaiver Request, Dissolution method and specifications--- <b>FILING REVIEW</b>		
<b>REVIEW SUMMARY:</b>			
<p>Saxagliptin (Trade name: Onglyza) is an inhibitor of dipeptidyl peptidase-4 (DPP-4) and was approved by the FDA as an anti-diabetic drug on July 31, 2009, under NDA 22-350. Metformin (Trade name: Glucophage) XR is an anti-diabetic drug of the biguanide class and was approved by the FDA on October 13, 2000, under NDA 21-202. Both drug products are marketed by BMS.</p> <p>Fixed Dose Combination (FDC) tablets of saxagliptin with metformin XR have been developed in the following 3 different dose strengths to allow once-daily dosing of saxagliptin with metformin at total daily doses up to 5 mg saxagliptin and 2000 mg metformin (i.e., the highest recommended once-daily doses of saxagliptin and metformin):</p> <ul style="list-style-type: none"> <li>• 5 mg saxagliptin/500 mg metformin XR</li> <li>• 5 mg saxagliptin/1000 mg metformin XR</li> <li>• 2.5 mg saxagliptin/1000 mg metformin XR.</li> </ul> <p>(b) (4)</p> <p>Therefore, separate bioequivalence studies were conducted for the 500 mg and 1000 mg metformin XR FDCs.</p> <p>This submission includes data from 5 Bioequivalence studies, including the report for justifying 3 biowaiver requests, and the dissolution method development and specifications.</p>			

**Bioequivalence Studies:**

The bioequivalence (BE) studies conducted in support of Saxa/Met XR development are listed below.

1. Study CV181060 was conducted to demonstrate bioequivalence of Saxa 5/Met XR 500, and co-administered 5-mg saxagliptin film-coated tablet and a GLUCOPHAGE XR 500 tablet in fed healthy subjects.
2. Study CV181074 was conducted to demonstrate bioequivalence of metformin XR (1 x 1000-mg tablet), and metformin XR (2 x 500-mg tablets) in fed healthy subjects using tablets manufactured at the BMS Evansville, Indiana, facility.
3. Study CV181076 was conducted to establish bioequivalence of a Saxa 5/Met XR 1000 FDC tablet, and co-administered saxagliptin 5-mg tablet and metformin XR 1000-mg tablet in fed and fasted healthy subjects.
4. Study CV138098 was conducted to demonstrate bioequivalence of GLUCOPHAGE XR 500 manufactured in Mt. Vernon, Indiana, and GLUCOPHAGE XR 500 manufactured in Evansville, Indiana, in fasted and fed healthy subjects.
5. Study CV138100 was conducted to demonstrate bioequivalence of Met XR 1000 manufactured in Mt. Vernon, Indiana, and Met XR 1000 manufactured in Evansville, Indiana, in fasted and fed healthy subjects.

**Biowaiver Requests:**

There are three biowaiver requests included in this submission. The first biowaiver request is for the 2.5/1000 mg. According to the sponsor, the data from the bioequivalence study which used the FDC tablet of 5 mg saxagliptin/1000 mg metformin XR are applicable to the lower strength FDC tablet of 2.5 mg saxagliptin/1000 mg metformin XR formulation, and no separate bioequivalence study is needed with the lower saxagliptin strength with 1000 mg metformin XR formulation.

The second biowaiver request is to waive the requirement to repeat the BE study using Saxa 5/Met XR 500 manufactured at the commercial scale. The sponsor used a batch size of (b) (4) ( ) which was less than the “10% of the commercial scale or 100,000 units, whichever is greater” criterion for a biobatch for a pivotal BE study. The commercial scale (b) (4) will be conducted at about (b) (4)

The third biowaiver request is to waive any requirement to conduct a bioequivalence study of Saxa 5/Met XR 500, Saxa 5/Met XR 1000, and Saxa 2.5/Met XR 1000 manufactured using Mt. Vernon Met XR (b) (4) with the same Saxa/Met XR products manufactured using Evansville Met XR (b) (4)

**Dissolution Method and Specifications:**

A single method was developed for the dissolution testing of both immediate-release saxagliptin and extended-release metformin components in all three strengths of Saxa/Met XR. The proposed dissolution method is equivalent to the dissolution method conditions described in the USP monograph for Metformin Hydrochloride Extended-Release Tablets (Test 1) for tablets labeled to contain 750 mg (i.e., USP apparatus 1 (baskets), 100 rpm, pH 6.8 phosphate buffer, 1000 mL, 37°C). This method was used to support i) clinical release of Saxa/Met XR used in bioequivalence studies, ii) long-term stability studies, and iii) quality control release testing.

A specification limit of NLT Q <sup>(b)</sup><sub>(4)</sub> in 30 minutes is proposed for the saxagliptin component of Saxa/Met XR. The proposed dissolution specification for saxagliptin in Saxa/Met XR is the same as the current approved dissolution specification for saxagliptin in ONGLYZA tablets.

A common specification for metformin in all three formulations is being proposed: <sup>(b)</sup><sub>(4)</sub> at 1 hour, <sup>(b)</sup><sub>(4)</sub> at 3 hours, and NLT <sup>(b)</sup><sub>(4)</sub> at 10 hours.

**Dose Dumping:**

The influence of ethanol on the release of metformin from the <sup>(b)</sup><sub>(4)</sub> tablets was examined in-vitro. Dissolution assessments of metformin, in saxagliptin/metformin XR FDC tablets, were performed on two strengths; 5 mg saxagliptin/500 mg metformin XR and 5 mg saxagliptin/1000 mg metformin XR, using NDA (21-202) approved method 249209 (USP Apparatus 1 at 100 rpm in 1000 mL of 50mM potassium phosphate buffer, pH 6.8, at 37 °C) in the presence of 0, 5, 10, and 25% v/v ethanol solution. The sponsor stated that the range of alcohol concentrations in the dissolution medium mimics the levels that are likely to be reached in the fluid of the stomach, and proximal GI tract, following alcohol consumption (i.e., 5-25%). Dissolution testing was performed over a 12-hour time period using an automated sampling device.

The biopharmaceutics review will be focused on the evaluation of the biowaiver requests, the proposed dissolution method and specifications, and the effect of alcoholic medium on the in-vitro dissolution behavior of <sup>(b)</sup><sub>(4)</sub> tablets.

**RECOMMENDATION:**

The ONDQA/biopharmaceutics team has reviewed NDA 200-678(000) for filing purposes. We found this NDA filable from biopharmaceutics perspective. The sponsor has submitted a reviewable submission. There are no comments to be conveyed to the sponsor at this time.

**Houda Mahayni, Ph. D.**  
Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Patrick J. Marroum, Ph. D.**  
Biopharmaceutics Expert  
Office of New Drugs Quality Assessment

cc: NDA 200-678, MHai, PPeri, STran, ADorantes

APPEARS THIS WAY ON  
ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200678	ORIG-1	BRISTOL MYERS SQUIBB	(b) (4) (saxagliptin + metformin XR) Tablets

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

/s/

HOUDA MAHAYNI  
02/19/2010

PATRICK J MARROUM  
02/22/2010