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RESEARCH**

APPLICATION NUMBER:
202270Orig1s000

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

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:202270	Submission Date: August 02, 2011
Brand Name	Janumet XR
Generic Name	Sitagliptin/metformin HCl extended fixed dose combination (FDC) tablets
Reviewer	Jee Eun Lee, Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Metabolism and Endocrinology Products
Sponsor	Merck Sharp Dohme
Relevant IND, NDA	IND 101,964; NDA 22-044 (Janumet®), NDA 21-748 (Glumetza®), NDA 21-995 (Januvia®)
Submission Type	Resubmission NDA 505(b)(1)
Formulation; Strength(s)	FDC products of sitagliptin/metformin XR at dose strengths 50 mg/500 mg, 50 mg/1000 mg, 100 mg/1000 mg
Indication	Treatment of Type 2 Diabetes Mellitus

1 Executive Summary

This 505(b)(1) application by Merck Sharp Dohme is in pursuit of approval for the fixed dose combination (FDC) 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg of sitagliptin/metformin extended release (MK-0431A XR, Janumet XR) tablets. For complete review of clinical pharmacology information from the original NDA, readers can refer to the original clinical pharmacology review of NDA 20-2770 in DAARTS dated 6/17/2011

Prior to this resubmission, Merck received a complete response letter for the original NDA, 20-2270. Janumet XR contains sitagliptin and metformin XR and the registration of this product is based on demonstration of bioequivalence (BE) between Janumet XR (MK-0431A XR) and co-administration of sitagliptin and an approved metformin XR formulation (Glumetza®, NDA 21-748). In the complete response letter issued on July 22, 2011, the sponsor was asked to submit the updated completed study report (CSR) for the pivotal BE study 147. This comment was based on the recommendation of office of

scientific investigation (OSI). Division of Bioequivalence and GLP Compliance (DBGC) of OSI issued FDA-483 at the bioanalytical laboratory, (b) (4) which analyzed blood samples obtained from the pivotal BE study. (b) (4) response to the Form FDA-483 was submitted on July 11, 2011, and reviewed by DBGC (see Dr. Gopa Biswas' review dated to July 15, 2011). Deficiencies listed in the Form FDA-483 were resolved and consequently the bioanalytical data were updated. Therefore, the sponsor repeated the bioequivalence assessment with the reintegrated data and updated the CSR accordingly. This review is focused on the updated study results of the pivotal BE study.

2 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-II (OCP/DCP-II) has reviewed the clinical pharmacology data submitted under NDA 202270 resubmission dated 8/02/2011 and finds it acceptable to support approval.

3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The pivotal BE study compared the administration of Janumet XR to the co-administration of sitagliptin IR and GLUMETZA®, and also the administration of two tablets of 50 mg/500 mg and the administration of one tablet of 100 mg/1000 mg in terms of pharmacokinetic characteristics. This study was conducted with the final market composition (FMC) of Janumet XR tablets, demonstrated BE between the Janumet XR tablets for both 50 mg/500 mg and 100 mg/1000 mg strengths, and between the Janumet XR tablets and co-administration of corresponding doses of sitagliptin and GLUMETZA®. The treatment arms were:

- TRT A: sitagliptin 50 mg + GLUMETZA® 500 mg**
- TRT B: single Janumet XR 50 mg/500 mg tablet**
- TRT C: sitagliptin 100 mg + GLUMETZA® 1000 mg**
- TRT D: single Janumet XR 100 mg/1000 mg tablet**
- TRT E: two tablets of Janumet XR 50 mg/500 mg**

The resulting data allows for the bridging of the existing safety and efficacy data from studies with JANUVIA® (sitagliptin), GLUMETZA® (metformin XR) and the combination of sitagliptin and metformin IR (from the JANUVIA® and JANUMET® programs) to Janumet XR (MK-0431A XR).

The sponsor repeated the pharmacokinetic analysis with the revised bioanalytical data and the summary statistics for metformin and sitagliptin was updated in the resubmission accordingly. The estimated values for PK parameters with revised data are very similar to the original estimates, rendering no change in the bioequivalence assessment results. As shown in the Tables 1 and 2 that the 90% confidence intervals (CIs) of the geometric least square mean ratios for the pharmacokinetic parameters ($AUC_{0-\infty}$ and C_{max}) for sitagliptin (Table 1) and metformin (Table 2) after administration of single tablet of

Janumet XR 100 mg/1000 mg tablet and those after administration of sitagliptin 100 mg + GLUMETZA® 1000 mg fell within the range of [0.80, 1.25]. The bioequivalence between FDC and co-administration of sitagliptin and Glumetza® has been established for two strength levels.

Furthermore, the BE between two tablets of FDC Janumet XR 50 mg/ 500 mg and one tablet of FDC Janumet XR 100 mg/1000 mg has been established in as seen in both tables. Likewise, the 90% CIs of the geometric least square mean ratios for AUC_{0-∞} and C_{max} of sitagliptin (Table 1) and metformin (Table 2) after administration of single tablet of Janumet XR 100 mg/1000 mg tablet and those after administration of two tablets of Janumet XR 50 mg/500 mg fell within the range of [0.80, 1.25].

Table 1. Summary statistics and statistical comparisons for the potency unadjusted plasma PK parameters of sitagliptin after administration of a single Janumet XR 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza®) in healthy adult subjects

Treatment	A	B	C	D	E
PK Parameter	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)
AUC _{0-∞} (hr*ng/mL)	3994 (3883, 4161)	4010 (3849, 4178)	7773 (7461, 8098)	7837 (7521, 8166)	7835 (7520, 8164)
AUC _{0-last} (hr*ng/mL)	3893 (3736, 4057)	3917 (3758, 4082)	7667 (7357, 7989)	7728 (7415, 8054)	7719 (7407, 8044)
C _{max} (ng/mL)	356 (333, 381)	342 (320, 366)	778 (727, 832)	780 (728, 835)	747 (698, 800)
Between-Treatment Comparison (Geometric Mean Ratio [90% CI])					
Parameter	FDC vs. Co-ad 50/500 mg		FDC vs. Co-ad 100/1000 mg	2×FDC 50/500 mg vs. FDC 100/1000 mg	
AUC _{0-∞} (hr*ng/mL)	1.00 (0.99, 1.02)		1.01 (0.99, 1.03)	1.00 (0.98, 1.02)	
AUC _{0-last} (hr*ng/mL)	1.01 (0.99, 1.02)		1.01 (0.99, 1.02)	1.00 (0.98, 1.02)	
C _{max} (ng/mL)	0.96 (0.92, 1.01)		1.00 (0.96, 1.05)	0.96 (0.92, 1.00)	

GM: Geometric Mean; CI: Confidence Interval

Table 2. Summary statistics and statistical comparisons for the potency unadjusted plasma PK parameters of metformin after administration of a single Janumet XR 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza®) in healthy adult subjects

Treatment	A	B	C	D	E
PK Parameter	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)
AUC _{0-∞} (hr*ng/mL)	6614 (6090, 7184)	7045 (6492, 7645)	12458 (11493, 13504)	11963 (11017, 12990)	12286 (11339, 13312)
AUC _{0-last} (hr*ng/mL)	6570 (6093, 7084)	6874 (6374, 7412)	12187 (11304, 13139)	11840 (10976, 12772)	12006 (11133, 12946)
C _{max} (ng/mL)	560 (526, 596)	607 (570, 646)	866 (813, 922)	986 (925, 1051)	999 (937, 1064)
Between-Treatment Comparison (Geometric Mean Ratio [90% CI])					
Parameter	FDC vs. Co-ad 50/500 mg		FDC vs. Co-ad 100/1000 mg	2×FDC 50/500 mg vs. FDC 100/1000 mg	

AUC _{0-∞} (hr*ng/mL)	1.07 (1.01, 1.13)	0.96 (0.91, 1.01)	1.03 (0.97, 1.08)
AUC _{0-last} (hr*ng/mL)	1.05 (1.00, 1.09)	0.97 (0.93, 1.02)	1.01 (0.97, 1.06)
Cmax (ng/mL)	1.08 (1.03, 1.14)	1.14 (1.09, 1.19)	1.01 (0.97, 1.06)

GM: Geometric Mean; CI: Confidence Interval

Reviewer's Comments:

The key results from the revised data indicate that co-administration of sitagliptin and GLUMETZA® and administration of Janumet XR are bioequivalent, and the Janumet XR tablets for both 50 mg/500 mg and 100 mg/1000 mg strengths are bioequivalent for both sitagliptin and metformin XR components. The results obtained from reviewer's independent analysis with raw data provided by the sponsor are in agreement with the sponsor's results. The conclusions made from the original submission regarding BE assessment have not changed by revised bioanalytical data.

Appendix: Synopsis Summary of Pivotal BE Study (Protocol 147)

Title: A Definitive Bioequivalence Study for Sitagliptin/Metformin XR FDC Tablets in Healthy Subjects

Objectives	Primary: <ul style="list-style-type: none"> To demonstrate bioequivalence between the final market composition (FMC) sitagliptin/metformin (Janumet) extended release (XR) 50 mg/500 mg tablet and co-administration of corresponding doses of sitagliptin and Glumetza as individual tablets To demonstrate bioequivalence between the FMC Janumet XR 100 mg/1000 mg tablet and co-administration of corresponding doses of sitagliptin and Glumetza as individual tablets To demonstrate bioequivalence between two FMC Janumet XR 50 mg/500 mg tablets and a single FMC Janumet XR 100 mg/1000 mg tablet 				
Study Design	Open-label, randomized, five-period crossover				
Study population	Forty-eight (male 28, female 20, age 18-45 years) enrolled and 39 subjects completed.				
Investigational drug	Drug	Potency	Formulation #	Dosage Form	Control #
	Sitagliptin*	50 mg	WL00030296	Tablet	WL00034966
	Sitagliptin*	100 mg	WL00032275	Tablet	WL00034978
	Glumetza**	500 mg	WL00034364	Tablet	WL00034968
	Glumetza**	1000 mg	WL00034365	Tablet	WL00034972
	Janumet XR	50 mg/500 mg	WL00033696	FDC tablet	WL00034970
	Janumet XR	50 mg/500 mg	WL00033696	FDC tablet	WL00034974

	<table border="1"> <tr> <td>Janumet XR</td> <td>100 mg/1000 mg</td> <td>WL00034323</td> <td>FDC tablet</td> <td>WL00034976</td> </tr> </table> <p>*Sitagliptin was the sponsor's approved product, Januvia® **Glumetza® (a registered product of Depomed Inc) required for the study was purchased by the sponsor † n=2 for Janumet XR tablet; n=10 for Glumetza; n=72 for 100-mg sitagliptin tablet and n=168 for 50-mg sitagliptin tablet</p>	Janumet XR	100 mg/1000 mg	WL00034323	FDC tablet	WL00034976													
Janumet XR	100 mg/1000 mg	WL00034323	FDC tablet	WL00034976															
Treatments	<table border="1"> <thead> <tr> <th></th> <th>Sitagliptin + Glumetza</th> <th>FDC MK-0431 A XR</th> </tr> </thead> <tbody> <tr> <td>TRT A</td> <td>50 mg + 500 mg</td> <td></td> </tr> <tr> <td>TRT B</td> <td></td> <td>50 mg/500 mg</td> </tr> <tr> <td>TRT C</td> <td>100 mg + 1000 mg</td> <td></td> </tr> <tr> <td>TRT D</td> <td></td> <td>100 mg/1000 mg</td> </tr> <tr> <td>TRT E</td> <td></td> <td>2 × (50 mg/500 mg)</td> </tr> </tbody> </table>		Sitagliptin + Glumetza	FDC MK-0431 A XR	TRT A	50 mg + 500 mg		TRT B		50 mg/500 mg	TRT C	100 mg + 1000 mg		TRT D		100 mg/1000 mg	TRT E		2 × (50 mg/500 mg)
	Sitagliptin + Glumetza	FDC MK-0431 A XR																	
TRT A	50 mg + 500 mg																		
TRT B		50 mg/500 mg																	
TRT C	100 mg + 1000 mg																		
TRT D		100 mg/1000 mg																	
TRT E		2 × (50 mg/500 mg)																	
PK Assessment	PK parameters such as AUC _{0-∞} , AUC _{0-last} , C _{max} , T _{max} and apparent terminal half-life for sitagliptin and metformin after administration of a single Janumet XR 50 mg/500 mg or 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and Glumetza as individual tablets, and two Janumet XR 50 mg/500 mg tablets were determined.																		
Safety Assessment	The safety and tolerability after administration of each treatment were assessed by clinical evaluation, including vital signs, physical examination, ECGs, and standard laboratory safety tests (hematology, chemistry, and urinalysis).																		

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/s/

JEE E LEE
11/30/2011

JAYABHARATHI VAIDYANATHAN
11/30/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:202270	Submission Date: September 23, 2010
Brand Name	Janumet XR
Generic Name	Sitagliptin/metformin HCl extended fixed dose combination (FDC) tablets
Reviewer	Jee Eun Lee, Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Metabolism and Endocrinology Products
Sponsor	Merck Sharp Dohme
Relevant IND, NDA	IND 101,964; NDA 22-044 (Janumet®), NDA 21-748 (Glumetza®), NDA 21-995 (Januvia®)
Submission Type	Original NDA 505(b)(2)
Formulation; Strength(s)	FDC products of sitagliptin/metformin XR at dose strengths 50 mg/500 mg, 50 mg/1000 mg, 100 mg/1000 mg
Indication	Glycemic Control for Type 2 Diabetes Mellitus

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1 Executive Summary

Merck Sharp Dohme submitted the NDA 20-2270 for Janumet XR (MK-0431A XR) as a fixed-dose combination (FDC) product, which contains sitagliptin and metformin XR. The sponsor is in pursuit of registration of this product based on 505(b)(2) application by demonstration of bioequivalence between Janumet XR (MK-0431A XR) and co-administration of sitagliptin and an approved metformin XR formulation (Glumetza®, NDA 21-748).

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 202270 dated 9/23/2010 and finds it acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

This 505(b)(2) application by Merck Sharp Dohme is in pursuit of approval for the fixed dose combination (FDC) 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg of sitagliptin/metformin extended release (MK-0431A XR, Janumet XR) tablets.

Pivotal Bioequivalence (BE)

The pivotal BE study compared Janumet XR to co-administration of sitagliptin IR and GLUMETZA®, and also the administration of two tablets of 50 mg/500 mg and the administration of one tablet of 100 mg/1000 mg as per the Agency recommendation via comments on the questions submitted in EOP2 meeting package on October 31, 2008 (See Dr. Sang Chung's review dated February 18, 2009). This study was conducted with the final market composition (FMC) of Janumet XR tablets, demonstrated BE between the Janumet XR tablets for both 50 mg/500 mg and 100 mg/1000 mg strengths, and between the Janumet XR tablets and co-administration of corresponding doses of sitagliptin and GLUMETZA®. The treatment arms were:

- TRT A: sitagliptin 50 mg + GLUMETZA® 500 mg
- TRT B: single Janumet XR 50 mg/500 mg tablet
- TRT C: sitagliptin 100 mg + GLUMETZA® 1000 mg
- TRT D: single Janumet XR 100 mg/1000 mg tablet
- TRT E: two tablets of Janumet XR 50 mg/500 mg

The resulting data allows for the bridging of the existing safety and efficacy data from studies with JANUVIA® (sitagliptin), GLUMETZA® (metformin XR) and the combination of sitagliptin and metformin IR (from the JANUVIA® and JANUMET® programs) to Janumet XR (MK-0431A XR).

The key results indicate that that co-administration of sitagliptin and GLUMETZA® and administration of Janumet XR are bioequivalent, and the Janumet XR tablets for both 50 mg/500 mg and 100 mg/1000 mg strengths are bioequivalent for both sitagliptin and metformin XR components (See Figures 1 and 2)

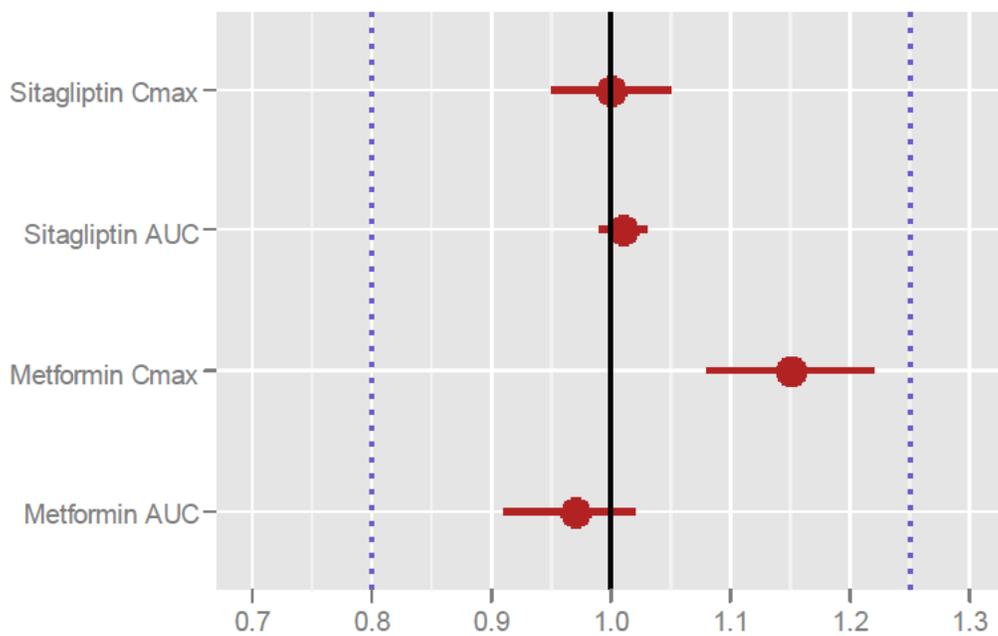


Figure 1. Forest plot for the geometric least square mean ratio for PK parameters comparing co-administration of sitagliptin and GLUMETZA® and administration of Janumet XR

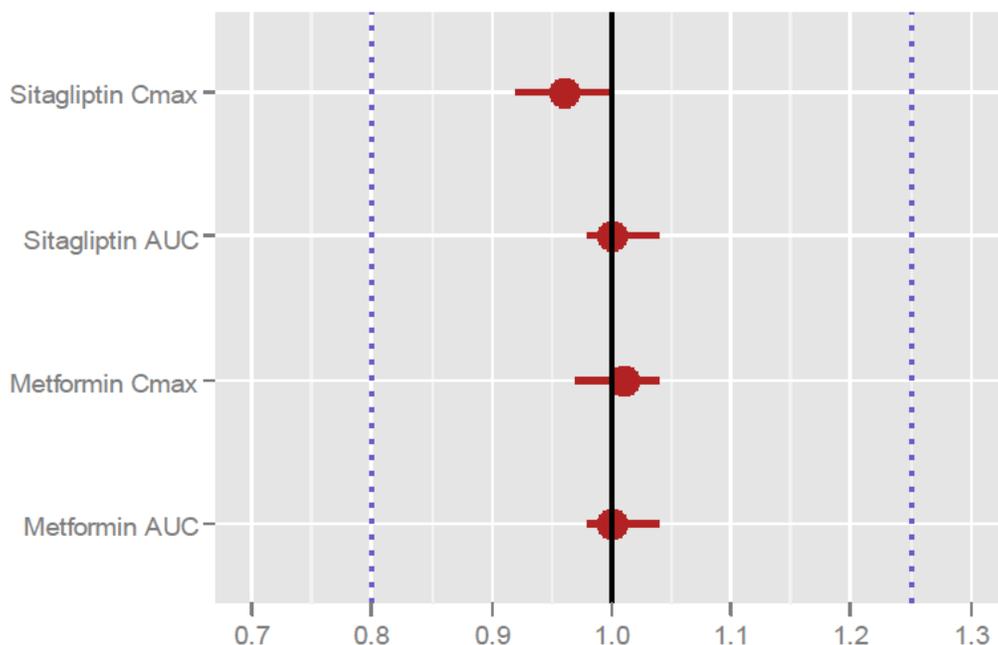


Figure 2. Forest plot for the geometric least square mean ratio for PK parameters comparing two tablets of 50 mg/500 mg and one tablet of 100 mg/1000 mg of Janumet XR

Food Effect

The food effect was evaluated for both Janumet® and Janumet XR. The pharmacokinetics (PK) of sitagliptin and metformin from Janumet® and Janumet XR was evaluated when given with or without high-fat diet. The treatment arms were:

- TRT A: Two tablets Janumet XR 50 mg/1000 mg fasted
- TRT B: Two tablets Janumet XR 50 mg/1000 mg after high-fat breakfast
- TRT C: Two tablets JANUMET® 50 mg/1000 mg fasted
- TRT D: Two tablets JANUMET® 50 mg/1000 mg after high-fat breakfast

The results indicated that there was a significant food effect on metformin PK following administration of Janumet XR. After administration of 2 Janumet XR 50 mg/1000 mg tablets after consumption of a high-fat breakfast, the $AUC_{0-\infty}$ for metformin increased by 62% compared to that under the fasted state. The $AUC_{0-\infty}$ and C_{max} for sitagliptin and the C_{max} for metformin decreased by approximately 6%, 17%, and 9%, respectively, as compared to that under the fasted state. The observed effect of food on the pharmacokinetics of metformin was generally consistent with the effect of food for marketed metformin XR formulations (e.g., GLUCOPHAGE® XR: fed state metformin AUC increased by 50%, no food effect on C_{max}). After administration of two tablets of Janumet® 50 mg/1000 mg after consumption of a high-fat breakfast, the $AUC_{0-\infty}$ and C_{max} for sitagliptin increased by approximately 6%, and 12%, respectively, compared with fasted state. The $AUC_{0-\infty}$ and C_{max} for metformin decreased by approximately 6%,

and 28%, respectively, compared with fasted state. The observed effect of food on the pharmacokinetics of metformin was somewhat less than the effect of food for marketed metformin IR formulations (e.g., GLUCOPHAGE®, AUC decreased by 25%, Cmax decreased by 40% with food, and 35 minutes prolongation of time to peak plasma concentration following 850 mg metformin).

2 Question Based Review

2.1 General Attributes

The sponsor submitted the NDA 20-2270 for Janumet XR (MK-0431A XR) as a fixed-dose combination (FDC) product, which contains sitagliptin and metformin XR. The sponsor is in pursuit of registration of this product based on 505(b)(2) application by demonstration of bioequivalence between Janumet XR (MK-0431A XR) and co-administration of sitagliptin and an approved metformin XR formulation (Glumetza®, NDA 21-748). The safety and efficacy data from studies with sitagliptin (Januvia®, NDA 21-995), metformin XR (Janumet®, NDA 22-044), and the combination of sitagliptin and metformin IR (from the JANUVIA® and Janumet® programs) are utilized to bridge to those of Janumet XR (MK-0431A XR).

Janumet® (MK-0431A) was approved as a fixed dose combination (FDC) tablet that contains sitagliptin and metformin IR for glycemic control in T2DM. It is administered twice a day because of IR formulation of metformin was used for the FDC. The sponsor developed Janumet XR formulation, which replaces metformin IR with metformin XR enabling once a day dosing regimen.

Janumet® was approved based on bridging with a Canadian metformin IR, (b) (4) (b) (4) was bridged with Glucophage IR in ANDA 75984)

Metformin: Metformin is a biguanide. There are several metformin products approved and marketed as follows:

- Glucophage (metformin IR, BMS)
- Glucophage XR (metformin XR, BMS)
- Glumetza (metformin XR, Depomed)
- Fortamet (metformin ER, Andrx labs)
- Riomet (solution, Ranbaxy)

The following FDC tablets containing metformin have been approved:

- ActoPlus Met (pioglitazone/metformin, Takeda)
- ActoPlus Met XR (pioglitazone/metformin ER, Takeda)
- Glucovance (glyburide/metformin, BMS)
- Metaglip (glipizide/metformin, BMS)
- Avandamet (rosiglitazone/metformin, SB PHARMCO)
- Janumet (sitagliptin/metformin, Merck)
- Prandimet (repaglinide/metformin, Novo Nordisk)

Sitagliptin: This is the first compound as a DPP-4 inhibitor. The sponsor's sitagliptin product, JANUVIA® (NDA 21-995) was approved in 2006.

2.1.1 What are 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?

Formulation: Janumet XR tablets are film coated tablets containing an immediate release dose of sitagliptin phosphate and an extended release dose of metformin hydrochloride (core) for once daily use (Figure 1). The FDC formulation can be separated into three main components as follows:

1. A matrix release tablet (MRT) core that provides an extended release (ER) profile of metformin hydrochloride.
2. A sitagliptin active coating over the MRT core designed to provide immediate release of sitagliptin.
3. A polymeric film coating over the active coating to provide taste masking and product differentiation by color.

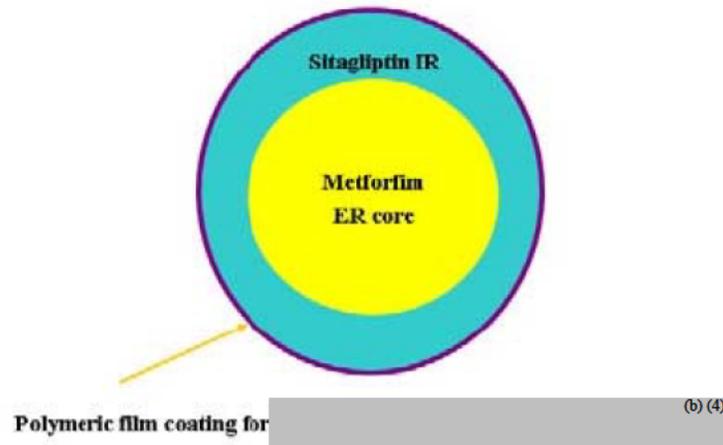


Figure 3. Schematic representation of Janumet XR tablets

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

While the sponsor owns an approved product of sitagliptin IR (Januvia®), they do not have their own approved product for metformin XR formulation. Thus the performance

of the metformin XR incorporated in the FDC is compared to an approved metformin XR product, Glumetza® in the pivotal BE study.

Figure 2 shows the bridging information for metformin XR component. NDA 22044 (Janumet®) was approved based on bridging with a Canadian metformin IR (b) (4) which was approved based on bridging with Glucophage IR (ANDA 75984). The bridge between metformin IR (Glucophage®) and metformin XR is supported by NDA 21748 (Glumetza®).

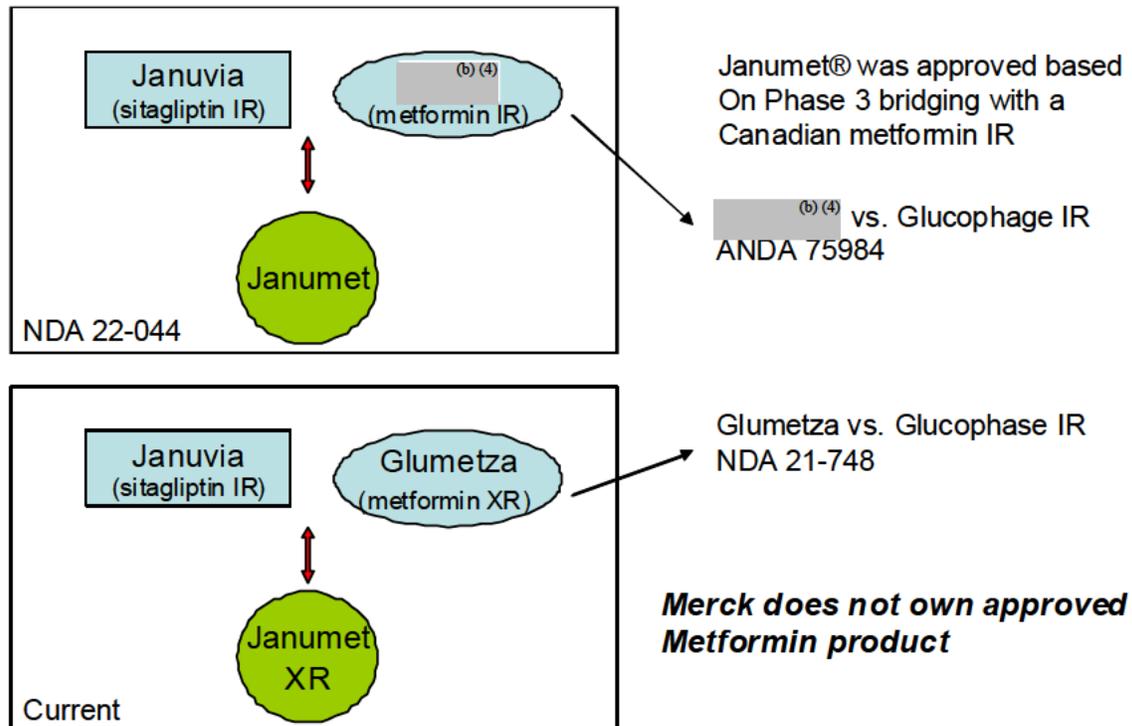


Figure 4. Bridging history for relevant formulations

2.1.3 What is the proposed indication and route of administration?

The proposed indication for the FDC formulations is to improve glycemic control in type 2 diabetes mellitus patients.

2.1.4 Is there any DSI inspection requested for any of the clinical studies?

Yes. The Division of Scientific Investigation's inspection was requested for the pivotal BE study (P147). The clinical site inspection indicated that the study was conducted

following Good Clinical Practice. The final report from DSI regarding pivotal BE study is still pending.

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 (Janumet®), is supported by Phase 3 clinical trials that were submitted under NDA 22-044, where sitagliptin and metformin IR was found to be safe and efficacious when co-administered. FDC tablets of sitagliptin with metformin XR have been developed in three different dose strengths (50/500 mg to be given as 2 tablets, 50/1000 mg to be given as 2 tablets, and 100/1000 mg to be given as 1 tablet) to allow once-daily (QD) dosing of sitagliptin with metformin.

The clinical pharmacology program includes a pivotal BE study that demonstrates BE between MK-0341 XR and co-administration of sitagliptin and an approved metformin XR product (GLUMETZA®). In the study, BE between two tablets of 50 mg/500 mg and one tablet of 100 mg/1000 mg was demonstrated as well. A biowaiver for the 50 mg/1000 mg tablet was requested. The biopharmaceutics reviewer has found the biowaiver request acceptable and agreed for the dissolution specification (See Dr. Sandra Suarez's review).

The submission also includes a food effect study where the *in vivo* performance of MK-0431 XR with and without high-fat breakfast was compared. This study also compares the PK of JANUMET® IR 50 mg/1000 mg and JANUMET® XR 50 mg/1000 mg under either fasted or fed condition.

Eight Clinical Pharmacology studies, including four biopharmaceutics studies (P112, P163, P164, and P147), two pharmacokinetic studies (P012 and P165), and two pharmacodynamic studies (P050 and P 110) were submitted to support the application. A list of completed clinical pharmacology is provided in the Table 1 below and the summary of the studies are provided in the appendix.

Table 1. Clinical Pharmacology Studies Supporting NDA 202270

Study Type	Protocol Number
Biopharmaceutics Studies	
A Low-Dose Probe Formulation Biocomparison Study [†]	112
A High-Dose Probe Formulation Biocomparison Study [†]	163
A Food-Effect Study [†]	164
A Definitive Bioequivalence Study [†]	147
Clinical Pharmacology/Pharmacokinetic Studies	
A Sitagliptin-Metformin Drug Interaction Study [†]	012
A Multiple-Dose Safety, Tolerability and Pharmacokinetic Study [†]	165
Pharmacodynamic Studies	
A Mechanism-of-Action Study in Healthy Subjects [‡]	050
A Mechanism-of-Action Study in Treatment-Naïve Patients with T2DM [‡]	110
[†] Studies where MK-0431A XR was administered	
[‡] Studies where metformin IR was administered	

2.2.2 What is the pharmacokinetic characteristics of the FDC and the comparison results of the BE?

Pivotal BE study (P147) characterized the single dose PK of sitagliptin and metformin following administration of 50 mg/500 mg or 100 mg/1000 mg of Janumet XR in healthy subjects. As shown in the Table 2 that the 90% CIs of the geometric mean ratios for the pharmacokinetic parameters (AUC_{0-∞} and C_{max}) for sitagliptin and metformin after administration of single tablet of Janumet XR 100 mg/1000 mg tablet and those after administration of sitagliptin 100 mg + GLUMETZA® 1000 mg fell within the range of [0.80, 1.25]. The bioequivalence between FDC and co-administration of sitagliptin and Glumetza® has been established for two strength levels (details are provided in Appendix).

Table 2. Summary statistics and statistical comparisons for the plasma PK parameters of sitagliptin after administration of a single Janumet XR 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza®) in healthy adult subjects

Pharmacokinetic parameters	Geometric Mean (95% CI)		
	Sitagliptin 100 mg + Glumetza® 1000 mg (Reference)	Janumet XR 100 mg/1000 mg (Test)	Test/Ref Ratio (90% CI)
Sitagliptin			
AUC _{0-∞} (hr*ng/mL)	7766 (7449, 8097)	7831 (7511, 8166)	1.01 (0.99, 1.03)

AUC _{0-last} (hr*ng/mL)	7661 (7346, 7989)	7721 (7403, 8052)	1.01 (0.99, 1.02)
Cmax (ng/mL)	778 (727, 833)	778 (727, 834)	1.00 (0.95, 1.05)
Tmax (hr)	2.0 (1.0, 7.0)	3.0 (1.0, (5.0)	
Apparent t _{1/2} (hr) **	12.3 (2.8)	12.2 (3.1)	
Metformin			
AUC _{0-∞} (hr*ng/mL)	12490 (11540, 13519)	12009 (11077, 13019)	0.97 (0.91, 1.02)
AUC _{0-last} (hr*ng/mL)	12194 (11305, 13152)	11845 (10976, 12783)	0.97 (0.94, 1.01)
Cmax (ng/mL)	868 (815, 924)	988 (927, 1052)	1.15 (1.08 1.22)
Tmax (hr)	10.0 (5.0, 16.0)	7.0 (4.0, 12.0)	
Apparent t _{1/2} (hr) **	12.2	12.0 (6.8)	

Furthermore, the BE between two tablets of FDC Janumet XR 50 mg/ 500 mg and one tablet of FDC Janumet XR 100 mg/1000 mg has been established in this pivotal BE study. Likewise, The 90% CIs of the geometric least square mean ratios for the pharmacokinetic parameters (AUC_{0-∞} and Cmax) for sitagliptin and metformin after administration of single tablet of Janumet XR 100 mg/1000 mg tablet and those after administration of two tablets of Janumet XR 50 mg/500 mg fell within the range of [0.80, 1.25] (Table 3).

Table 3. Summary statistics and statistical comparisons for the plasma PK parameters of sitagliptin after administration of two Janumet XR 50 mg/500 mg tablets, or one Janumet XR 100 mg/1000 mg tablet in healthy adult subjects

Pharmacokinetic parameters	Geometric Mean (95% CI)		
	Two tablet of Janumet XR 50 mg/500 mg (Test)	One tablet of Janumet XR 100 mg/1000 mg (reference)	Test/Ref Ratio (90% CI)
Sitagliptin			
AUC _{0-∞} (hr*ng/mL)	7828 (7508, 8162)	7831 (7511, 8166)	1.00 (0.98, 1.02)
AUC _{0-last} (hr*ng/mL)	7712 (7395, 8042)	7721 (7403, 8052)	1.00 (0.98, 1.02)
Cmax (ng/mL)	746 (697, 799)	778 (727, 834)	0.96 (0.92, 1.00)
Tmax (hr)	3.0 (1.0, 6.0)	3.0 (1.0, (5.0)	
Apparent t _{1/2} (hr) **	12.2 (3.1)	12.2 (3.1)	
Metformin			
AUC _{0-∞} (hr*ng/mL)	12302 (11367, 13315)	12009 (11077, 13019)	1.00 (0.98, 1.04)
AUC _{0-last} (hr*ng/mL)	12015 (11138, 12962)	11845 (10976, 12783)	1.01 (0.97, 1.04)
Cmax (ng/mL)	1000 (939, 1065)	988 (927, 1052)	1.01 (0.97, 1.04)
Tmax (hr)	5.5 (3.0, 10.0)	7.0 (4.0, 12.0)	
Apparent t _{1/2} (hr) **	13.5 (7.4)	12.0 (6.8)	

Reviewer's Comments: The resulting data allows bridging of the existing safety and efficacy data from studies with JANUVIA® (sitagliptin), GLUMETZA® (metformin XR) and the combination of sitagliptin and metformin IR (from the JANUVIA® and JANUMET® programs) to Janumet XR. The key results of the pivotal pharmacokinetic BE study showed that co-administration of sitagliptin and GLUMETZA® and administration of Janumet XR are equivalent for both dose levels tested.

2.2.3 What is the pediatric plan for NDA 202270?

The sponsor will have a pediatric post-marketing requirement (PMR) to evaluate dosing, safety, and efficacy of sitagliptin/metformin XR in pediatric patients 10 through 17 years (inclusive) of age with T2DM. This PMR will include one (b) (4) clinical trial and a single dose PK study. (1) A (b) (4), randomized, double-blind placebo-controlled trial to evaluate the efficacy and safety of Janumet XR vs. metformin (b) (4) in pediatric patients who are inadequately controlled. As part of this study, the swallowability of the formulation will be evaluated. (b) (4)

(2) A (b) (4) pharmacokinetic study of Janumet XR in pediatric patients 10 through 17 years (inclusive) of age with T2DM. As part of this study the sponsor will evaluate pediatric patients can safely swallow the Janumet XR tablets. (b) (4)

2.2.4 What are the characteristics of multiple-dose PK?

After administration of two Janumet XR 50 mg/1000 mg tablets once daily with the evening meal for 7 days, steady state for sitagliptin and metformin is reached by Day 4 and 5, respectively. There were no significant changes in PK parameters such as $T_{1/2}$ and T_{max} at steady state compared to single dose PK. No time-dependent non-linearity for sitagliptin and metformin after multiple-dose administration of Janumet XR were observed.

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 response?

No intrinsic factors were evaluated under the current NDA.

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

The drug interaction was assessed by comparing sitagliptin and metformin pharmacokinetics following administration of multiple doses of 50-mg sitagliptin with and without 1000-mg metformin in T2DM patients (n=13, the individual study summary

for P012 is included in Appendix). The study report was submitted under NDA 21-995 (Januvia®) and reviewed by Dr. Xiaoxiong Wei (See his review dated August 30, 2006).

Sitagliptin does not alter the plasma pharmacokinetics of metformin in patients with type 2 diabetes. Metformin does not alter the plasma pharmacokinetics or renal clearance of sitagliptin.

2.4.1.2 Food Effect

The food effect was evaluated for both Janumet® and Janumet XR. The pharmacokinetics of sitagliptin and metformin from the two formulations with and without high-fat diet was compared and the PK between Janumet® and Janumet XR was compared. The treatment arms were:

- TRT A: Two tablets Janumet XR 50/1000 mg fasted
- TRT B: Two tablets Janumet XR 50/1000 mg after high-fat breakfast
- TRT C: Two tablets Janumet® 50 mg/1000 mg fasted
- TRT D: Two tablets Janumet® 50 mg/1000 mg after high-fat breakfast

The results indicated that there was a significant food effect on metformin PK following Janumet XR. After administration of 2 Janumet XR 50 mg/1000 mg tablets following consumption of a high-fat breakfast, the AUC_{0-∞} for metformin increased by 62% compared with the fasted state. The AUC_{0-∞} and C_{max} for sitagliptin and the C_{max} for metformin decreased by approximately 6%, 17%, and 9%, respectively, compared with the fasted state (Table 4).

Table 4. Food effect for Janumet XR

Pharmacokinetic parameters	Geometric Mean		
	Janumet XR Fasted	Janumet XR Fed	Fed/Fasted Ratio (90% CI)
Sitagliptin			
AUC _{0-∞} (hr*ng/mL)	7531	7139	0.94 (0.90, 0.99)
AUC _{0-last} (hr*ng/mL)	7435	7036	0.95 (0.90, 0.99)
C _{max} (ng/mL)	883	736	0.83 (0.75, 0.92)
T _{max} (hr)	2.5	2.1	
Apparent t _{1/2} (hr) **	12.6 (4.7)	121. (4.1)	
Metformin			
AUC _{0-∞} (hr*ng/mL)	13975	22622	1.62 (1.35, 1.94)
AUC _{0-last} (hr*ng/mL)	13816	21710	1.57 (1.38, 1.78)
C _{max} (ng/mL)	1802	1644	0.91 (0.79, 1.05)
T _{max} (hr)	3.0	5.0	
Apparent t _{1/2} (hr) **	12.3 (7.1)	9.3 (4.4)	

The observed effect of food on the pharmacokinetics of metformin was generally consistent with the effect of food for marketed metformin XR formulations (e.g., Glucophage® XR: fed state metformin AUC increased by 50%, no food effect on C_{max}).

After administration of two tablets of Janumet® 50 mg/1000 mg following consumption of a high-fat breakfast, the AUC_{0-∞} and C_{max} for sitagliptin increased by approximately 6%, and 12%, respectively, compared with fasted state. The AUC_{0-∞} and C_{max} for metformin decreased by approximately 6%, and 28%, respectively, compared with fasted state (Table 4). The observed effect of food on the pharmacokinetics of metformin was somewhat less than the effect of food for marketed metformin IR formulations (e.g., Glucophage®, AUC decreased by 25%, C_{max} decreased by 40% with food, and 35 minutes prolongation of time to peak plasma concentration following 850 mg metformin).

Table 5. Food effect for Janumet®

Pharmacokinetic parameters	Geometric Mean (95% CI)		
	Janumet® Fasted	Janumet® Fed	Fed/Fasted Ratio (90% CI)
Sitagliptin			
AUC _{0-∞} (hr*ng/mL)	6687	7096	1.06 (1.01, 1.11)
AUC _{0-last} (hr*ng/mL)	6544	6990	1.07 (1.02, 1.12)
C _{max} (ng/mL)	595	667	1.12 (1.01, 1.24)
T _{max} (hr)	2.5	3.0	
Apparent t _{1/2} (hr) **	12.2 (4.5)	11.6 (3.5)	
Metformin			
AUC _{0-∞} (hr*ng/mL)	19967	18691	0.94 (0.77, 1.14)
AUC _{0-last} (hr*ng/mL)	19689	18130	0.92 (0.81, 1.04)
C _{max} (ng/mL)	3174	2271	0.72 (0.63, 0.82)
T _{max} (hr)	2.0	3.5	
Apparent t _{1/2} (hr) **	11.6 (4.6)	12.1 (5.6)	

Furthermore, Janumet XR was compared with Janumet® (IR) in this food effect study. The results indicate that both AUC and C_{max} for sitagliptin following administration of Janumet® and Janumet XR were bioequivalent under fed condition and only AUC for sitagliptin was bioequivalent under fasted condition. C_{max} for metformin was not bioequivalent for both fed and fasted conditions and C_{max} for sitagliptin was not bioequivalent for fasted condition. Both Janumet® and Janumet XR are recommended to be taken with food and the bioequivalence for metformin C_{max} is not expected for the XR formulation. Thus, the results seem to be sufficient to bridge two FDC products.

2.5 General Biopharmaceutics

2.5.1 What is the impact of fixed dose combination formulation on systemic exposure of sitagliptin and metformin?

See Section 2.2.2 in the summary description of pivotal BE study results.

2.5.2 What are the batch size of the FDC formulation in the pivotal BE study?

Clinical supplies of the Janumet XR tablets all were derived from manufacturing batches that were (b) (4) of the final production scale used to produce commercial supplies.

2.5.3 What are the dose dumping potential of FDC product?

The agency raised a concern that the extended release formulation may generate premature release of the drug and recommended that this be addressed *in vitro* (See Dr. Immo Zdrojewski's review dated on April 30, 2010). The sponsor conducted *in vitro* studies to evaluate the dose-dumping potential of Janumet XR with alcohol, in response to discussions with the Agency. The ONDQA concludes that dose dumping of Janumet XR with alcohol does not occur (See Dr. Sandra Suarez's biopharmaceutics review dated Nov 1, 2010).

2.6 Analytical Section

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

Sitagliptin phosphate and metformin hydrochloride in human plasma were determined by liquid chromatographic-tandem mass spectrometric (LC-MS/MS) methods.

2.6.2 What bioanalytical methods are used to assess concentrations?

The analytical methods for sitagliptin and metformin were developed by (b) (4). (b) (4) and the final analytical report includes detailed information of the method and its validation. The lower limits of quantification (LLOQ) for sitagliptin and metformin were 0.99 ng/mL and 2.00 ng/mL, respectively. The quantification ranges were 0.99 to 989.0 ng/mL and 2.00 to 2001.00 ng/mL for sitagliptin and metformin, respectively. The assays were validated and both inter- and intra-day precision of the mean concentrations of both components were less than 10% and inter- and intra-day accuracy was within 100±10% (Table 6).

Table 6. Summary of analytical validation

	Metformin	Sitagliptin
Standard curve range	2.00 to 2001.00 ng/mL	0.99 to 989.00 ng/mL
QC Sample concentrations	6.04, 201.28, 603.84, and 1408.96 ng/mL	3.01, 100.30 and 802.40 ng/mL
Precision (%CV)	1.37-6.87% (initial)	0.57-10.2%
Accuracy (%CV)	92.84-94.42% (initial)	92.93-104.04%
Internal standard	(b) (4)	(b) (4)
Stability	Demonstrated storage stability: 498 days at -20°C	Demonstrated storage stability 13 months at -20°C

	and at -80°C Maximum sample storage duration from collection to analysis: 165 days at -20°C (within stability limits)	Maximum sample storage duration from collection to analysis: 158 days at -20°C (within stability limits)
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3 Labeling

The sponsor's proposed language in the label is acceptable from the Clinical Pharmacology perspectives.

4 Appendix

4.1 Individual Clinical Study Review

4.1.1 Pivotal BE Study: Protocol 147

Title: A Definitive Bioequivalence Study for Sitagliptin/Metformin XR FDC Tablets in Healthy Subjects

Objectives	Primary: <ul style="list-style-type: none"> To demonstrate bioequivalence between the final market composition (FMC) sitagliptin/metformin (Janumet) extended release (XR) 50 mg/500 mg tablet and co-administration of corresponding doses of sitagliptin and Glumetza as individual tablets To demonstrate bioequivalence between the FMC Janumet XR 100 mg/1000 mg tablet and co-administration of corresponding doses of sitagliptin and Glumetza as individual tablets To demonstrate bioequivalence between two FMC Janumet XR 50 mg/500 mg tablets and a single FMC Janumet XR 100 mg/1000 mg tablet 				
Study Design	Open-label, randomized, five-period crossover				
Study population	Forty eight (male 28, female 20, age 18-45 years) enrolled and 39 subjects completed.				
Investigational drug	Drug	Potency	Formulation #	Dosage Form	Control #
	Sitagliptin*	50 mg	WL00030296	Tablet	WL00034966
	Sitagliptin*	100 mg	WL00032275	Tablet	WL00034978
	Glumetza**	500 mg	WL00034364	Tablet	WL00034968
	Glumetza**	1000 mg	WL00034365	Tablet	WL00034972

	Janumet XR	50 mg/500 mg	WL00033696	FDC tablet	WL00034970																		
	Janumet XR	50 mg/500 mg	WL00033696	FDC tablet	WL00034974																		
	Janumet XR	100 mg/1000 mg	WL00034323	FDC tablet	WL00034976																		
	<p>*Sitagliptin was the sponsor's approved product, Januvia®</p> <p>**Glumetza® (a registered product of Depomed Inc) required for the study was purchased by the sponsor</p> <p>† n=2 for Janumet XR tablet; n=10 for Glumetza; n=72 for 100-mg sitagliptin tablet and n=168 for 50-mg sitagliptin tablet</p>																						
Treatments	<table border="1"> <thead> <tr> <th></th> <th>Sitagliptin + Glumetza</th> <th>FDC MK-0431 A XR</th> </tr> </thead> <tbody> <tr> <td>TRT A</td> <td>50 mg + 500 mg</td> <td></td> </tr> <tr> <td>TRT B</td> <td></td> <td>50 mg/500 mg</td> </tr> <tr> <td>TRT C</td> <td>100 mg + 1000 mg</td> <td></td> </tr> <tr> <td>TRT D</td> <td></td> <td>100 mg/1000 mg</td> </tr> <tr> <td>TRT E</td> <td></td> <td>2 × (50 mg/500 mg)</td> </tr> </tbody> </table>						Sitagliptin + Glumetza	FDC MK-0431 A XR	TRT A	50 mg + 500 mg		TRT B		50 mg/500 mg	TRT C	100 mg + 1000 mg		TRT D		100 mg/1000 mg	TRT E		2 × (50 mg/500 mg)
	Sitagliptin + Glumetza	FDC MK-0431 A XR																					
TRT A	50 mg + 500 mg																						
TRT B		50 mg/500 mg																					
TRT C	100 mg + 1000 mg																						
TRT D		100 mg/1000 mg																					
TRT E		2 × (50 mg/500 mg)																					
PK Assessment	<p>PK parameters such as AUC_{0-∞}, AUC_{0-last}, C_{max}, T_{max} and apparent terminal half-life for sitagliptin and metformin after administration of a single Janumet XR 50 mg/500 mg or 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and Glumetza as individual tablets, and two Janumet XR 50 mg/500 mg tablets were determined.</p>																						
Safety Assessment	<p>The safety and tolerability after administration of each treatment were assessed by clinical evaluation, including vital signs, physical examination, ECGs, and standard laboratory safety tests (hematology, chemistry, and urinalysis).</p>																						

The PK for sitagliptin and metformin after administration of Janumet XR and Janumet® were compared and showed that after administration of Janumet XR, the total exposure (AUC) for metformin was similar, but the rate of absorption was slower (C_{max} is decreased and T_{max} occurred later) compared with after administration of Janumet®. These results were expected for the extended release formulation. Among marketed extended release metformin product, Glumetza® was selected as the comparator for the pivotal BE study.

The pivotal BE study compared Janumet XR to co-administration of sitagliptin IR and Glumetza®, as the Agency recommended in the meeting on October 31, 2008. This study, conducted with final market composition (FMC) of Janumet XR tablets, demonstrated BE between the Janumet XR tablets at tablet strengths of both 50 mg/500 mg and 100 mg/1000 mg, and between the FMC Janumet XR tablets and co-administration of corresponding doses of sitagliptin and Glumetza®. The treatment arms were:

- TRT A: Sitagliptin 50 mg + Glumetza®, 500 mg
- TRT B: Single Janumet XR 50 mg/500 mg tablet
- TRT C: Sitagliptin 100 mg + Glumetza®, 1000 mg
- TRT D: Single Janumet XR 100 mg/1000 mg tablet
- TRT E: Two tablets of Janumet XR 50 mg/500 mg

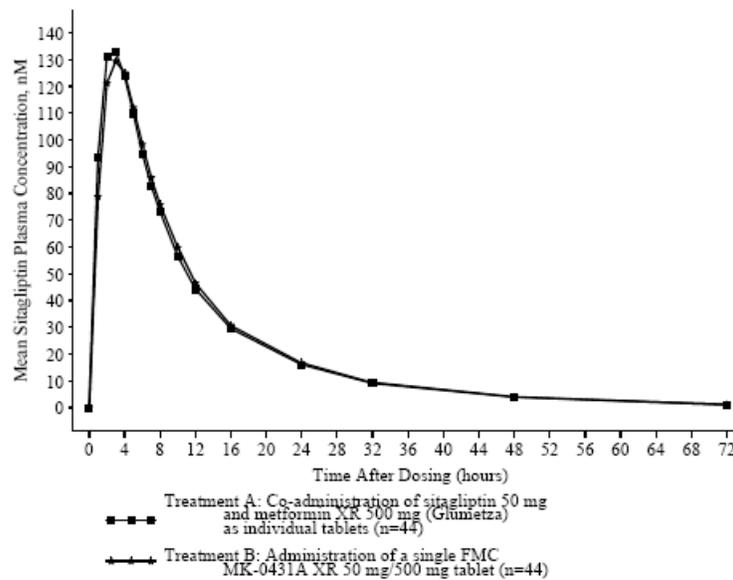
The resulting data allow bridging of the existing safety and efficacy data from studies with Januvia® (sitagliptin), Glumetza® (metformin XR) and the combination of sitagliptin and metformin IR (from the Januvia® and Janumet® programs) to Janumet XR.

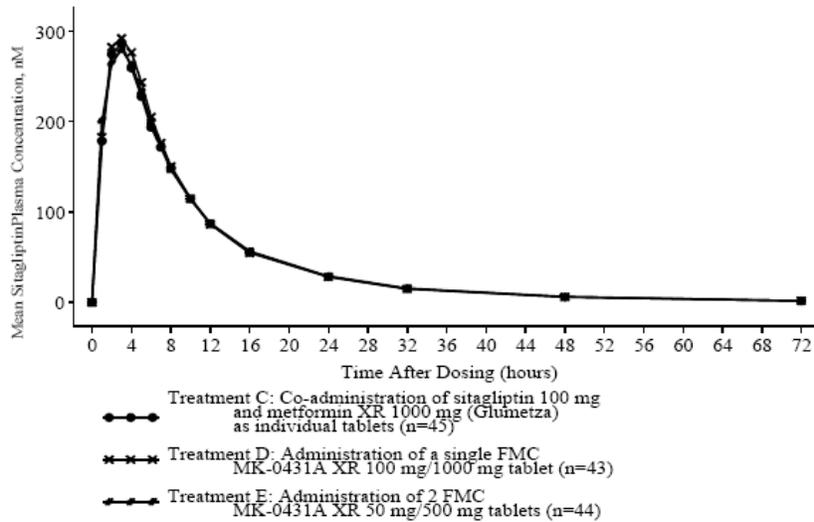
Results:

The key results of the pivotal pharmacokinetic BE study are described below (Appendix Tables 1 through 4, Figures 1 and 2).

Appendix Table 1. Summary statistics and statistical comparisons for the plasma PK parameters of sitagliptin after administration of a single Janumet XR 50 mg/500 mg or 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza) as individual tablets, or two Janumet XR 50 mg/500 mg tablets in healthy adult subjects

Treatment	A		B		C		D		E	
PK Parameter	N	GM (95% CI)								
AUC _{0-∞} [‡] (nM•hr)	44	3993 (3830, 4163)	44	4006 (3842, 4177)	45	7766 (7449, 8097)	43	7831 (7511, 8166)	44	7828 (7508, 8162)
AUC _{0-last} [‡] (nM•hr)	44	3892 (3732, 4059)	44	3912 (3752, 4080)	45	7661 (7346, 7989)	43	7721 (7403, 8052)	44	7712 (7395, 8042)
C _{max} [‡] (nM)	44	356 (332, 381)	44	342 (320, 367)	45	778 (727, 833)	43	778 (727, 834)	44	746 (697, 799)
T _{max} (hr)	44	2.5 (1.0, 7.0)	44	3.0 (1.0, 7.0)	45	2.0 (1.0, 7.0)	43	3.0 (1.0, 5.0)	44	3.0 (1.0, 6.0)
Apparent terminal t _{1/2} [§] (hr)	44	12.9 (3.5)	44	12.6 (3.2)	45	12.3 (2.8)	43	12.2 (3.1)	44	12.5 (3.4)

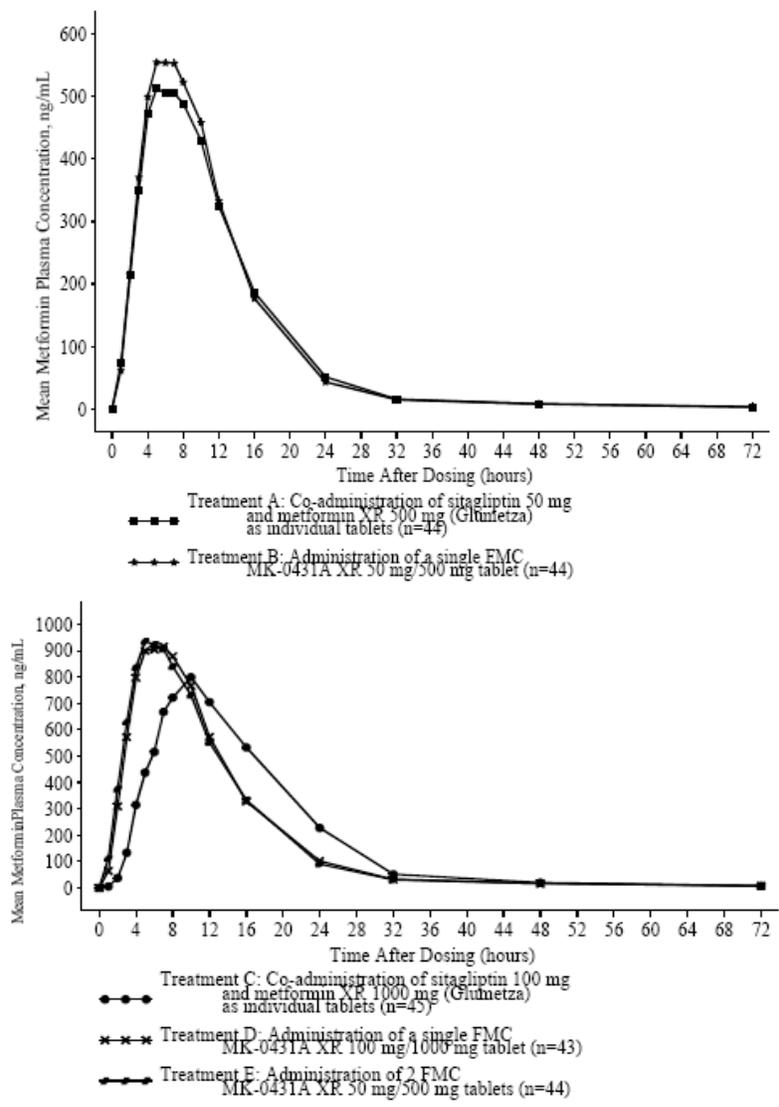




Appendix Figure 1. Concentration profiles of sitagliptin after administration of a single Janumet XR 50 mg/500 mg or 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza) as individual tablets, or two Janumet XR 50 mg/500 mg tablets in healthy adult subjects

Appendix Table 2. Summary statistics and statistical comparisons for the plasma PK parameters of metformin after administration of a single Janumet XR 50 mg/500 mg or 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza®) as individual tablets, or two Janumet XR 50 mg/500 mg tablets in healthy adult subjects

Treatment	A		B		C		D		E	
PK Parameter	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)
$AUC_{0-\infty}^{\ddagger}$ (ng•hr/mL)	36	6639 (6128, 7192)	36	7047 (6504, 7636)	39	12490 (11540, 13519)	35	12009 (11077, 13019)	39	12302 (11367, 13315)
AUC_{0-last}^{\ddagger} (ng•hr/mL)	44	6576 (6096, 7094)	44	6874 (6372, 7416)	45	12194 (11305, 13152)	43	11845 (10976, 12783)	44	12015 (11138, 12962)
C_{max}^{\ddagger} (ng/mL)	44	560 (526, 597)	44	607 (570, 647)	45	868 (815, 924)	43	988 (927, 1052)	44	1000 (939, 1065)
T_{max}^{\parallel} (hr)	44	6.0 (3.0, 10.0)	44	6.0 (3.0, 10.0)	45	10.0 (5.0, 16.0)	43	7.0 (4.0, 12.0)	44	5.5 (3.0, 10.0)
Apparent terminal $t_{1/2}^{\S}$ (hr)	36	11.8 (6.4)	36	12.6 (7.9)	39	12.2 (3.8)	35	12.0 (6.8)	39	13.5 (7.4)



Appendix Figure 2. Concentration profiles of metformin after administration of a single Janumet XR 50 mg/500 mg or 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza) as individual tablets, or two Janumet XR 50 mg/500 mg tablets in healthy adult subjects

The 90% CIs of the geometric mean ratios for the pharmacokinetic parameters ($AUC_{0-\infty}$ and C_{max}) for sitagliptin and metformin after administration of single tablet of FMC Janumet XR 50 mg/500 mg tablet and those after administration of sitagliptin 50 mg + GLUMETZA® 500 mg fell within the range of [0.80, 1.25]. Likewise, The 90% CIs of the geometric mean ratios for the pharmacokinetic parameters ($AUC_{0-\infty}$ and C_{max}) for sitagliptin and metformin after administration of single tablet of FMC Janumet XR 100 mg/1000 mg tablet and those after administration of two tablets of FMC Janumet XR 50 mg/500 mg fell within the range of [0.80, 1.25].

Appendix Table 3. BE assessment for sitagliptin pharmacokinetic parameters

	FMC MK-0431A XR Tablets vs. Co-administration of Sitagliptin and Metformin XR (Glumetza)		2 x MK-0431A XR 50 mg/500 mg Tablets vs. 1 x MK-0431A XR 100 mg/1000 mg Tablet
Parameter	MK-0431A XR 50 mg/500 mg Tablet	MK-0431A XR 100 mg/1000 mg Tablet	
AUC _{0-∞}	1.00 (0.99, 1.02)	1.01 (0.99, 1.03)	1.00 (0.98, 1.02)
AUC _{0-last}	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)
C _{max}	0.96 (0.92, 1.01)	1.00 (0.96, 1.05)	0.96 (0.92, 1.00)

Appendix Table 4. BE assessment for metformin pharmacokinetic parameters

	FMC MK-0431A XR Tablets vs. Co-administration of Sitagliptin and Metformin XR (Glumetza)		2 x MK-0431A XR 50 mg/500 mg Tablets vs. 1 x MK-0431A XR 100 mg/1000 mg Tablet
Parameter	MK-0431A XR 50 mg/500 mg Tablet	MK-0431A XR 100 mg/1000 mg Tablet	
AUC _{0-∞}	1.06 (1.01, 1.12)	0.96 (0.91, 1.01)	1.02 (0.97, 1.08)
AUC _{0-last}	1.05 (1.00, 1.09)	0.97 (0.93, 1.01)	1.01 (0.97, 1.06)
C _{max}	1.08 (1.03, 1.14)	1.14 (1.09, 1.19)	1.01 (0.97, 1.06)

Drop-out: Due to early dropouts, PK data were not available for all of the treatments for nine subjects. The sponsor believes that missing at random (MAR) was a reasonable assumption to apply to the missing data. In the linear mixed-effect model approach, these incomplete cases were included in the primary PK analyses together with complete cases assuming MAR.

Nine subjects discontinued from the study for the following reasons:

1. family emergency
2. abdominal pain (co-administration of sitagliptin 50 mg and Glumetza 500 mg)
3. protocol deviation (co-medication)
4. two subjects: rash (co-administration of sitagliptin 100 mg and Glumetza 1000 mg)
5. protocol deviation (co-medication)
6. urticaria (co-administration of sitagliptin 50 mg and Glumetza 50 mg)
7. conflict of schedule
8. urinary retention (a single Janumet XR 50 mg/500 mg)

4.1.2 Food Effect Study: Protocol 164

Title: Definitive Bioequivalence Study for Sitagliptin/Metformin XR FDC Tablets in Healthy Subjects

Objectives	Primary: To assess the effect of a high-fat breakfast on the final market composition (FMC) Janumet extended-release (XR) tablets at the
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	<p>highest recommended dose (sitagliptin 100 mg, metformin XR 2000 mg).</p> <p>Secondary: To assess the effect of a high-fat breakfast on Janumet® tablets at the highest recommended dose (sitagliptin 100 mg, metformin 2000 mg).</p> <p>Tertiary: To evaluate the effect</p>			
Study Design	Open-label, randomized, four-period crossover			
Study population	12 (male 9, female 3, age 19-44 years) enrolled and 12 completed			
Investigational drug	Drug	Potency	Formulation Number	Dosage form
	Janumet XR (sitagliptin/metformin XR)	50 mg/1000 mg	WL00034321	FDC tablet
	Janumet® (sitagliptin/metformin)	50 mg/1000 mg	WL00035048	tablet
Treatments	<p>TRT A: 2 tablets Janumet XR 50/1000 mg fasted</p> <p>TRT B: 2 tablets Janumet XR 50/1000 mg after high-fat breakfast</p> <p>TRT C: 2 tables Janumet® 50 mg/1000 mg fasted</p> <p>TRT D: 2 tables Janumet® 50 mg/1000 mg after high-fat breakfast</p>			
PK Assessment	<p>PK parameters such as $AUC_{0-\infty}$, AUC_{0-last}, C_{max}, T_{max} and apparent terminal half-life for sitagliptin and metformin after administration of two Janumet XR 50 mg/1000 mg tablets or two Janumet® 50 mg/1000 mg tablets fasted and after consumption of a high-fat breakfast were determined.</p>			
Safety Assessment	<p>Safety after administration of two Janumet XR 50 mg/1000 mg tablets and two Janumet® 50 mg/1000 mg tablets fasted and after consumption of a high-fat breakfast was assessed by clinical evaluation of adverse experiences, medical history and physical examination, routine laboratory safety tests (hematology, serum chemistry, and urinalysis), 12-lead electrocardiograms (ECGs), and vital sign assessments. A serum β-human chorionic gonadotropin assay was performed for female subjects of childbearing potential and was confirmed negative prior to study drug administration in each treatment period.</p>			

Results:

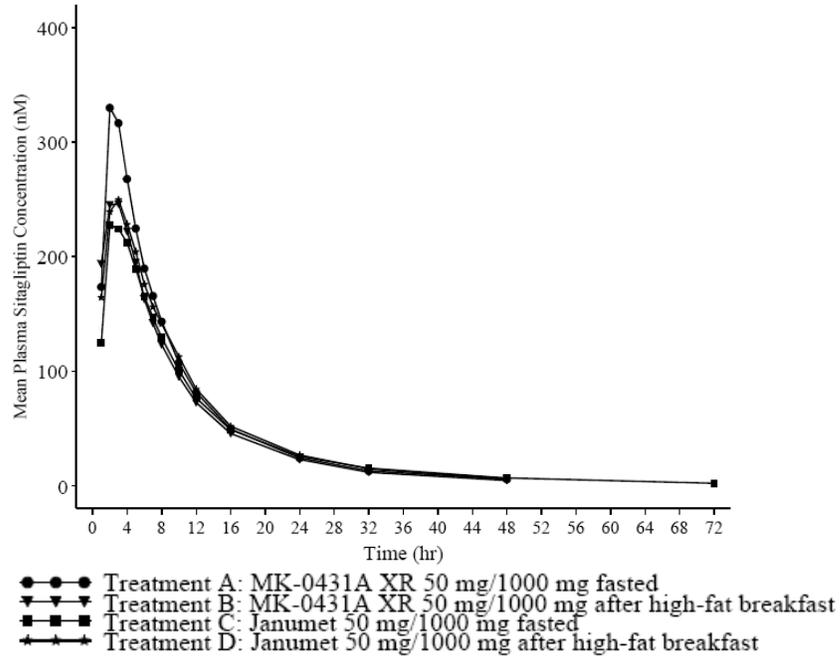
Summary statistics and statistical comparisons of the plasma pharmacokinetic parameters for sitagliptin and metformin after administration of two Janumet XR 50 mg/1000 mg tablets or two Janumet® 50 mg/1000 mg tablets fasted or after consumption of a high-fat breakfast in healthy adult subjects are provided in the tables below.

Appendix Table 5. Summary of food effect on pharmacokinetics of sitagliptin and metformin following two tablets of 50 mg/1000 mg of Janumet® and Janumet XR

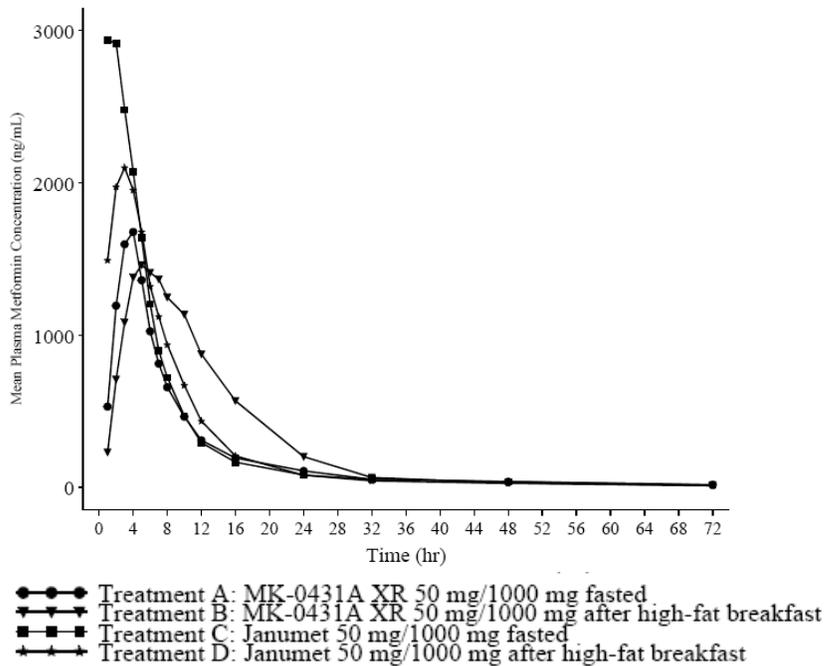
Treatment	MK-0431A XR Fasted		MK-0431A XR Fed		Janumet Fasted		Janumet Fed	
	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)
Sitagliptin								
AUC _{0-∞} [‡] (nM•hr)	12	7581 (6799, 8452)	11	7139 (6398, 7964)	12	6687 (5998, 7455)	12	7096 (6365, 7912)
AUC _{0-last} [‡] (nM•hr)	12	7435 (6680, 8275)	11	7036 (6317, 7836)	12	6544 (5879, 7283)	12	6990 (6281, 7780)
C _{max} [‡] (nM)	12	883 (754, 1034)	11	736 (626, 864)	12	595 (508, 697)	12	667 (569, 781)
T _{max} (hr)	12	2.5 (2.0, 5.0)	11	2.1 (1.0, 5.0)	12	2.5 (1.0, 4.0)	12	3.0 (1.0, 7.0)
Apparent terminal t _{1/2} [§]	12	12.6 (4.7)	11	12.1 (4.1)	12	12.2 (4.5)	12	11.6 (3.5)
Metformin								
AUC _{0-∞} [‡] (ng•hr/mL)	9	13975 (11682, 16717)	8	22622 (18773, 27259)	7	19967 (16233, 24560)	10	18691 (15782, 22138)
AUC _{0-last} [‡] (ng•hr/mL)	12	13816 (12133, 15731)	11	21710 (18979, 24835)	12	19689 (17292, 22418)	12	18130 (15923, 20643)
C _{max} [‡] (ng/mL)	12	1802 (1554, 2089)	11	1644 (1410, 1916)	12	3174 (2737, 3681)	12	2271 (1959, 2634)
T _{max} (hr)	12	3.0 (2.0, 5.0)	11	5.0 (4.0, 7.0)	12	2.0 (1.0, 4.0)	12	3.5 (2.0, 5.0)
Apparent terminal t _{1/2} [§]	9	12.3 (7.1)	8	9.3 (4.4)	7	11.6 (4.6)	10	12.1 (5.6)
Between-Treatment Comparison: Fed vs. Fasted								
Parameter	GMR [‡] (Fed/Fasted) and 90% CI							
FMC MK-0431A XR Tablets								
	Sitagliptin				Metformin			
AUC _{0-∞}	0.94 (0.90, 0.99)				1.62 (1.35, 1.94)			
AUC _{0-last}	0.95 (0.90, 0.99)				1.57 (1.38, 1.78)			
C _{max}	0.83 (0.75, 0.92)				0.91 (0.79, 1.05)			
Janumet Tablets								
	Sitagliptin				Metformin			
AUC _{0-∞}	1.06 (1.01, 1.11)				0.94 (0.77, 1.14)			
AUC _{0-last}	1.07 (1.02, 1.12)				0.92 (0.81, 1.04)			
C _{max}	1.12 (1.01, 1.24)				0.72 (0.63, 0.82)			

Effect of Food on Janumet XR: After administration of two Janumet XR 50 mg/1000 mg tablets fasted or after consumption of a high-fat breakfast, the geometric least square mean ratio (GLSMR; fed/fasted) and 90% CI of the AUC_{0-∞} and C_{max} for sitagliptin were 0.94 (0.90, 0.99) and 0.83 (0.75, 0.92), respectively. The GLSMR and 90% CI of the AUC_{0-∞} and C_{max} for metformin were 1.62 (1.35, 1.94) and 0.91 (0.79, 1.05), respectively.

Effect of Food on Janumet®: After administration of two Janumet® 50 mg/1000 mg tablets fasted or after consumption of a high-fat breakfast, the GLSMR (fed/fasted) and 90% CI of the AUC_{0-∞} and C_{max} for sitagliptin were 1.06 (1.01, 1.11) and 1.12 (1.01, 1.24), respectively. The GLSMR and 90% CI of the AUC_{0-∞} and C_{max} for metformin were 0.94 (0.77, 1.14) and 0.72 (0.63, 0.82), respectively.



Appendix Figure 3. Arithmetic mean plasma sitagliptin concentration-time profiles after single dose administration of two Janumet XR 50 mg/1000 mg tablets or two Janumet® 50 mg/1000 mg tablets fasted or after consumption of a high-fat breakfast in healthy adult subjects (n=12)



Appendix Figure 4. Arithmetic mean plasma metformin concentration-time profiles after single dose administration of two Janumet XR 50 mg/1000 mg tablets or two Janumet® 50 mg/1000 mg tablets fasted or after consumption of a high-fat breakfast in healthy adult subjects (n=12)

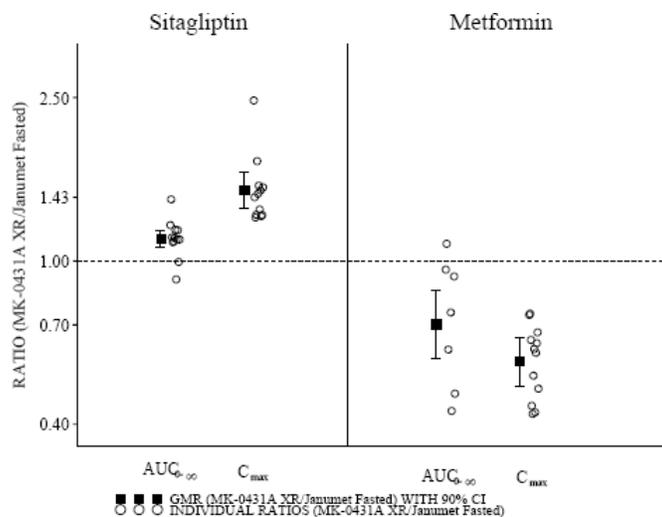
The results indicated that there was a significant food effect on metformin PK following Janumet XR. After administration of two tablets of Janumet XR 50 mg/1000 mg after consumption of a high-fat breakfast, the $AUC_{0-\infty}$ for metformin increased by 62% compared with the fasted state. The $AUC_{0-\infty}$ and C_{max} for sitagliptin and the C_{max} for metformin decreased by approximately 6%, 17%, and 9%, respectively, compared with the fasted state.

The observed effect of food on the pharmacokinetics of metformin was generally consistent with the effect of food for marketed metformin XR formulations (e.g., Glucophage® XR: fed state metformin AUC increased by 50%, no food effect on C_{max}). After administration of two tablets of Janumet® 50 mg/1000 mg after consumption of a high-fat breakfast, the $AUC_{0-\infty}$ and C_{max} for sitagliptin increased by approximately 6%, and 12%, respectively, compared with fasted state. The $AUC_{0-\infty}$ and C_{max} for metformin decreased by approximately 6%, and 28%, respectively, compared with fasted state. The observed effect of food on the pharmacokinetics of metformin was somewhat less than the effect of food for marketed metformin IR formulations (e.g., GLUCOPHAGE, AUC decreased by 25%, C_{max} decreased by 40% with food, and 35 minutes prolongation of time to peak plasma concentration following 850 mg metformin)

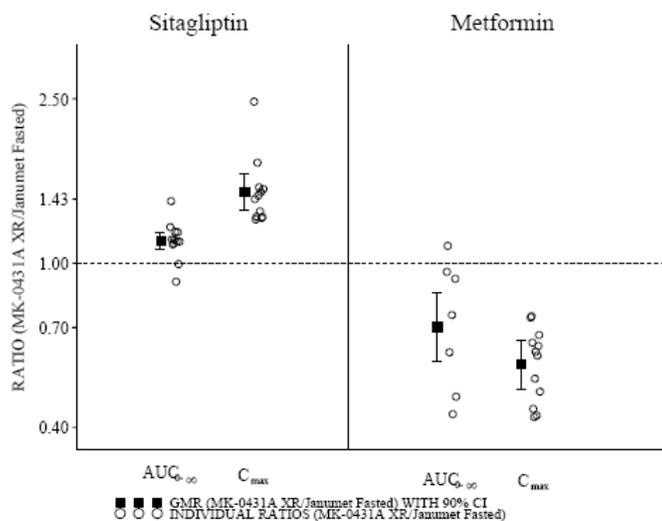
Furthermore, mean plasma metformin concentration-time profiles after administration of two tablets 50 mg/1000 mg of Janumet XR or Janumet®, fasted or after consumption of a high-fat breakfast in healthy adult subjects were compared in the table below.

Appendix Table 6. Summary of comparisons between Janumet XR and Janumet® after administration of two Janumet XR 50 mg/1000 mg tablets or two Janumet® 50 mg/1000 mg tablets fasted or after consumption of a high-fat breakfast in healthy adult subjects (n=12)

Parameter	GMR [†] (FMC MK-0431A XR/Janumet) and 90% CI			
	Fed		Fasted	
	Sitagliptin	Metformin	Sitagliptin	Metformin
$AUC_{0-\infty}$	1.01 (0.96, 1.05)	1.21 (1.02, 1.44)	1.13 (1.08, 1.19)	0.70 (0.58, 0.85)
AUC_{0-last}	1.01 (0.96, 1.06)	1.20 (1.06, 1.36)	1.14 (1.08, 1.19)	0.70 (0.62, 0.79)
C_{max}	1.10 (0.99, 1.22)	0.72 (0.63, 0.83)	1.48 (1.34, 1.64)	0.57 (0.50, 0.65)



Appendix Figure 5. Individual ratios (Janumet XR fasted/Janumet® fasted), geometric least square mean ratios, and 90% confidence intervals of the $AUC_{0-\infty}$ and C_{max} for sitagliptin and metformin after administration of two Janumet® 50 mg/1000 mg tablets or two Janumet XR 50 mg/1000 mg tablets fasted in healthy adult subjects (N=12)



Appendix Figure 6. Individual ratios (Janumet XR fasted/Janumet® fasted), geometric least square mean ratios, and 90% confidence intervals of the $AUC_{0-\infty}$ and C_{max} for sitagliptin and metformin after administration of t Janumet® 50 mg/1000 mg tablets or two Janumet XR 50 mg/1000 mg tablets fasted in healthy adult subjects (N=12)

The GLSMRs (Janumet XR Fed/Janumet® Fed) and the 90% CIs of the $AUC_{0-\infty}$ and C_{max} for sitagliptin after consumption of a high-fat breakfast were 1.01 (0.96, 1.05) and 1.10 (0.99, 1.22), respectively. The GLSMRs (Janumet XR Fed/Janumet® Fed) and the 90% CIs of the $AUC_{0-\infty}$ and C_{max} for metformin were 1.21 (1.02, 1.44) and 0.72 (0.63, 0.83), respectively.

The GLSMRs (Janumet XR Fasted/Janumet® Fasted) and 90% CIs of $AUC_{0-\infty}$ and C_{max} for sitagliptin were 1.13 (1.08, 1.19) and 1.48 (1.34, 1.64), respectively. The GLSMRs (Janumet XR Fasted/Janumet® Fasted) and 90% CIs of $AUC_{0-\infty}$ and C_{max} for metformin were 0.70 (0.58, 0.85) and 0.57 (0.50, 0.65), respectively.

The results indicate that both AUC and C_{max} for sitagliptin following administration of Janumet® and Janumet XR were bioequivalent under fed condition and only AUC for sitagliptin was bioequivalent under fasted condition. C_{max} for metformin was not bioequivalent for both fed and fasted conditions and C_{max} for sitagliptin was not bioequivalent for fasted condition.

Reviewer's note: Both Janumet® and Janumet XR are recommended to be administered with food. Thus, the sponsor's conclusion for the consistency in food effect is acceptable.

4.1.3 Multiple-Dose Study: Protocol 165

Title: A Multiple-Dose Study to Assess the Pharmacokinetics of MK-4031 XR

Open-label, multiple-dose study to assess the safety, tolerability, and PK of sitagliptin and metformin after administration of the Janumet XR FDC tablet once daily for 7 days. Prior to administration of the drug, subjects also self-administered 1000 mg of extended-release metformin (metformin XR) as Glucophage® XR once daily with evening meal for 4 days to minimize gastrointestinal intolerance potentially associated with subsequent administration of Janumet XR. Thereafter, subjects received two Janumet XR 50 mg/1000 mg tablets (100 mg of sitagliptin and 2000 mg of metformin) once daily with the evening meal for 7 days.

Dropouts: Twelve subjects enrolled and all of them completed the study. No subjects were discontinued from the study.

Results:

After administration of two Janumet XR 50 mg/1000 mg tablets once daily with the evening meal for 7 days, steady state for sitagliptin and metformin is reached by Day 4 and 5, respectively (See Appendix Table 8). As shown in Appendix Table 7, the PK parameters were comparable with those results obtained following a single dose two tablets of Janumet XR 50 mg/100 mg in the food effect study (protocol 164, See Appendix Table 5). There were no significant changes in PK parameters such as $T_{1/2}$ and T_{max} at steady state compared to single dose PK. No time-dependent non-linearity for sitagliptin and metformin after multiple-dose administration of Janumet XR were observed.

Appendix Table 7. Descriptive statistics of pharmacokinetic parameters for sitagliptin and metformin after administration of two Janumet XR 50 mg/1000 mg tablets (100 mg of sitagliptin and 2000 mg of metformin) once daily for 7 days in healthy adult subjects (n=12)

	AUC _{0-24hr} [†] (nM·hr)	C _{max} [†] (nM)	C _{24hr} [†] (nM)	T _{max} [‡] (hr)	Apparent Terminal t _{1/2} [§] (hr)
Sitagliptin	6851 (6298, 7453)	736 (653, 829)	66 (54, 81)	3.0 (1.0, 5.0)	12.0 (4.6)
	AUC _{0-24hr} [†] (ng·hr/mL)	C _{max} [†] (ng/mL)	C _{24hr} [†] (ng/mL)	T _{max} [‡] (hr)	Apparent Terminal t _{1/2} [§] (hr)
Metformin	20199 (17872, 22829)	1687 (1492, 1908)	200 (162, 247)	8.0 (6.0, 12.0)	14.1(4.2)

Appendix Table 8. Summary statistics of plasma sitagliptin and metformin concentration at predose on days 4, 5, 6 and 7 after administration of two Janumet XR 50 mg/1000 mg tablets (100 mg of sitagliptin and 2000 mg of metformin) once daily for 7 days in healthy adult subjects (n=12)

Day	N	Min	Median	Max	Geometric Mean [†] (95% CI) [‡]
Sitagliptin (nM)					
4	12	44	77	101	70 (58, 84)
5	12	46	67	137	70 (58, 84)
6	12	39	60	117	62 (52, 75)
7	12	38	68	108	69 (58, 83)
Metformin (ng/mL)					
4	12	66	180	291	164 (128, 209)
5	12	100	181	455	209 (164, 268)
6	12	94	212	308	193 (151, 247)
7	12	92	225	355	205 (160, 262)

Safety: Four adverse events reported from one subjects (nausea and 3 incidents of diarrhea) was determined to be treatment-related. There were no consistent treatment-related changes in laboratory safety tests, vital sign measurement, or ECG parameters.

4.1.4 Low Dose Probe Formulation Biocomparison Study: Protocol 112

Title: A Crossover Study to Assess the Pharmacokinetics of Sitagliptin and Metformin after Administration of Sitagliptin/Metformin Fixed-Dose Combination (FDC) Tablet: Probe Formulations

Each subject receive two sitagliptin-metformin XR FDC tablet probe formulation, 90 mg/1000 mg sustained-release tablet (SRT) and 100 mg/1000 mg matrix-release tablet (MRT), and co-administration of sitagliptin and three marketed metformin XR formulations in a 5-period crossover study. There was a minimum of 7-day washout between each treatment. The duration of the study was approximately 8 weeks.

Treatment arms:

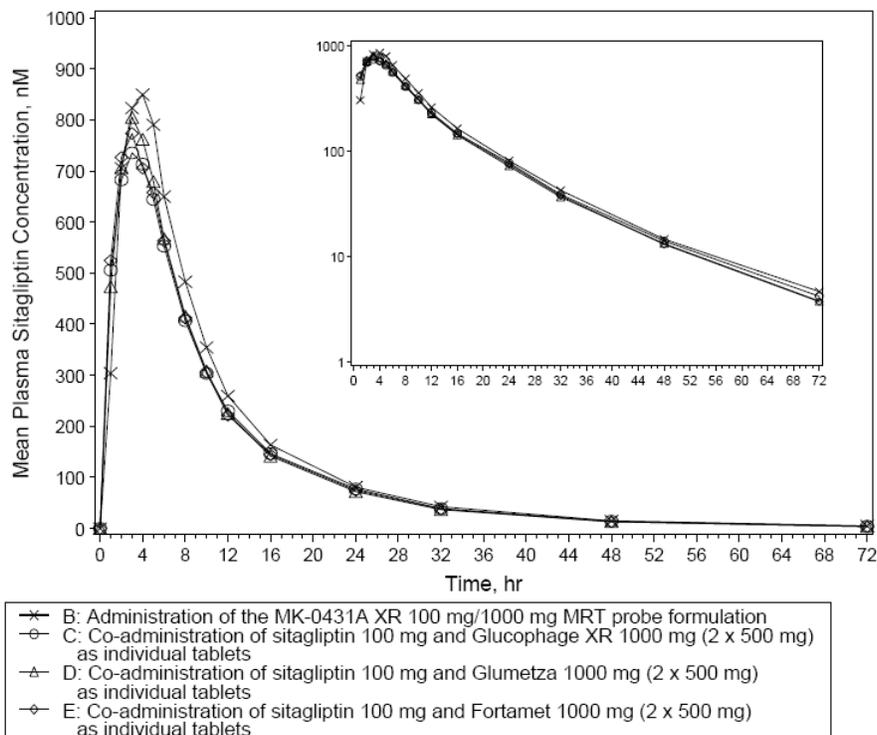
MK-0431A Fixed-Dose Combination Extended-Release Tablet	
Treatment A	MK-0431A XR 90 mg/1000 mg SRT
Treatment B	MK-0431A XR 100 mg/1000 mg MRT
Co-administration of Sitagliptin and Metformin Extended-Release Formulations	
Treatment C	Co-administration of sitagliptin 100 mg and GLUCOPHAGE® XR 1000 mg (2 x 500 mg)
Treatment D	Co-administration of sitagliptin 100 mg and GLUMETZA® 1000 mg (2 x 500 mg)
Treatment E	Co-administration of sitagliptin 100 mg and FORTAMET® XR 1000 mg (2 x 500 mg)

Dropouts: Twenty subjects enrolled and all of them completed the study. No subjects were discontinued from the study.

Results: The pharmacokinetics parameters following administration of single dose of MK-0431A XR 90 mg/1000 mg SRT probe formulation and MK-0431A XR 100 mg/1000 mg MRT probe formulation, and co-administration of sitagliptin 100 mg and metformin XR 1000 mg were shown in the table below.

Appendix Table 9. Statistical comparisons for the plasma PK parameters for sitagliptin after administration of a single dose of MK-0431A XR 90 mg/1000 mg SRT probe formulation, MK-0431A XR 100 mg/1000 mg MRT probe formulation and co-administration of sitagliptin 100 mg and marketed metformin XR formulations (Glucophage XR, Glumetza, and Fortamet) 1000 mg (2x500 mg) as individual tablets in healthy adult subjects

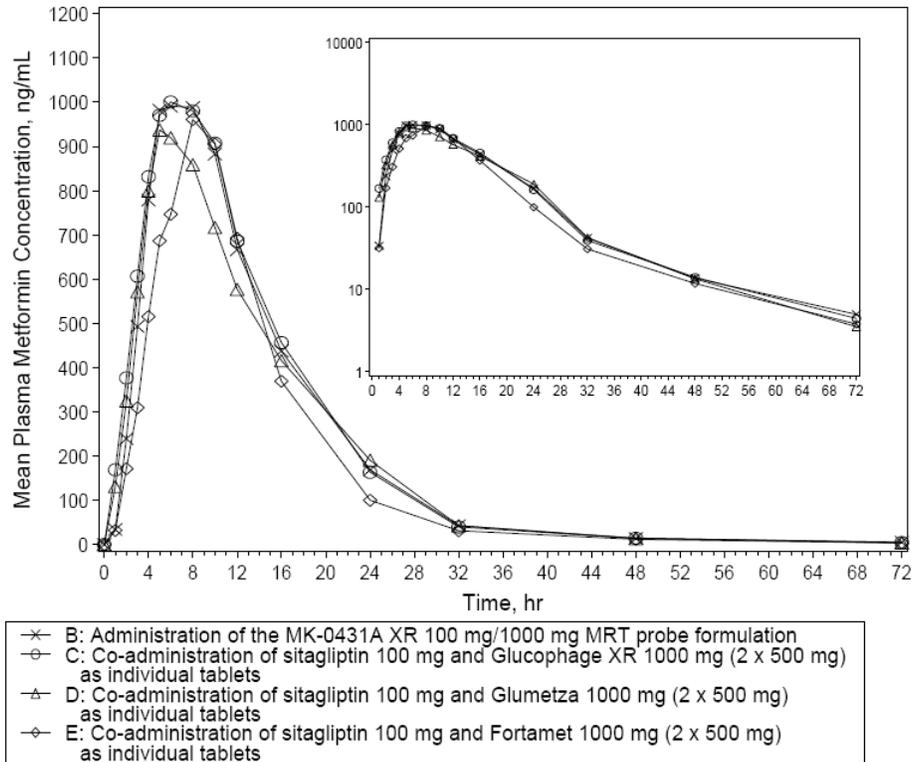
Parameter	Geometric Mean Ratio (96.7% CI) MK-0431A XR MRT Probe Formulation vs.		
	Sitagliptin + Glucophage XR	Sitagliptin + Glumetza	Sitagliptin + Fortamet
AUC _{0-∞}	1.09 (1.05, 1.14)	1.09 (1.05, 1.13)	1.09 (1.05, 1.13)
AUC _{0-last}	1.09 (1.05, 1.14)	1.09 (1.04, 1.13)	1.09 (1.04, 1.13)
C _{max}	1.13 (1.04, 1.24)	1.03 (0.94, 1.12)	1.04 (0.95, 1.13)
Parameter	MK-0431A XR SRT Probe Formulation vs.		
	Sitagliptin + Glucophage XR	Sitagliptin + Glumetza	Sitagliptin + Fortamet
AUC _{0-∞}	1.03 (0.99, 1.07)	1.02 (0.98, 1.06)	1.02 (0.98, 1.06)
AUC _{0-last}	1.03 (0.99, 1.07)	1.02 (0.98, 1.06)	1.02 (0.98, 1.06)
C _{max}	1.10 (1.01, 1.20)	1.00 (0.92, 1.09)	1.00 (0.92, 1.10)



Appendix Figure 7. Sitagliptin concentration-time profile after administration of a single dose of the MK-0431A XR 90 mg/1000 mg SRT probe formulation, the MK-0431A XR 100 mg/1000 mg MRT probe formulation and co-administration of sitagliptin 100 mg and marketed metformin XR Formulations (Glucophage XR, Glumetza, and Fortamet) 1000 mg (2x500 mg) as individual tablets in healthy adult subjects

Appendix Table 10. Statistical comparisons for the plasma PK parameters for metformin after administration of a single dose of the MK-0431A XR 90 mg/1000 mg SRT probe formulation, the MK-0431A XR 100 mg/1000 mg MRT probe formulation and co-administration of sitagliptin 100 mg and marketed metformin XR formulations (Glucophage XR, Glumetza, and Fortamet) 1000 mg (2x500 mg) as individual tablets in healthy adult subjects

Geometric Mean Ratio (96.7% CI)			
MK-0431A XR MRT Probe Formulation			
vs.			
Parameter	Sitagliptin + Glucophage XR	Sitagliptin + Glumetza	Sitagliptin + Fortamet
AUC _{0-∞}	0.97 (0.88, 1.06)	1.06 (0.97, 1.16)	1.21 (1.11, 1.33)
AUC _{0-last}	0.96 (0.88, 1.06)	1.06 (0.97, 1.16)	1.21 (1.11, 1.33)
C _{max}	0.99 (0.90, 1.09)	1.11 (1.01, 1.22)	1.05 (0.96, 1.16)
MK-0431A XR SRT Probe Formulation			
vs.			
Parameter	Sitagliptin + Glucophage XR	Sitagliptin + Glumetza	Sitagliptin + Fortamet
AUC _{0-∞}	0.94 (0.86, 1.02)	1.03 (0.94, 1.12)	1.18 (1.08, 1.29)
AUC _{0-last}	0.93 (0.86, 1.02)	1.02 (0.94, 1.12)	1.18 (1.08, 1.28)
C _{max}	1.08 (0.98, 1.18)	1.20 (1.10, 1.32)	1.14 (1.04, 1.25)



Appendix Figure 8. Metformin concentration-time profile after administration of a single dose of the MK-0431A XR 90 mg/1000 mg SRT probe formulation, the MK-0431A XR 100 mg/1000 mg MRT probe formulation and co-administration of sitagliptin 100 mg and marketed metformin XR formulations (Glucophage XR, Glumetza, and Fortamet) 1000 mg (2x500 mg) as individual tablets in healthy adult subjects.

Results: As shown in tables above, the AUC and C_{max} of sitagliptin and metformin following a single dose of Janumet XR 90 mg/1000 mg SRT probe formulation were bioequivalent to those following co-administration of sitagliptin 100 mg along with two tablets of 500 mg Glucophage XR or 500 mg Glumetza or 500 mg of Fortamet. Furthermore, a single dose of Janumet XR 100 mg/1000 mg MRT probe formulation were also bioequivalent to those following co-administration of sitagliptin 100 mg along with two tablets of 500 mg Glucophage XR or 500 mg Glumetza or 500 mg of Fortamet.

Reviewer’s comments: The sponsor conducted this study to compare SRT formulation and MRT formulation of the developing product (MK-0431A XR) to in the process of development of MRT formulation. As bioequivalence between these two formulations was established, data obtained from studies with SRT formulation could be utilized for the submission.

4.1.5 Drug Interaction between Metformin XR and Sitagliptin: Protocol 012

This study was submitted under NDA 21995 (See Dr. Xiaoxiong Wei's review dated August 30, 2006).

4.1.6 Phase I Mechanism-of-Action Study in Healthy Subjects: Protocol 050

Title: A Randomized, Placebo-Controlled, Double-Blind, Double-Dummy, Four-Period Crossover Study to Assess the Effects of Concomitant Administration of Sitagliptin and Metformin Alone and in Combination on Post-Meal Incretin Hormone Concentrations in Healthy Adult Subjects

Treatment: Each subject participated in four 2-day treatment periods (i.e., 2 doses of sitagliptin and 3 doses of metformin) in a crossover manner. There was a minimum of a 7-day washout between the last dose of study drug in one treatment period and the first dose of study drug in the subsequent treatment periods.

Objectives: To determine the effect of concomitant administration of sitagliptin and metformin on post-meal plasma incretin hormone concentrations (e.g., active and inactive and/or total glucagon-like peptide-1 [GLP-1] and gastric inhibitory peptide [GIP] concentrations, the ratio of active to total GLP-1 and GIP concentrations) in healthy adult subjects.

Hypothesis: The weighted average active plasma GLP-1 concentrations for 4 hours after the postdose meal will be increased upon concomitant administration of sitagliptin and metformin compared with weighted average active plasma GLP-1 concentrations after administration of sitagliptin alone (an increase on the order of 50% is expected).

Study design: Randomized, placebo-controlled, double-blind, double-dummy, 4-period crossover study to assess the effects of sitagliptin and metformin on post-meal incretin hormone (total and active GLP-1) concentrations after concomitant administration of sitagliptin and metformin and after administration of sitagliptin alone, metformin alone and placebo in healthy adult subjects. In each 2-day treatment period, subjects were randomized to receive either sitagliptin alone (active sitagliptin and placebo to metformin), metformin alone (placebo to sitagliptin and active metformin), concomitant administration of sitagliptin, and metformin or placebo (concomitant administration of placebo to sitagliptin and placebo to metformin) according to a computer-generated allocation schedule (see treatment schedule below). Each subject received all treatments and there was a minimum of a 7-day washout interval between the last dose of study drug in one treatment period and the first dose of study drug in subsequent treatment periods

Treatment Group	Treatment	Treatment Details
A	Sitagliptin alone	Day 1: AM (100 mg sitagliptin and placebo to 500 mg metformin) PM (Placebo to 500 mg metformin) Day 2: AM (100 mg sitagliptin and placebo to 1000 mg metformin)
B	Metformin alone	Day 1: AM (Placebo to 100 mg sitagliptin and 500 mg metformin) PM (500 mg metformin) Day 2: AM (Placebo to 100 mg sitagliptin and 1000 mg metformin)
C	Sitagliptin and metformin concomitantly	Day 1: AM (100 mg sitagliptin and 500 mg metformin) PM (500 mg metformin) Day 2: AM (100 mg sitagliptin and 1000 mg metformin)
D	Placebo	Day 1: AM (Placebo to 100 mg sitagliptin and placebo to 500 mg metformin) PM (Placebo to 500 mg metformin) Day 2: AM (Placebo to 100 mg sitagliptin and placebo to 1000 mg metformin)

Subjects: Eighteen (male 18, female 12) enrolled and 16 completed the study.

Dosage/Formulation: The dosage and formulation are summarized in the table below.

Drug	Potency	Formulation No.	Dosage Form	Control No.
Part I				
Sitagliptin	100 mg	WL00012945/0431 FCT009C002	Tablet	WP-M643
Metformin	500 mg	WL00017463	Tablet	WP-M643
Sitagliptin Placebo	--	WL00012141/P0431 FCT007R003	Tablet	WP-M643
Metformin placebo	--	WL00017464	Tablet	WP-M643

PK/PD Evaluation:

PK was evaluated with blood samples obtained at pre-meal and at 2 hour after the postdose meal.

PD was evaluated with blood sample on Day 2 of each treatment period by determining active and total GLP-1 and GIP concentrations, plasma glucose concentrations, and archive samples collected for possible determination of plasma DPP-4 inhibitory activity at pre-meal and at 2 hour after the postdose meal.

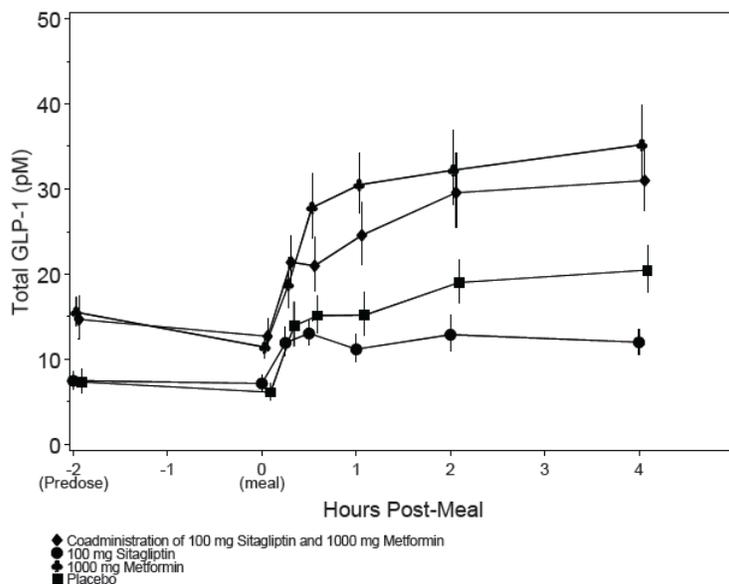
- Primary endpoint: 4-hour post-meal (meal consumed at 2 hour postdose; at the approximate Tmax for sitagliptin and metformin) weighted average active GLP-1 concentrations after co-administration of sitagliptin and metformin compared with administration of sitagliptin alone.
- Secondary endpoint: 4-hour post-meal weighted average active GLP-1 concentrations after co-administration of sitagliptin and metformin compared with administration of metformin alone and placebo, 4-hour post-meal weighted average total GLP-1, active and total GIP, ratio of active to total GLP-1 and GIP concentrations after co-administration of sitagliptin and metformin compared with administration of sitagliptin alone, metformin alone and placebo, 4-hour post-

meal weighted average total GLP-1, active and total GIP, ratio of active to total GLP-1 and GIP concentrations after co-administration of sitagliptin and metformin compared with administration of sitagliptin alone, metformin alone and placebo, 4-hour post-meal incremental glucose AUC and fasting and maximum glucose concentrations after concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone, metformin alone and placebo.

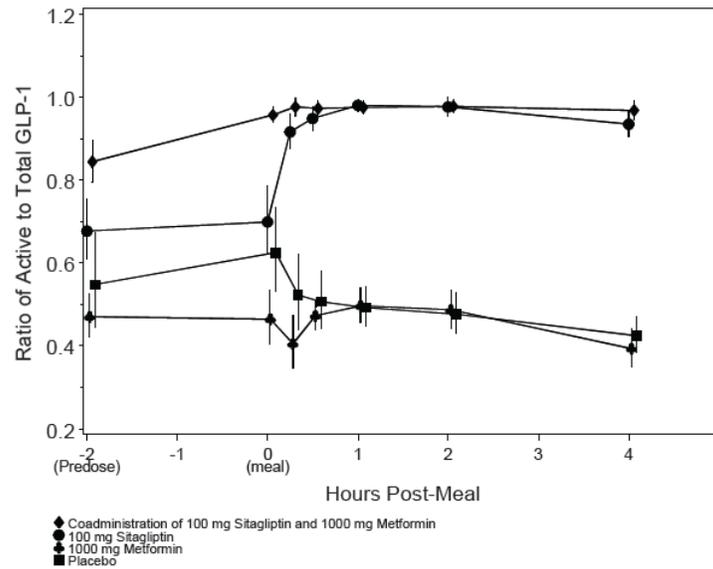
Results:

PK analysis was not reported (the sponsor indicated that it would be submitted when available in the future).

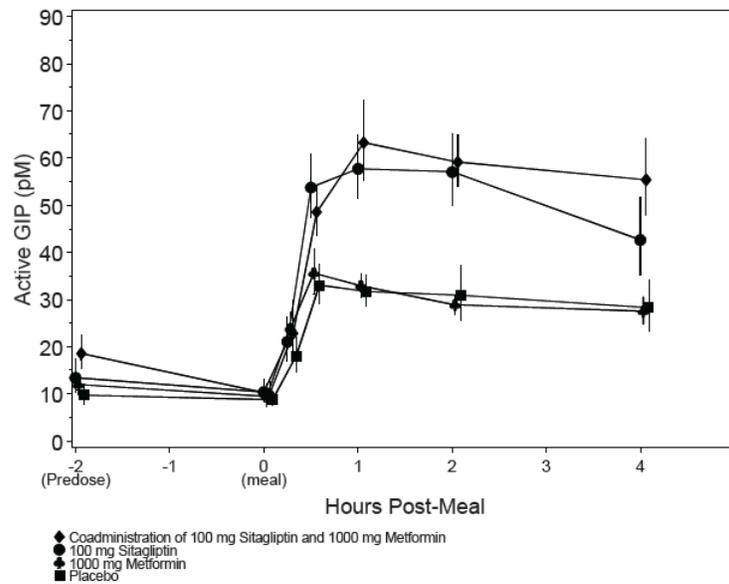
PD Results: (1) The 4-hour post-meal weighted mean active GLP-1 concentrations were increased by approximately 110% after co-administration of sitagliptin and metformin compared with administration of sitagliptin alone. (2) Administration of metformin alone increases circulating concentrations of both active and total GLP-1 to a similar extent (approximately 80%) suggesting that the effect of metformin on active GLP-1 levels is primarily due to an increase in total GLP-1 concentrations. (3) The ratio of active to total GLP-1 concentrations after administration of sitagliptin alone is increased by approximately 100% indicating that sitagliptin stabilizes active GLP-1. (4) The 4-hour post-meal weighted average active GIP concentrations after co-administration of sitagliptin and metformin compared with administration of sitagliptin alone were similar. (5) Sitagliptin, but not metformin alone enhances active GIP concentrations by stabilization of active versus total GIP concentrations.



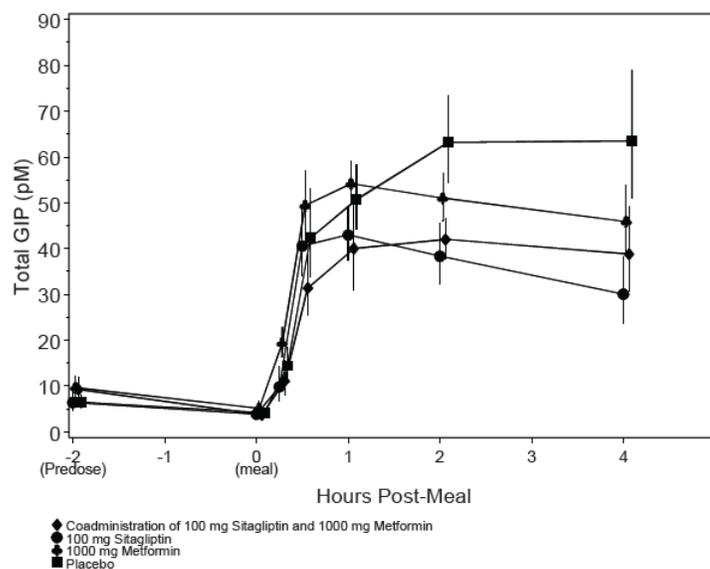
Appendix Figure 9. Geometric least square mean pre-/post-meal total GLP-1 plasma Concentrations-time profile on Day 2 after concomitant administration of sitagliptin and metformin and after administration of sitagliptin alone, metformin alone and placebo in healthy adult subjects (Source: Figure 11-2 of the CSR) (Mean \pm SE)



Appendix Figure 10. Geometric least square mean active/total GLP-1 plasma Concentrations-time profile on Day 2 after concomitant administration of sitagliptin and metformin and after administration of sitagliptin alone, metformin alone and placebo in healthy adult subjects (Mean \pm SE)



Appendix Figure 11. Geometric least square mean pre-/post-meal active GIP plasma concentrations-time profile on Day 2 after concomitant administration of sitagliptin and metformin and after administration of sitagliptin alone, metformin alone and placebo in healthy adult subjects (Mean \pm SE)



Appendix Figure 12. Geometric least square mean pre-/post-meal total GIP plasma concentrations-time profile on Day 2 after concomitant administration of sitagliptin and metformin and after administration of sitagliptin alone, metformin alone and placebo in healthy adult subjects (Mean \pm SE)

Safety Results: A total of 14 subjects reported a total of 38 adverse experiences. Thirty five of them were rated by the investigator to be related to study drug. The most common drug related adverse experiences were headache and gastrointestinal symptoms. All adverse experiences were rated as mild in intensity. There were no laboratory or serious adverse events reported in this study. No subjects were discontinued due to an adverse experience.

4.1.7 Phase I PD study in T2DM Patients: Protocol 110

Title: A Study to Assess the Effects of Co-administration of sitagliptin and Metformin on Incretin Hormone Concentrations

Duration of treatment: Four 2-day treatment periods where sitagliptin alone, metformin alone, co-administration of sitagliptin and metformin or placebo were administered with minimum of a 7-day washout between treatment periods. Total duration of the study was 8 weeks.

Objectives:

- Primary: To assess the effects of sitagliptin alone, metformin alone and co-administration of sitagliptin and metformin on post-prandial active glucagon-like peptide-1 (GLP-1) concentrations in patients with type-2 diabetes mellitus (T2DM).

- Secondary:
 - To assess the effects of sitagliptin alone, metformin alone and co-administration of sitagliptin and metformin on post-prandial C-peptide and insulin concentrations in patients with T2DM.
 - To assess the effects of sitagliptin alone, metformin alone and co-administration of sitagliptin and metformin on post-prandial plasma glucose concentrations in patients with T2DM.

- Exploratory objectives:
 - To assess the effects of sitagliptin alone, metformin alone and co-administration of sitagliptin and metformin on post-prandial plasma active and/or total GLP-1 and GIP concentrations in patients with T2DM.
 - To assess the effects of sitagliptin alone, metformin alone and co-administration of sitagliptin and metformin on postprandial serum C-peptide, insulin and glucagon concentrations in patients with T2DM.
 - To assess the effects of sitagliptin alone, metformin alone and co-administration of sitagliptin and metformin on postprandial GLP-2 concentrations in patients with T2DM.

Study design: Randomized, placebo-controlled, double-blind, double-dummy, four-period crossover study

Treatment Scheme:

Treatment Group	Treatment	Treatment Details	Number of Tablets
A	Sitagliptin alone	Day 1: AM - sitagliptin 100 mg and placebo to metformin 500 mg PM - placebo to metformin 500 mg Day 2: AM - sitagliptin 100 mg and placebo to metformin 1000 mg [†]	Day 1: AM (2 tablets) PM (1 tablet) Day 2: AM (3 tablets)
B	Metformin alone	Day 1: AM - placebo to sitagliptin 100 mg and metformin 500 mg PM - metformin 500 mg Day 2: AM - placebo to sitagliptin 100 mg and metformin 1000 mg [†]	Day 1: AM (2 tablets) PM (1 tablet) Day 2: AM (3 tablets)
C	Co-administration of sitagliptin and metformin	Day 1: AM - sitagliptin 100 mg and metformin 500 mg PM - metformin 500 mg Day 2: AM - sitagliptin 100 mg and metformin 1000 mg [†]	Day 1: AM (2 tablets) PM (1 tablet) Day 2: AM (3 tablets)
D	Placebo	Day 1: AM - placebo to sitagliptin 100 mg and placebo to metformin 500 mg PM - placebo to metformin 500 mg Day 2: AM - placebo to sitagliptin 100 mg and placebo to metformin 1000 mg [†]	Day 1: AM (2 tablets) PM (1 tablet) Day 2: AM (3 tablets)
[†] Metformin 1000 mg = 2 x 500 mg metformin tablets (or placebo tablets x 2).			

Subjects: Eighteen patients were randomized and all of them completed the study.

Dosage/Formulation: The dosage and formulation are summarized in the table below.

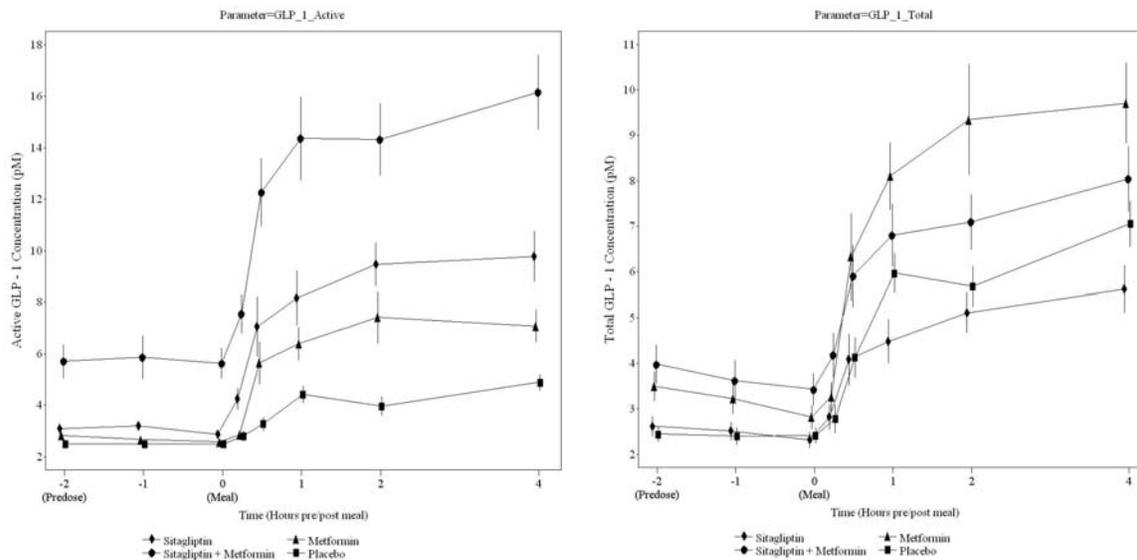
Drug	Potency	Formulation Number	Dosage Form	Control Number
Sitagliptin	100 mg	WL 00027978	tablet	WL00030754
Placebo to sitagliptin	--	WL00014482	tablet	WL00030754
Metformin HCl	500 mg	WL00026296	tablet	WL00030754
Placebo to Metformin HCl	--	WL00025566	tablet	WL00030754

PD assessment:

The primary endpoint was the incremental post-prandial (meal given 2 hours postdose; approximate C_{max} for sitagliptin and metformin) 4-hour weighted mean active GLP-1 concentrations after co-administration of sitagliptin and metformin compared with placebo. Secondary endpoints, postprandial β -cell sensitivity and plasma glucose concentrations are also included.

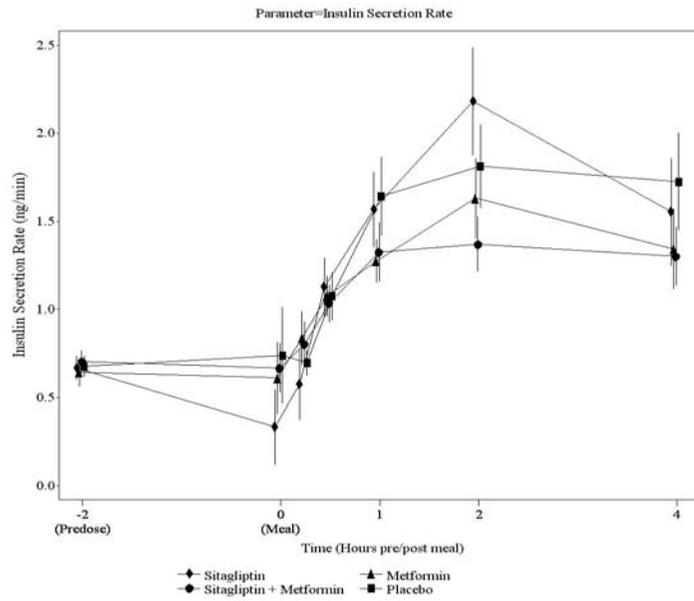
The effects of sitagliptin alone, metformin alone or after co-administration of sitagliptin and metformin on post-prandial active and total GLP-1 concentrations, β -cell sensitivity, and plasma/serum glucose, C-peptide, insulin, and glucagon concentrations in patients with T2DM are summarized in the table below.

Incremental Post-Prandial 4-hour Weighted Mean Active GLP-1 Concentrations:



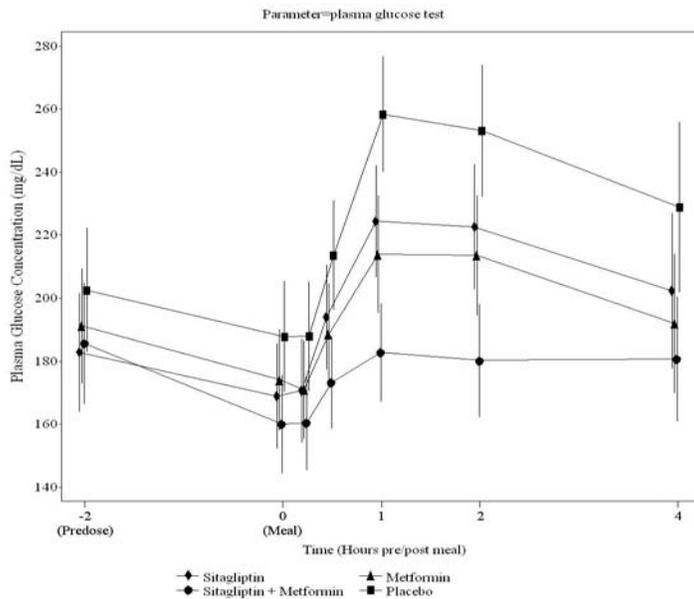
Appendix Figure 13. Geometric least square mean (SE) pre-/post-prandial plasma active (left) and total (right) GLP-1 concentration-time profile on Day 2 after administration of sitagliptin alone, metformin alone, co-administration of sitagliptin and metformin, and placebo in patients with T2DM (n=18)

β -cell Sensitivity:



Appendix Figure 14. Arithmetic mean (SE) pre-/post-prandial plasma insulin secretion rate (ng/min) vs. time (hr) on Day 2 after administration of sitagliptin alone, metformin alone, co-Administration of sitagliptin and metformin, and placebo in patients with T2DM (n=18)

Incremental Post-Prandial 4-hour Weighted Mean Plasma Glucose Concentrations:



Appendix Figure 15. Arithmetic mean (SE) pre-/post-prandial plasma glucose concentration-time profile on Day 2 after administration of sitagliptin alone, metformin alone, co-Administration of sitagliptin and metformin, and placebo in patients with T2DM (n=18)

Appendix Table 11. Between-treatment comparisons for the incremental post-prandial 4-hour weighted mean of GLP-1, glucose, glucagon, C-peptide and insulin concentration, and β -cell sensitivity on Day 2 after administration of sitagliptin alone, metformin alone, co-administration of sitagliptin and metformin, and placebo in patients with T2DM (n=18)

GMR [†] (95% CI)			
Endpoint	Sitagliptin / PBO	Metformin / PBO	(Sitagliptin + Metformin) / PBO
Active GLP-1	3.87 (2.93, 5.12)	2.64 (2.00, 3.50)	4.66 (3.53, 6.16)
Total GLP-1	0.79 (0.61, 1.03)	1.69 (1.30, 2.21)	0.89 (0.69, 1.16)
Ratio of Active to Total GLP-1 [§]	2.36 (2.20, 2.53)	1.06 (0.99, 1.14)	2.69 (2.51, 2.89)
β -cell sensitivity	1.26 (0.87, 1.83)	1.67 (1.15, 2.41)	1.71 (1.19, 2.46)
Difference [‡] (95% CI)			
Endpoint	Sitagliptin - PBO	Metformin - PBO	(Sitagliptin + Metformin) - PBO
Glucose	-8.72 (-15.95, -1.49)	-21.69 (-28.93, -14.45)	-31.00 (-38.23, -23.77)
Glucagon	-4.90 (-10.65, 0.85)	11.71 (5.95, 17.47)	0.81 (-4.94, 6.56)
C-peptide	0.16 (-0.42, 0.73)	-0.68 (-1.26, -0.11)	-1.17 (-1.74, -0.61)
Insulin	3.07 (-12.09, 18.22)	-10.42 (-25.59, 4.74)	-22.28 (-37.14, -7.43)

Conclusions:

1. Sitagliptin and metformin have complementary effects on post-prandial active GLP-1 concentrations in patients with T2DM: a synergistic effect on active GLP-1 when the two medications are compared.
2. Metformin alone or co-administration with sitagliptin enhances post prandial β -cell sensitivity compared with placebo, whereas sitagliptin alone does not appear to enhance β -cell sensitivity.
3. Metformin alone or co-administration with sitagliptin decrease the incremental post-prandial 4-hour weighted mean plasma glucose concentrations (compared with placebo). The magnitude of the decrease for this endpoint with co-administration of sitagliptin and metformin is greater than that associated with either treatment alone.
4. As compared with placebo, sitagliptin administered alone or co-administered with metformin almost completely inhibits in vivo DPP-4 activity, where metformin does not inhibit in vivo DPP-4 activity.

4.2 Cover Sheet and OCP Filing

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

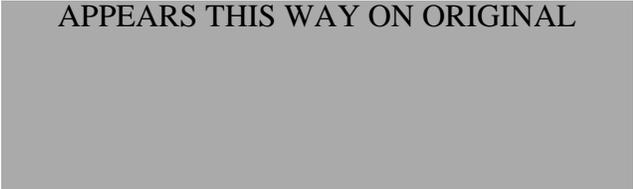
	Information		Information	
NDA Number	202270	Brand Name	Janumet® XR	
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Sitagliptin/metformin XR (MK-0431A XR)	
Medical Division	DMEP	Drug Class	DPP4-Inhibitor/biguanide	
OCP Reviewer	Jee Eun Lee, Ph.D.	Indication(s)	Glycemic control in T2DM	
OCP Pharmacometrics Reviewer		Dosage Form	FDA of sitagliptin and extended release formulation of metformin	
OCP Team Leader	Sally Choe, Ph.D.	Dosing Regimen	once daily	
Date of Submission	9/23/2010	Route of Administration	Oral	
Estimated Due Date of OCP Review		Sponsor	MERCK SHARP DOHME	
PDUFA Due Date	7/23/2011	Priority Classification	Standard	
Division Due Date				

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Carton and Container Labels
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		
multiple dose:	X	1		
Patients				
single dose:	X	1		DDI of metformin IR and MK-0431 A
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:	X	2		PD of sitagliptin and metformin IR in healthy subjects and T2DM patients
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		Pivotal BE
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		Food effect and comparison between Janumet® and MK-0431 XR
Dissolution: (IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		8		
Filability				
	"X" if yes	Comments		
Application filable?	X	Comments to the Sponsor:		
Submission in Brief: See the details below.	Reviewer's Comments (to the project manager): The consult for DSI inspection was sent for the study P147 clinical site and its bioanalytical lab.			

APPEARS THIS WAY ON ORIGINAL



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/s/

JEE E LEE
06/17/2011

JAYABHARATHI VAIDYANATHAN
06/17/2011

BIOPHARMACEUTICS REVIEW			
Office of New Drugs Quality Assessment			
Application No.:	NDA 202-270 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DMEP		
Sponsor:	Merck	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	Janumet XR Tablets	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Metformin/sitagliptin ER FDC Tablets	Date Assigned:	Oct 15, 2010
Indication:	Type II diabetes	Date of Review:	May 17, 2011
Formulation/strengths	Extended Release tablets, 50/500 mg 50/1000mg; 100/1000 mg		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Sep 24, 2011, Jan 10, 2011, April 11, 2011, April 29, 2011, May 11, 2011, May 18, 2011	Sep 24, 2010	Oct 5, 2010	Jul 23, 2010
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications/ biowaiver request for lower strength/ biowaiver request for change in manufacturing process.		
REVIEW SUMMARY:			
<p>Januvia® (sitagliptin phosphate) 25 mg, 50 mg and 100 mg, immediate release tablets were approved by the Agency for the treatment of type 2 diabetes Mellitus (T2DM) on Oct 16, 2006. Glumetza (metformin hydrochloride) extended release tablets, 500 mg and 1000 mg were approved for the treatment of T2DM in June 5, 2005. Janumet® (sitagliptin phosphate and metformin hydrochloride) 50/500 mg and 50/1000 mg, IR tablets were approved on March 30, 2007 for the twice daily treatment of T2DM.</p> <p>The sponsor, Merck has developed a new formulation for Janumet consisting of an extended release, film-coated tablets for the once daily treatment of T2DM. Three fixed dose combinations (FDC) have been developed for registration: 50/500, 50/1000, and 100/1000 (mg sitagliptin as free base/mg metformin hydrochloride). The proposed dosing regimen is sitagliptin/metformin XR 50 mg/500 mg and 50 mg/1000 mg to be given as 2 tablets once daily and sitagliptin/metformin XR 100 mg/1000 mg to be given as 1 tablet once daily. The clinical development program for this new drug formulation for the proposed indication is based on demonstration of BE between Janumet ER product and co-administration of sitagliptin and an approved metformin XR formulation (GLUMETZA®) in order to bridge the existing safety and efficacy data from studies with sitagliptin, metformin XR, and the combination of sitagliptin and metformin IR (from the Januvia and Janumet programs) to Janumet ER tablets. Several additional Clinical Pharmacology studies were also conducted to support the registration of Janumet ER tablets.</p> <p>According to the sponsor, BE was demonstrated between the FMC XR tablets, at tablet strengths of both 50 mg/500 mg and 100 mg/1000 mg, and co-administration of corresponding doses of sitagliptin and GLUMETZA® as monoproducts. The sponsor requested a biowaiver of the in vivo BE requirements for the 50/1000 mg strength based on dissolution profile comparisons of all strengths in different media.</p>			

The Biopharmaceutics review is focused on: a) the acceptability of the dissolution method and specifications; b) in vitro alcohol interaction study, c) acceptability of a waiver request supporting the approval of the 50/1000 mg strength; d) acceptability of a biowaiver request supporting the approval of the manufacturing process change, and e) the role of dissolution in Quality by Design (QbD).

a) Dissolution Method and Specifications

The following dissolution method and specifications were originally proposed by the sponsor for both active ingredients and for the three strengths of the product under review:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Merformin/sitagliptin	ER Tablets	USP Paddle	75	(50mM Phosphate Buffer, pH 6.8	Sitagliptin: Min. (b) (4) in 45 minutes Metformin: (b) (4) in 1 hour (b) (4) in 3 hours Min. (b) (4) in 10 hours

The sponsor provided sufficient information to support the acceptability of the dissolution method for both components of Janumet ER tablets.

On May 17, 2011 the sponsor agreed upon the following recommended dissolution specifications for ALL the strengths of Janumet ER tablets:

Acceptance criteria
Sitagliptin: Q= (b) (4) in 30 minutes Metformin: (b) (4) in 1 hour (b) (4) in 3 hours Min. (b) (4) in 10 hours

These recommended dissolution acceptance criteria is based on analysis of data obtained during release and extended testing of 9 formal stability study (FSS) batches, including 3 biobatches with extended testing, as well as simulations/statistical analysis of formal stability data through 52 weeks.

It is noted that the lower strengths (50/500 mg and the 50/1000 mg) have a mean dissolution at 30 min for the sitagliptin component which is higher than that for the 100/1000 mg strength suggesting that a specification of Q= (b) (4) at 30 min may be appropriate for these two lower strengths. However, given that the 50/500 mg and the 100/1000 mg strengths were bioequivalent and in order to have consistent specifications across strengths, the same dissolution specification is also recommended for the sitagliptin component of ALL the Janumet XR strengths.

b) in vitro alcohol interaction study

There were no signs of an uncontrolled drug release from the formulation of Janumet ER tablets when dissolved in 5, 20 or 40% ethanol. On the contrary, the release profiles became slower in the presence of alcohol.

c) Waiver request to support the approval of Janumet ER tablets, 50/1000 mg.

Merck submitted a meeting package for the pre-NDA meeting for IND 101964 (sitagliptin-metformin XR FDC), scheduled for May 10, 2010. The meeting package contained several inquiries including concurrence with the statement about meeting the biowaiver requirements for the 50 mg/1000 mg tablet strength of Janumet XR. The Agency concurred with this statement proposed during pre-NDA submission. In this submission, the sponsor included information supporting the biowaiver for the Sitagliptin Phosphate (+) Metformin Hydrochloride Tablets, 50 mg/1000 mg. The justification for the biowaiver is based on the results of the pivotal BE Study (Protocol 147) on the 50 mg/500 mg and 100 mg/1000 mg tablets, and on *in vitro* dissolution profiles in four different media (water and USP buffer at pH 1.2, 4.5, and 6.8) conducted on all tablet strengths (b)(4). For all tablet strengths in all media, the metformin dissolution profiles were similar as determined by an *F2* similarity factor of > 50. However, dissolution profile comparisons between the 100/1000 mg strength of Janumet ER tablets and the 50/1000 mg and 50/500 mg strengths failed *F2* testing ($F2 < 50$) for the sitagliptin component. Nevertheless, the middle strength is considered comparable (bioequivalent) to the higher strength based on:

- BE findings between low and high strength: the 50/500 mg and 100/1000 mg strengths were bioequivalent (refer to Clinical Pharmacology review).
- For the sitagliptin component, the dissolution profile for the middle strength is in between the dissolution profiles for the low and high strengths, indicating that the *in vitro* and *in vivo* performance of this middle strength is similar to the lower and higher strengths.

It is noted that the 50/1000 mg strength is not proportionally similar to the higher or lower strengths. However, cross-study comparison on the systemic exposure (C_{max} and AUC) for equivalent doses of sitagliptin (50 mg) and metformin (1000 mg) indicates equivalent exposure of the 50/1000 mg compared to the other two strengths. Therefore, the waiver request of the BE requirements for the middle strength, namely Janumet ER 50/1000 mg, tablets is granted.

d) Acceptability of a biowaiver request supporting the approval of the manufacturing process change

The proposed commercial process and formulation for the final product of Janumet ER tablets is the same as that used for manufacture of the FSS/biobatches with the following exceptions; commercial batches will utilize optimized (b)(4) coating parameters, including debossing and (b)(4) (b)(4) wax than the FSS/biobatches. The CMC team considers these manufacturing changes as Level 2 defined according to SUPAC-MR guidance. The sponsor is requesting approval of these changes based on dissolution profiles comparisons (*F2* testing) in three different media in lieu of *in vivo* BE studies.

Debossing and wax reduction did not affect the *in vitro* performance of the Janumet components since *F2* values were > 50 (merformin component) or the dissolution profile for the formulation with debossing (sitagliptin component) was in between the dissolution profile for two formulations without debossing which were found to be bioequivalent. Therefore, the biowaiver supporting the approval of the manufacturing changes is granted.

e) The role of dissolution on the construction of the design space for Metformin Cores

Changes in process parameters (b)(4) did not affect dissolution profiles of metformin cores, suggesting that dissolution should not be used as a critical quality attribute in guiding the construction/acceptability of the proposed design space for metformin. The sitagliptin control strategy did not follow the principles of QbD.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 202-270 (000) submitted on Sep 24, 2010, Jan 10, 2011, April 11, 2011, April 29, 2011, May 11, 2011 and May 18, 2011. This NDA was found to be acceptable from the Biopharmaceutics perspective. The following dissolution method and specifications have been found acceptable and agreed upon with the sponsor (refer to submission dated May 18, 2011) for ALL the strengths of Janumet ER Tablets:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Merformin/ sitagliptin	ER Tablets	USP Paddle	75	(50mM Phosphate Buffer, pH 6.8	Sitagliptin: Q=(b)(4) in 30 minutes Metformin: (b)(4) in 1 hour (b)(4) in 3 hours Min. (b)(4) in 10 hours

Sandra Suarez Sharp, Ph. D.
 Biopharmaceutics Reviewer
 Office of New Drugs Quality Assessment

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

c.c. RChiang, ADorantes, STran, OStephens, VPratt

INTRODUCTION

Januvia® (sitagliptin phosphate) 25 mg, 50 mg and 100 mg, immediate release tablets were approved by the Agency for the treatment of type 2 diabetes Mellitus (T2DM) on Oct 16, 2006. Glumetza (metformin hydrochloride) extended release tablets, 500 mg and 1000 mg were approved for the treatment of T2DM in June 5, 2005. Janumet® (sitagliptin phosphate and metformin hydrochloride) 50/500 mg and 50/1000 mg, IR tablets were approved on March 30, 2007 for the twice daily treatment of T2DM.

The sponsor, Merck has developed a new formulation for Janumet consisting of an extended release, film-coated tablets for the once daily treatment of T2DM. Three fixed dose combinations (FDC) have been developed for registration: 50/500, 50/1000, and 100/1000 (mg sitagliptin as free base/mg metformin hydrochloride). The proposed dosing regimen is sitagliptin/metformin XR 50 mg/500 mg and 50 mg/1000 mg to be given as 2 tablets once daily and sitagliptin/metformin XR 100 mg/1000 mg to be given as 1 tablet once daily. The clinical development program for this new drug formulation for the proposed indication is based on demonstration of bioequivalence between the new ER product and co-administration of sitagliptin and an approved metformin XR formulation (GLUMETZA®) in order to bridge the existing safety and efficacy data from studies with sitagliptin, metformin XR, and the combination of sitagliptin and metformin IR (from the Januvia and Janumet programs) to the new ER product. Several additional Clinical Pharmacology studies were also conducted to support the registration of MK-0431A XR.

This review is focused on the acceptability of the biowaiver requests, in vitro alcohol interaction study, the dissolution method and specifications, and the role of dissolution in QbD. The OCP will review the bioequivalence studies.

CHEMISTRY

Drug Substances

Sitagliptin Phosphate

Sitagliptin is formulated as the monohydrate phosphate salt; this salt form was selected and extensively characterized during the JANUVIA® development program. The monohydrate phosphate salt is non-hygroscopic, chemically and physically stable, and highly soluble in aqueous media. It is highly soluble over the entire physiological pH range (Table 1) and its absolute BA is about 87%. Therefore, it is classified as a BCS Class III.

Table 1. Solubility of Sitagliptin phosphate

Solution (form)	Final pH	Solubility of sitagliptin phosphate (mg/mL)
Water, 25 °C (monohydrate)	4.5	69.5
0.01 M HCl (monohydrate)	3.2	68.1
0.10 M sodium citrate (monohydrate)	4.1	66.1
0.10 M sodium carbonate (free base)	7.1	42.2

Metformin Hydrochloride

Metformin hydrochloride is a stable, white crystalline powder. It is freely soluble in water and across physiological pHs. There are no known polymorphs, hydrates or solvates formed at room temperature.

Drug Product

Janumet ER tablets are film coated tablets containing an immediate release dose of sitagliptin phosphate and an extended release dose of metformin hydrochloride (core) for once daily use (Figure 1). Three fixed dose combinations (FDC) have been developed for registration: 50/500, 50/1000, and 100/1000 (mg sitagliptin as free base/mg metformin hydrochloride). The Sitagliptin Phosphate (+) Metformin Hydrochloride Extended Release Tablets formulation can be separated into three main components as follows:

1. A (b) (4) release table (b) (4) core that provides an extended release profile of metformin hydrochloride.
2. A sitagliptin active coating over the (b) (4) core designed to provide immediate release of sitagliptin.
3. A polymeric film coating over the active coating to (b) (4)

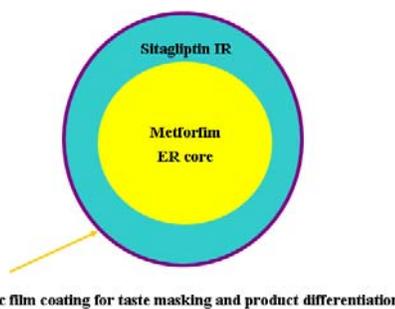


Figure 1. Schematic representation of Janumet ET tablets.

The qualitative and quantitative compositions of Janumet extended-release tablets are shown in Table 2.

Table 2. Final Market Image (FMI) MK-0431A XR Tablet Formulations

Components	Compendial Testing [§]	Function	Unit Strength sitagliptin/metformin		
			50 mg/ 500 mg	50 mg/ 1000 mg	100 mg/ 1000 mg (b) (4)
Core Tablet					
Metformin Hydrochloride Povidone (b) (4)	USP-NF, Ph.Eur USP-NF, Ph.Eur USP-NF, Ph.Eur				
Hypromellose (b) (4)	USP-NF, Ph.Eur				
Microcrystalline Cellulose	USP-NF, Ph.Eur				
Silicon Dioxide, Colloidal	USP-NF, Ph.Eur				
Sodium Stearyl Fumarate	USP-NF, Ph.Eur				
Core Tablet Weight (b) (4)					
Sitagliptin Phosphate ¹	-----				
Propyl Gallate (b) (4)	USP-NF, Ph.Eur				
Hypromellose (b) (4)	USP-NF, Ph.Eur				
Polyethylene Glycol (b) (4)	USP-NF, Ph.Eur				
Kaolin (b) (4)	USP-NF, Ph.Eur USP-NF, Ph.Eur				
Opadry Film Coating					
Suspension (b) (4)	USP-NF, Ph.Eur ----- ----- -----				
Carnauba Wax	USP-NF, Ph.Eur				
Total Tablet Weight					(b) (4)

Dissolution Method

The dissolution method proposed by the sponsor for Janumet ER tablets is based on the in vitro performance of clinical batches, and stability batches are as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium
Merformin/ sitagliptin	ER Tablets	USP Paddle	75	50mM Phosphate Buffer, pH 6.8

It is noted that the above dissolution method is the same to that approved for metformin tablets¹

Dissolution method development



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Final Dissolution Specifications Recommendation

On May 11, 2011 the sponsor submitted the following dissolution specification proposal for the sitagliptin component of Janumet XR tablets, 100/1000 mg strength: Q ^{(b) (4)} in 30 min.

According to the sponsor, this dissolution specification recommendation of $Q = (b) (4)$ at 30 min for the sitagliptin component is based on the results of the dissolution failure rates for sitagliptin at 30 min determined based on simulations/statistical analysis (Table 5).

Table 5. Summary of statistical analysis and Failure Rate

Active	DissHr	Strength	FSS Stability Data				FSS/FSD/Validation Release Data	FSS/FSD/Validation Release Data and FSS Stability Data
			Intercept (%)	Slope (%/week)	Slope P-value	Change based on FSS Data (%)	Estimated Overall Mean (%)	Predicted Mean Value at 104 weeks (%) (Overall Mean + Change)
Sitagliptin	30min	100/1000 (mg/mg)	86.3	0.001	0.962	0.1	84.1	84.2

Data	Strength	Qs	Individual Failure Rates (%)		
		Sitagliptin 30 min	Sitagliptin 30 min		
		Lower	First Stage	Second Stage	Third Stage
FSS/FSD/Validation Release Data and FSS Stability Data	100/1000 (mg/mg)	(b) (4)	53.4	0.1	0.0
		(b) (4)	93.2	7.5	6.0

The simulation procedure taken by the sponsor can be summarized as follows:

A. Analysis of the Full Scale Development (FSD)/Validation and Formal Stability Study (FSS) Data



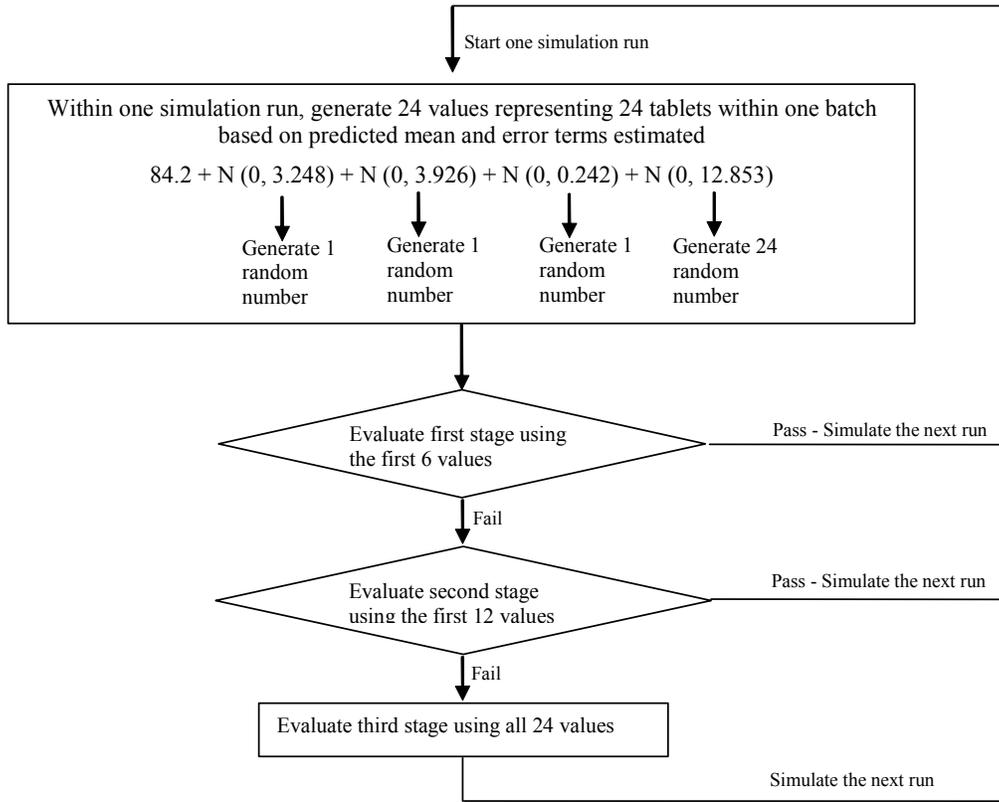
- Estimate the predicted mean at 104 weeks taking into account both FSD/Validation data and FSS data:

$$\text{Predicted mean} = \text{overall mean (Release Data)} + \text{change (Stability Data)}$$

This estimation is under the assumption that FSD/Validation batches will have the same stability profile as the FSS batches.

B. Simulation Steps

The simulation steps are summarized in the diagram below.



The first three normal distributions [N(0, 3.248), N(0,3.926), and N(0,0.242)] added to predicted mean of 84.2 simulate the appropriate variation associated with prediction of the mean, batch to batch variation and the time point to time point variation. The final 24 results generated then include the assay and tablet to tablet variation [N(0,12.853)] which is included for each of the individual tablet dissolution results. This step was repeated 10,000 times representing 10,000 batches and the rate of first, second and third stage failures were calculated as shown below:

First stage failure rate (%) = $100 \times \text{number of failures in the first stage} / 10,000$;

Second stage failure rate (%) = $100 \times \text{number of failures in the second stage} / 10,000$;

Third stage failure rate (%) = $100 \times \text{number of failures in the third stage} / 10,000$.

Figure 7 shows a histogram 10,000 average results of the 24 simulated values within each simulation run. Blue dotted lines represent the predicted results at 104 weeks for the 5 FSD/Validation batches and the 3 FSS batches.

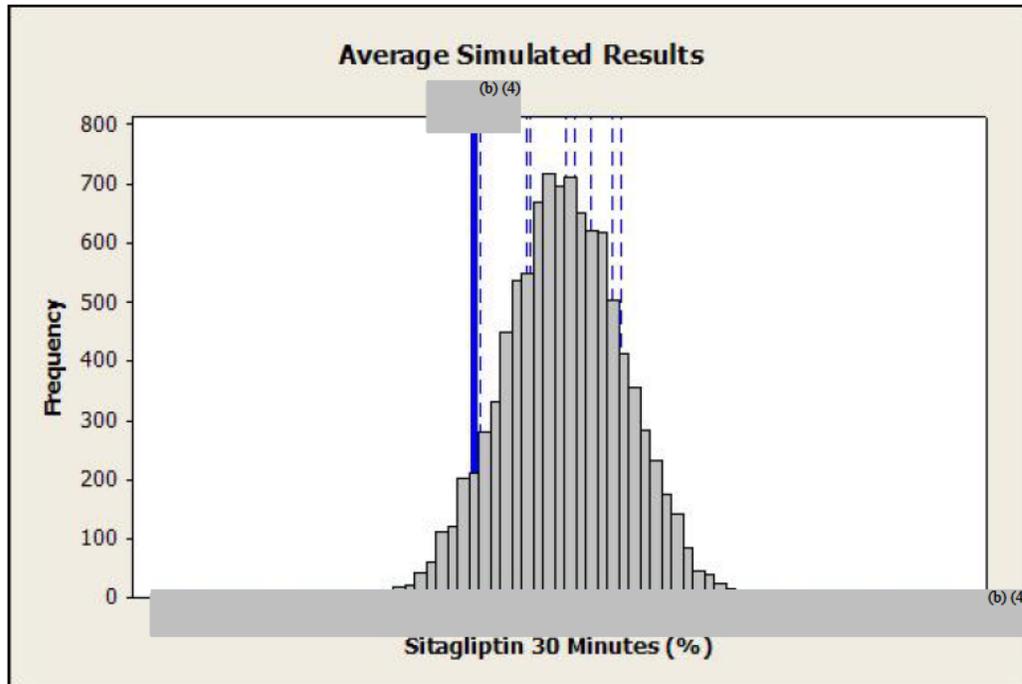


Figure 7. Histogram of average simulated results

According to the sponsor, the probability of having results below $Q_{(b) (4)}\%$ is 6.8% and the simulation predicts 6.0% batches fail the third stage. The sponsor concludes that a dissolution specification of $Q_{(b) (4)}$ in 30 minutes for the 100 mg/1000 mg potency takes into account the variability observed for this product based on eight batches manufactured to date, thereby eliminating stage III failures for batches that fall within the expected distribution.

Reviewer's Comments

Actual dissolution results for 100 mg/1000 mg batches meet a $Q_{(b) (4)}$ in 30 minutes originally recommended by this reviewer; however, this recommendation did not take into account the distribution of values associated with batch to batch, time point to time point, process and analytical method variability presented by the sponsor on May 11, 2011. Therefore, based on these simulations/statistical data, this reviewer agrees with the sponsor's proposed specifications for the sitagliptin component of Jamumet XR Tablets, 100/1000mg.

It is noted that the lower strengths (50/500 mg and the 50/1000 mg) have a mean dissolution at 30 min which is higher than that for the highest strength suggesting that a

specification of $Q = \text{(b) (4)}$ at 30 min may be appropriate for them. However, given that the 50/500 mg and the 100/1000 mg strengths were bioequivalent and in order to have consistent specifications across strengths, the following dissolution specification is recommended for the sitagliptin component of ALL the Janumet XR strengths:

Acceptance criteria
Sitagliptin: $Q = \text{(b) (4)}$ in 30 minutes

Information Supporting the Waiver's Request for the Intermediate Strength (50/1000 mg)

Merck submitted a meeting package for the pre-NDA meeting for IND 101,964 (sitagliptin-metformin XR FDC), scheduled for May 10, 2010. The meeting package contained the following biopharmaceutics question:

The sponsor considers the biowaiver requirements for the 50 mg/1000 mg tablet strength of MK-0431A XR to be met. Does the Agency concur?

The Agency's response to this question (Yes, we concur) was conveyed to the sponsor.

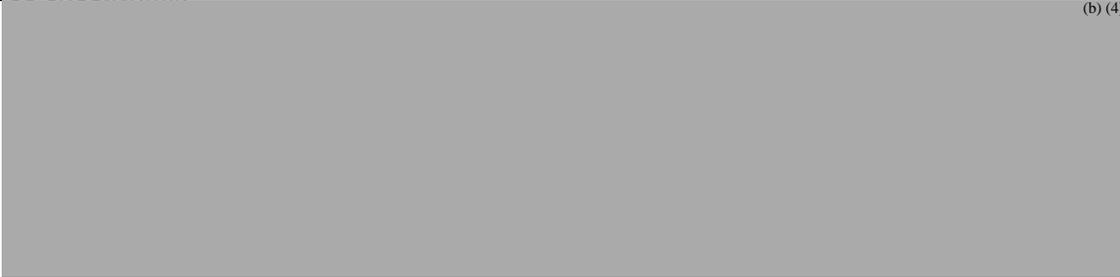
In the present submission, the sponsor provided information supporting the biowaiver for the Sitagliptin Phosphate (+) Metformin Hydrochloride Tablets, 50 mg/1000 mg strength. The justification for the biowaiver is based on the results of the pivotal BE Study (Protocol 147) on the 50 mg/500 mg and 100 mg/1000 mg tablets, and on *in vitro* dissolution profiles in four different media (water and USP buffer at pH 1.2, 4.5, and 6.8) conducted on all tablet potencies (b) (4) .

The pivotal bioequivalence study (Protocol 147) was conducted to demonstrate BE between the Sitagliptin Phosphate (+) Metformin Hydrochloride Tablets, 50 mg/500 mg and 100 mg/1000 mg and co-administration of corresponding doses of Januvia and Glumetza (metformin extended release tablets) as monoproductions, and between two (2) Sitagliptin Phosphate (+) Metformin Hydrochloride Tablets, 50 mg/500 mg and a single Sitagliptin Phosphate (+) Metformin Hydrochloride Tablets, 100 mg/1000 mg.

Study 147 was an open-label, randomized, 5-period crossover study consisting of the following arms:

- **Treatment A:** Co-administration of sitagliptin 50 mg and Glumetza 500 mg as individual tablets
- **Treatment B:** Administration of a single MK-0431A XR 50 mg/500 mg tablet
- **Treatment C:** Co-administration of sitagliptin 100 mg and Glumetza 1000 mg as individual tablets
- **Treatment D:** Administration of a single MK-0431A XR 100 mg/1000 mg tablet
- **Treatment E:** Administration of 2 MK-0431A XR 50 mg/500 mg tablets

The MK-0431A XR tablets used in the BE study 147 were manufactured at the commercial site, using commercial equipment, and are identical to the FMI tablets, with three exceptions.



According to the sponsor, treatments D and E were bioequivalent (see Clinical Pharmacology review for details on this study). An analysis of the information provided indicates that for all tablet strengths in all media, the metformin dissolution profiles are similar as determined by an *F2* similarity factor of >50 (Table 6).

Table 6. *F2* values for metformin in 4 different media

Media	Metformin <i>F2</i> testing (ref 100/1000)
pH 6.8 USP Phosphate Buffer	79
pH 4.5 USP Acetate Buffer	82
pH 1.2 USP Hydrochloric Acid Buffer	76
Water	79

For sitagliptin, the dissolution profiles of the 50 mg/500 mg and 50 mg/1000 mg potencies are considered similar based on an *F2* value of >50, however, comparison between the 100 mg/1000 mg potency and the lower strengths failed *F2* testing (Figure 8).



Figure 8. Sitagliptin Dissolution Results for Janumet ER Tablets in pH 6.8 USP Buffer.

Reviewer's Comments

Dissolution profile comparisons between the higher strength of Janumet ER tablets and both lower strengths failed F_2 testing ($F_2 < 50$) for the sitagliptin component. However, the middle strength is considered comparable (bioequivalent) to the higher strength based on:

- BE findings between low and high strength: the 50/500 mg and 100/1000 mg strengths were bioequivalent (refer to Clinical Pharmacology review).
- The dissolution profile for the middle strength is in between the dissolution profiles for the low and high strengths, indicating that the in vitro and in vivo performance of this middle strength is similar to the lower and higher strengths.

It is noted that the 50/1000 mg strength is not proportionally similar to the higher or lower strength. However, cross-study comparison of the systemic exposure (C_{max} and AUC) for equivalent doses of sitagliptin (50 mg) and metformin (1000 mg) indicates equivalent exposure of the 50/1000 mg compared to the other two strengths. Therefore, the waiver request of the BE requirements for the middle strength, namely Janumet ER 50/1000 mg, tablets is granted.

Data supporting the Waiver Request for Addition of Tablet Debossing

According to the sponsor, the proposed commercial process and formulation is the same as that used for manufacture of the FSS/biobatches with the following exceptions; commercial batches will utilize optimized (b) (4) coating parameters, include debossing and (b) (4) (b) (4) wax than the FSS/biobatches. The CMC team considers these manufacturing changes as Level 2 defined according to SUPAC-MR guidance.

In support of these changes, multi-media dissolution profiles (water and USP buffer pH 1.2, 4.5, 6.8) were performed comparing the biobatches (50 mg/500 mg and 100 mg/1000 mg)/biowaiver batch (50 mg/1000 mg) and final market image batches (FSD#4) which include debossing.

An analysis of the data indicates that debossing does not impact the metformin extended release dissolution profile as indicated by $F2$ values > 50 . For sitagliptin, the immediate release component of the formulation, all potencies achieve an $F2 \geq 50$ in all media except for the 50 mg/500 mg potency in pH 4.5 media. In this media, the comparison between tablets that are debossed and tablets that are not debossed results in an $F2$ that is marginally below 50 (Figure 9).



Figure 9. Average Sitagliptin Dissolution Profiles of 50 mg/500 mg and 100 mg/1000 Sitagliptin Phosphate (+) Metformin Hydrochloride Tablet biobatch Lots vs. 50 mg/500 mg FSD#4 in pH 4.5 media.

Reviewer's Comments

Debossing and wax reduction did not affect the dissolution profiles of the Janumet components since $F2$ values were > 50 (merformin component) or the dissolution profile for the formulation with debossing (sitagliptin component) was in between the dissolution profile for two formulations without debossing which were found to be bioequivalent.

In vitro Alcohol Interaction Study

The 50mg/1000 mg (sitagliptin/metformin hydrochloride) potency was selected for this evaluation. This potency is considered the worst case scenario for dose-dumping as it contains the lowest level of the rate-controlling polymer, HPMC, and contains the highest amount of drug substance in question of being released prematurely, metformin. The dissolution test parameters used are as follows:

The dissolution test parameters are given below.

Apparatus: USP II (paddle)

Rotation Speed: 75 RPM

Dissolution Medium: 0.1N HCl containing: 0% ethanol, 5% ethanol, and 40% ethanol

Dissolution Volume (Du): 900 mL

Medium Temperature: $37 \pm 0.5^\circ\text{C}$

Sampling Volume: Autosampler: 1.5 mL

Sample Filter: Acrodisc 0.45 μm Nylon Filter

Sampling Time: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2hrs

Sinker: Extra Large Helical Sinker (QLA, 4-spiral, XL)

Replicates: n=12

Figure 10 indicates that the amount of Sitagliptin Phosphate (+) Metformin Hydrochloride Extended Release Tablets, 50 mg/1000 mg, the % metformin dissolved in alcohol at 2 hours is less than the % dissolved in alcohol-free media, indicating that the formulation of Janumet ER tablets is not susceptible to dose-dumping in the presence of alcohol.

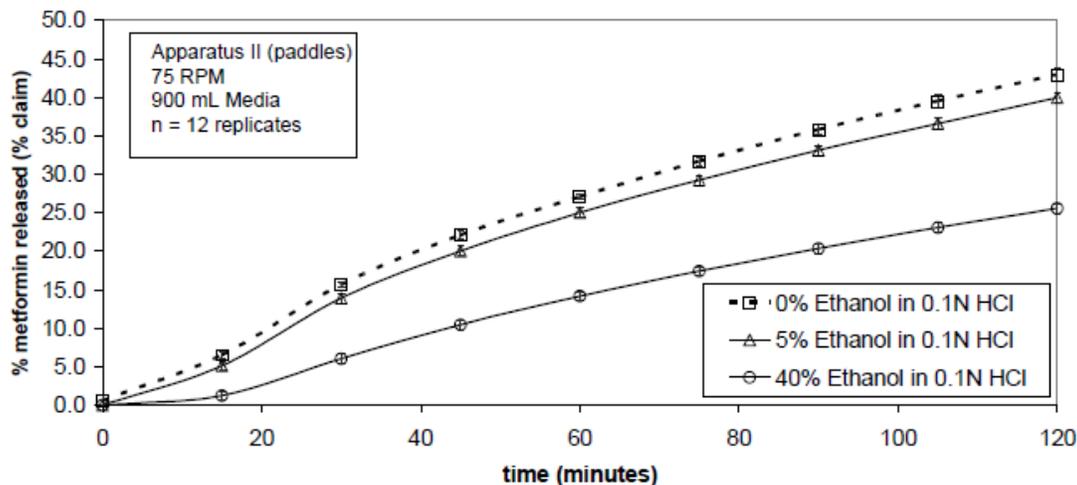


Figure 10. Dissolution Profiles of Sitagliptin Phosphate (+) Metformin Hydrochloride Extended Release Tablets, 50 mg/1000 mg, in Dissolution Media Containing 0%, 5% and 40% Ethanol

The role of dissolution on the construction of the design space for Metformin Cores

(b) (4)



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The following responses to the IR letter were received on April 11, 2011:

According to the sponsor, the impact of analytical methodology changes on the dissolution profile of sitagliptin was fully characterized using a design of experiments (DOE) studying six critical variables. In addition the dissolution method was screened against four separate media pH and the proposed method was evaluated against two dissolution baths by two different manufacturers. Since sitagliptin (b) (4)

impact was found on the metformin dissolution. No (b) (4)

(b) (4)

Reviewer's Comments

The metformin dissolution profile is not affected by changes in dissolution conditions or manufacturing changes, therefore, it should not be used as a guide to set the design space specifications.

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/s/

SANDRA SUAREZ
05/19/2011

PATRICK J MARROUM
05/19/2011

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	202270	Brand Name	Janumet® XR
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Sitagliptin/metformin XR (MK-0431A XR)
Medical Division	DMEP	Drug Class	DPP4-Inhibitor/biguanide
OCP Reviewer	Jee Eun Lee, Ph.D.	Indication(s)	Glycemic control in T2DM
OCP Pharmacometrics Reviewer		Dosage Form	FDA of sitagliptin and extended release formulation of metformin
OCP Team Leader	Sally Choe, Ph.D.	Dosing Regimen	once daily
Date of Submission	9/23/2010	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	MERCK SHARP DOHME
PDUFA Due Date	7/23/2011	Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Carton and Container Labels
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		
multiple dose:	X	1		
Patients-				
single dose:	X	1		DDI of metformin IR and MK-0431 A
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:	X	2		PD of sitagliptin and metformin IR in healthy subjects and T2DM patients
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		Pivotal BE
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		Food effect and comparison between Janumet® and MK-0431 XR
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		8		
Filability				
	"X" if yes	Comments		
Application filable?	X	Comments to the Sponsor:		
Submission in Brief: See the details below.	Reviewer's Comments (to the project manager): The consult for DSI inspection was sent for the study P147 clinical site and its bioanalytical lab.			

Relevant IND: IND 101964

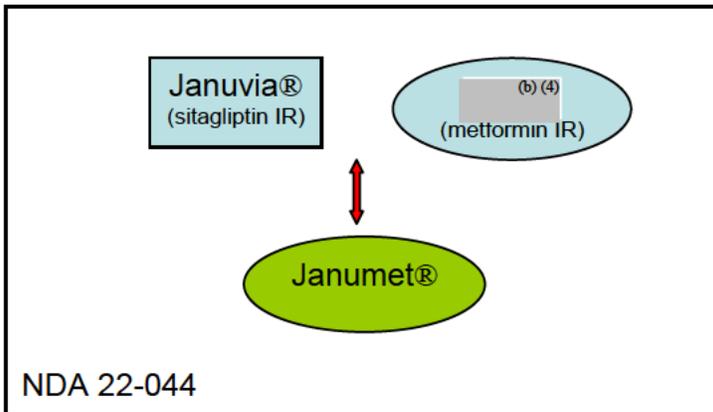
Relevant NDAs: NDA 22-044 (JANUMET®), NDA 21-748 (GLUMETZA®), NDA 21-995 (JANUVIA®)

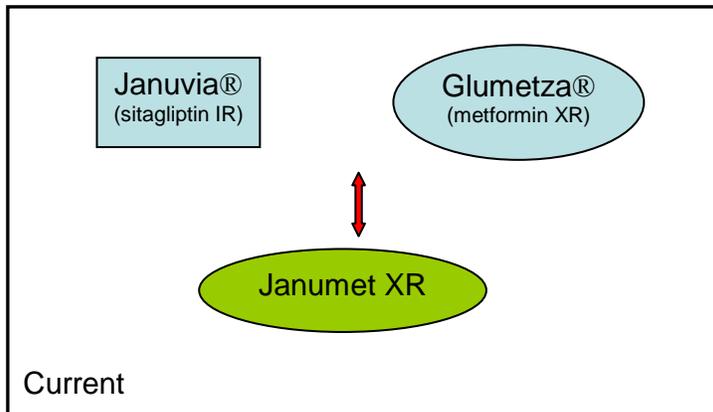
Background for the Submission:

The sponsor submitted the NDA 202270 for JANUMET® XR (MK-0431A XR) as a fixed-dose combination (FDC) product, which contains sitagliptin and metformin XR. The sponsor seeks for registration of this product based on 505(b)(2) application by demonstration of bioequivalence between JANUMET® XR (MK-0431A XR) and co-administration of sitagliptin and an approved metformin XR formulation (GLUMETZA®, NDA 21-748). The safety and efficacy data from studies with sitagliptin (JANUVIA®, NDA 21-995), metformin XR (JANUMET®, NDA 22-044), and the combination of sitagliptin and metformin IR (from the JANUVIA® and JANUMET® programs) are utilized to bridge to those of MK-0431 A XR.

JANUMET® (MK-0431 A) was approved as a FDC tablet that contains sitagliptin and metformin IR for glycemic control in T2DM. It is administered twice a day because of IR formulation of metformin was used for the FDC. The sponsor developed JANUMET® XR formulation, which replaces metformin IR with metformin XR enabling once a day dosing regimen.

Janumet® was approved based on bridging with a Canadian metformin IR, (b)(4) (b)(4) was bridged with. Glucophage IR in ANDA 75984)





Metformin:

- Biguanide
- Marketed metformin products:
 - Glucophage®(metformin IR, BMS)
 - Glucophage XR® (metformin XR, BMS)
 - Glumetza™ (metformin XR, Depomed)
 - Fortamet® (metformin ER, Andrx labs)
 - Riomet® (solution, Ranbaxy)
- Approved FDC w/ Metformin
 - ActoPlus Met (pioglitazone/metformin, Takeda)
 - ActoPlus Met XR (pioglitazone/metformin ER, Takeda)
 - Glucovance (glyburide/metformin, BMS)
 - Metaglip (glipizide/metformin, BMS)
 - Avandamet (rosiglitazone/metformin, SB PHARMCO)
 - Janumet (sitagliptin/metformin, Merck)
 - Prandimet (repaglinide/metformin, Novo Nordisk)

Sitagliptin: A DPP-4 inhibitor. The sponsor's sitagliptin product, JANUVIA® (NDA 21-995) was approved in 2006.

Summary of the Submission:

The sponsor plans to market three strength combinations: 50 mg/500 mg (qd), 50 mg/1000 mg (qd), and 100 mg/1000 mg (qd).

The clinical pharmacology program includes a pivotal BE study that demonstrates BE between MK-0341 XR and co-administration of sitagliptin and an approved metformin XR product (GLUMETZA®). In the study, BE between two tablets of 50 mg/500 mg and one tablet of 100 mg/1000 mg was also demonstrated. A biowaiver for the 50 mg/1000 mg tablet was requested.

The submission also includes a food effect study where the *in vivo* performance of MK-0431 XR with and without high-fat breakfast was compared. This study also compares the PK of JANUMET® IR 50 mg/1000 mg and JANUMET® XR 50 mg/1000 mg under either fasted or fed condition.

A total of eight Clinical Pharmacology studies, including four biopharmaceutics studies (P112, P163, P164 and P147), two pharmacokinetic studies (P012 and P165) and two pharmacodynamic studies (P050 and P 110) were submitted to support the application.

A list of completed clinical pharmacology is provided in the table below:

Clinical Pharmacology Studies Supporting the MK-0431A XR Program

Study Type	Protocol Number
Biopharmaceutics Studies	
A Low-Dose Probe Formulation Biocomparison Study [†]	112
A High-Dose Probe Formulation Biocomparison Study [†]	163
A Food-Effect Study [†]	164
A Definitive Bioequivalence Study [†]	147
Clinical Pharmacology/Pharmacokinetic Studies	
A Sitagliptin-Metformin Drug Interaction Study [†]	012
A Multiple-Dose Safety, Tolerability and Pharmacokinetic Study [†]	165
Pharmacodynamic Studies	
A Mechanism-of-Action Study in Healthy Subjects [‡]	050
A Mechanism-of-Action Study in Treatment-Naïve Patients with T2DM [‡]	110
[†] Studies where MK-0431A XR was administered	
[‡] Studies where metformin IR was administered	

A brief list of Phase 2/3 clinical trials is provided in the table below.

Safety Exposure of Sitagliptin in co-administration With Metformin IR in Patients With T2DM (Completed Studies)

Study	Title	# Patients Randomized	# Arms	# Pts Exposed to Combination	Duration (weeks)	Approx. 12 weeks	Approx. 26 weeks	Approx. 52 weeks	Approx. 104 weeks
PN015	MK-0431 Crossover Study	28	2	28	4	0	0	0	0
PN020	MK-0431 Metformin Add-on Study	701	2	464	24/80	439	396	335	127
PN024	MK-0431 Active-Controlled Combination Study	1172	2	588	52/52	540	483	387	156
PN035	MK-0431 Add-on to Glimepiride	229	2	116	24/30	114	91	52	0
PN036	MK-0431 and Metformin Coadministration Factorial Study	372 + Open Label Cohort = 117	6 + OLC	372 117	24/30 OLC= 24 weeks	349 99	315 6	289 0	151 0
PN052	MK-0431 Metformin/PPAR γ Agonist Combination Therapy Add-on Study	262	2	170	18/36	166	151	110	0
PN053	Placebo-Controlled Combination Study	190	2	96	30	92	77	0	0
Total =						1799	1519	1173	434

Pivotal BE Study Results (Protocol # 147):

The PK for sitagliptin and metformin after administration of MK-0431A XR and JANUMET® were compared and showed that after administration of MK-0431A XR, the total exposure (AUC) for metformin was similar, but the rate of absorption was slower (C_{max} is decreased and T_{max} occurred later) compared with after administration of JANUMET®. These results were expected for the extended release formulation. GLUMETZA® (metformin XR) was selected as the comparator for the pivotal BE study.

The pivotal BE study compared MK-0431A XR to co-administration of sitagliptin IR and GLUMETZA®, as the Agency recommended in the meeting on October 31, 2008. This study, conducted with final market composition (FMC) of MK-0431A XR tablets, demonstrated BE between the FMC MK-0431A XR tablets at tablet strengths of both 50 mg/500 mg and 100 mg/1000 mg, and between the FMC MK-0431A XR tablets and co-administration of corresponding doses of sitagliptin and GLUMETZA®. The treatment arms were:

- TRT A: sitagliptin 50 mg + GLUMETZA® 500 mg
- TRT B: single FMC MK-0431A XR 50 mg/500 mg tablet
- TRT C: sitagliptin 100 mg + GLUMETZA® 1000 mg
- TRT D: single FMC MK-0431A XR 100 mg/1000 mg tablet
- TRT E: two tablets of FMC MK-0431A XR 50 mg/500 mg

The resulting data allow bridging of the existing safety and efficacy data from studies with JANUVIA® (sitagliptin), GLUMETZA® (metformin XR) and the combination of sitagliptin and metformin IR (from the JANUVIA® and JANUMET® programs) to MK-0431A XR.

The key results of the pivotal pharmacokinetic BE study were:

The 90% CIs of the geometric mean ratios for the pharmacokinetic parameters (AUC_{0-∞} and C_{max}) for sitagliptin and metformin after administration of single tablet of FMC MK-0431A XR 50 mg/500 mg tablet and those after administration of sitagliptin 50 mg + GLUMETZA® 500 mg fell within the range of [0.80, 1.25]. Likewise, The 90% CIs of the geometric mean ratios for the pharmacokinetic parameters (AUC_{0-∞} and C_{max}) for sitagliptin and metformin after administration of single tablet of FMC MK-0431A XR 100 mg/1000 mg tablet and those after administration of two tablets of FMC MK-0431A XR 50 mg/500 mg fell within the range of [0.80, 1.25].

Analysis for sitagliptin PK

Geometric Mean Ratio (90% CI)			
	FMC MK-0431A XR Tablets vs. Co-administration of Sitagliptin and Metformin XR (Glumetza)		2 x MK-0431A XR 50 mg/500 mg Tablets vs. 1 x MK-0431A XR 100 mg/1000 mg Tablet
Parameter	MK-0431A XR 50 mg/500 mg Tablet	MK-0431A XR 100 mg/1000 mg Tablet	
AUC _{0-∞}	1.00 (0.99, 1.02)	1.01 (0.99, 1.03)	1.00 (0.98, 1.02)
AUC _{0-last}	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)
C _{max}	0.96 (0.92, 1.01)	1.00 (0.96, 1.05)	0.96 (0.92, 1.00)

† Back-transformed least-squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values
 ‡ Median (min, max) reported for T_{max}
 § Harmonic mean, jack-knife standard deviation reported for apparent terminal t_{1/2}

Analysis for metformin PK

Geometric Mean Ratio (90% CI)			
	FMC MK-0431A XR Tablets vs. Co-administration of Sitagliptin and Metformin XR (Glumetza)		2 x MK-0431A XR 50 mg/500 mg Tablets vs. 1 x MK-0431A XR 100 mg/1000 mg Tablet
Parameter	MK-0431A XR 50 mg/500 mg Tablet	MK-0431A XR 100 mg/1000 mg Tablet	
AUC _{0-∞}	1.06 (1.01, 1.12)	0.96 (0.91, 1.01)	1.02 (0.97, 1.08)
AUC _{0-last}	1.05 (1.00, 1.09)	0.97 (0.93, 1.01)	1.01 (0.97, 1.06)
C _{max}	1.08 (1.03, 1.14)	1.14 (1.09, 1.19)	1.01 (0.97, 1.06)

† Back-transformed least-squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values
 ‡ Median (min, max) reported for T_{max}
 § Harmonic mean, jack-knife standard deviation reported for apparent terminal t_{1/2}

Food Effect Study:

The food effect on *in vivo* performance was evaluated for both Janumet® and Janumet® XR. The pharmacokinetics of sitagliptin and metformin with and without high-fat diet was compared and the PK between Janumet® and Janumet® XR was compared. The treatment arms were:

- TRT A: 2 tablets FMC MK-0431A XR 50/1000 mg fasted
- TRT B: 2 tablets FMC MK-0431A XR 50/1000 mg after high-fat breakfast
- TRT C: 2 tables JANUMET® 50 mg/1000 mg fasted
- TRT D: 2 tables JANUMET® 50 mg/1000 mg after high-fat breakfast

The results indicated that there was a significant food effect on metformin PK following MK-0431A XR. After administration of two FMC MK-0431A XR 50 mg/1000 mg tablets after consumption of a high-fat breakfast, the AUC_{0-∞} for metformin increased by 62% compared with the fasted state. The AUC_{0-∞} and C_{max} for sitagliptin and the C_{max} for metformin decreased by approximately 6%, 17%, and 9%, respectively, compared with the fasted state. The observed effect of food on the pharmacokinetics of metformin was generally consistent with the effect of food for marketed metformin XR formulations (e.g., GLUCOPHAGE XR: fed state metformin AUC increased by 50% with food, no food effect on C_{max}) . After administration of two tablets of Janumet 50

mg/1000 mg after consumption of a high-fat breakfast, the AUC_{0-∞} and C_{max} for sitagliptin increased by approximately 6%, and 12%, respectively, compared with fasted state. The AUC_{0-∞} and C_{max} for metformin decreased by approximately 6%, and 28%, respectively, compared with fasted state. The observed effect of food on the pharmacokinetics of metformin was somewhat less than the effect of food for marketed metformin IR formulations (e.g., GLUCOPHAGE, AUC decreased by 25%, C_{max} decreased by 40% with food)

Dose-Dumping Potential Examination

Sponsor conducted *in vitro* studies to evaluate the dose-dumping potential of MK-0431A XR with alcohol, in response to discussions with the Agency on April 30, 2010. The agency raised a concern that the extended release formulation may generate premature release of the drug. The sponsor concludes that dose-dumping of MK-0431A XR with alcohol does not occur.

Sponsor's overall conclusions from the clinical pharmacology program:

- Demonstration of bioequivalence between MK-0431A XR and co-administration of corresponding doses of sitagliptin and GLUMETZA® allows bridging of the existing safety and efficacy data from studies with sitagliptin (JANUVIA®), metformin XR (GLUMETZA®) and the combination of sitagliptin and metformin IR (from the JANUVIA® and JANUMET® programs) to MK-0431A XR.
- Demonstration of bioequivalence between a single FMC MK-0431A XR 100-mg/1000-mg tablet and two FMC MK-0431A XR 50-mg/500-mg tablets ensures that equivalent exposures are achieved if patients switch from taking two MK-0431A XR 50 mg/500 mg tablets to a single 100 mg/1000 mg tablet.
- The lack of a pharmacokinetic interaction between sitagliptin and metformin supports bridging of safety and efficacy data from sitagliptin and metformin to MK-0431A XR. The pharmacokinetics of sitagliptin and metformin, after administration of MK-0431A XR once daily, with the evening meal, for 7 days, are consistent with corresponding pharmacokinetic parameters after single-dose administration.

Clinical Pharmacology Review focus:

The review will evaluate the submission to answer the following preliminary key questions:

- **Are the design, conduct, and analysis of pivotal BE study appropriate?**
- **Are the results obtained from the reviewer's analysis consistent from those obtained from sponsor's report?**
- **What is the impact of formulation change on systemic exposure and pharmacodynamics response of sitagliptin and metformin following**

administration of FDC products compared to the co-administration of the individual components?

- **Is food effect consistent with that for marketed metformin XR or sitagliptin?**
- **Is labeling information acceptable?**

Recommendation: The submission is fileable from a Clinical Pharmacology perspective.

Appendix 1: Summary of Clinical Pharmacology Studies

Protocol #	ANs	Descriptive	Study Population	Design/Dosing	Results
012	13	PK	T2DM patients	R, DB DD, PC, 3-period, CO study TRT A: MK-0431 A 50 mg + metformin 1000 mg bid TRT B: metformin 100 mg + placebo to MK=0431 bid TRT C: MK-0431 50 mg and placebo to metformin bid	No DDI
050	16	PD	Young healthy	R, PC, DB, DD. 4-period, CO study TRT A: sitagliptin; TRT B: metformin TRT C: sitagliptin+metformin; TRT D: placebo	Sitagliptin, but not metformin alone enhances active GIP concentrations by stabilization of active versus total GIP concentrations
110	18	PD	T2DM patients	R, PC, DB, DD. 4-period, CO study TRT A: sitagliptin; TRT B: metformin TRT C: sitagliptin+metformin; TRT D: placebo	As compared with placebo, sitagliptin administered alone or coadministered with metformin inhibits in vivo DPP-4 activity, where metformin does not inhibit in vivo DPP-4 activity
112	20	PK formulation	Young healthy	OL, R, 5-TRT, 5-period CO study TRT A: MK-0431A XR 90 mg/1000 mg SRT TRT B: MK-0431A XR 100 mg/1000 mg MRT TRT C: sitagliptin 100 mg + GLUCOPHAGE® XR 1000 mg TRT D: sitagliptin 100 mg + GLUMETZA® XR 1000 mg TRT E: sitagliptin 100 mg + FORTAMET XR® XR 1000 mg	Similar PK among all TRTs
147	39	BE	Young healthy	OL, R, 5-TRT, 5-period CO study TRT A: sitagliptin 50 mg + GLUMETZA® 500 mg TRT B: single FMC MK-0431A XR 50 mg/500 mg tablet TRT C: sitagliptin 100 mg + GLUMETZA® 1000 mg TRT D: single FMC MK-0431A XR 100 mg/1000 mg tablet TRT E: two tablets of FMC MK-0431A XR 50 mg/500 mg	BE established between TRT A and TRT B, TRT C and TRT D, TRT D and TRT E
163	11	PK formulation	Young healthy	OL, R, 3-period CO study TRT A: single MK-0431A XR 50 mg/500 mg tablet TRT B: sitagliptin 50 mg + GLUMETZA® 500 mg TRT C: single JANUMET® 50 mg/500 mg tablet	PK between TRT A and TRT B are similar AUC and Cmax for metformin after TRT A were 30% lower and the median Tmax occurs 4 hours later compared with corresponding values after TRT C*
164	12	Food effect	Young healthy	OL, R, 4-period CO study TRT A: 2 tablets FMC MK-0431A XR 50/1000 mg fasted TRT B: 2 tablets FMC MK-0431A XR 50/1000 mg after high-fat breakfast TRT C: 2 tables JANUMET® 50 mg/1000 mg fasted	TRT B metformin AUC ↑ 60%, Cmax ↓ 9%, sitagliptin AUC ↓ 6%, Cmax ↓ 17% compared to TRT A TRT D metformin AUC ↓ 6%, Cmax ↓ 28%, sitagliptin AUC ↑ 6%, Cmax ↑ 12% compared to

				TRT D: 2 tables JANUMET® 50 mg/1000 mg after high-fat breakfast	TRT C
165	12	Multi dose PK	Young healthy	Two MK-0431A XR 50 mg/1000 mg tablets (or a total daily dose of 100 mg of sitagliptin and 1000 mg of metformin) once daily with the evening meal for 7 days TRT was administered following a 4-day run-in period during which metformin XR 1000 mg (GLYCOPHAGE XR) was administered once daily	SS for sitagliptin and metformin is reached by day 4 and 5, respectively.

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/s/

JEE E LEE
12/02/2010

SALLY Y CHOE
12/03/2010

BIOPHARMACEUTICS REVIEW			
Office of New Drugs Quality Assessment			
Application No.:	NDA 202-270 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DMEP		
Sponsor:	Merck	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	Janumet XR Tablets	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Metformin/sitagliptin ER FDC Tablets	Date Assigned:	Oct 15, 2010
Indication:	Type II diabetes	Date of Review:	Nov 1, 2010
Formulation/strengths	Extended Release tablets, 50/500 mg 50/1000mg; 100/1000 mg		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Sep 24, 2010	Sep 24, 2010	Oct 5, 2010	Jul 23, 2010
Type of Submission:	Original NDA		
Type of Consult:	FILING REVIEW Dissolution method and specifications/ biowaiver request for lower strength/ biowaiver request for change in manufacturing process.		
REVIEW SUMMARY:			
<p>Januvia® (sitagliptin phosphate) 25 mg, 50 mg and 100 mg, immediate release tablets were approved by the Agency for the treatment of type 2 diabetes Mellitus (T2DM) on Oct 16, 2006. Glumetza (metformin hydrochloride) extended release tablets, 500 mg and 1000 mg were approved for the treatment of T2DM in June 5, 2005. Janumet® (sitagliptin phosphate and metformin hydrochloride) 50/500 mg and 50/1000 mg, IR tablets were approved on March 30, 2007 for the twice daily treatment of T2DM.</p> <p>The sponsor, Merck has developed a new formulation for Janumet consisting of an extended release, film-coated tablets for the once daily treatment of T2DM. Three fixed dose combinations (FDC) have been developed for registration: 50/500, 50/1000, and 100/1000 (mg sitagliptin as free base/mg metformin hydrochloride). The proposed dosing regimen is sitagliptin/metformin XR 50 mg/500 mg and 50 mg/1000 mg to be given as 2 tablets once daily and sitagliptin/metformin XR 100 mg/1000 mg to be given as 1 tablet once daily. The clinical development program for this new drug formulation for the proposed indication is based on demonstration of BE between Janumet ER product and co-administration of sitagliptin and an approved metformin XR formulation (GLUMETZA®) in order to bridge the existing safety and efficacy data from studies with sitagliptin, metformin XR, and the combination of sitagliptin and metformin IR (from the Januvia and Janumet programs) to Janumet ER tablets. Several additional Clinical Pharmacology studies were also conducted to support the registration of Janumet ER tablets.</p> <p>According to the sponsor, BE was demonstrated between the FMC XR tablets, at tablet strengths of both 50 mg/500 mg and 100 mg/1000 mg, and co-administration of corresponding doses of sitagliptin and GLUMETZA® as monoproducts. The sponsor is requesting a biowaiver of the in vivo BE requirements for the 50/1000 mg strength base on dissolution profile comparisons of all strengths in different media.</p> <p>According to the sponsor, the proposed commercial process and formulation is the same as that used for manufacture of the FSS/biobatches with the following exceptions; commercial batches will utilize</p>			

optimized (b) (4) coating parameters, include debossing (b) (4) (b) (4) wax than the FSS/biobatches. The sponsor is requesting approval of these changes based on dissolution profiles comparisons in three different media in lieu of in vivo BE studies (biowaiver).

The biopharmaceutics review will focus on the two biowaiver requests, in vitro alcohol interaction study, and on the dissolution method and specifications. The level of change the addition of debossing as defined by SUPAC MR guidance was discussed with Dr. Tran. She considers these changes as Level 2 and therefore, the information submitted to support the waiver request is acceptable.

The following dissolution method and specifications are being proposed for both active ingredients and for the three strengths of the product under review:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Merformin/sitagliptin	ER Tablets	USP Paddle	75	(50mM Phosphate Buffer, pH 6.8	Sitagliptin: Min. (b) (4) Metformin: (b) (4) in 1 hour (b) (4) in 3 hours Min (b) (4) in 10 hours

According to the sponsor, determination of appropriate dissolution acceptance criteria was based on analysis of data obtained during release and extended testing of 9 FSS batches, including 3 biobatches with extended testing, as well as statistical analysis of formal stability data through 52 weeks.

The NDA is filable from biopharmaceutics perspective. The acceptability of the waiver requests, in vitro alcohol interaction study, and dissolution method and specifications will be a review issue.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 202-270 (000) for filing purposes. We found this NDA filable from the biopharmaceutics perspective. The following comments should be conveyed to the sponsor as part of the 74-day letter:

- *Submit the complete dissolution profile data (raw data, mean values, and SD) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values) for both components of Janumet ER tablets.*
- *Submit the dissolution method report including the complete dissolution profile (individual, mean, SD, profiles) data for both components of Janumet ER tablets collected during the development of the proposed dissolution method.*

Sandra Suarez Sharp, Ph. D.
 Biopharmaceutics Reviewer
 Office of New Drugs Quality Assessment

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

c.c. RChiang, ADorantes, STran

INTRODUCTION

Januvia® (sitagliptin phosphate) 25 mg, 50 mg and 100 mg, immediate release tablets were approved by the Agency for the treatment of type 2 diabetes Mellitus (T2DM) on Oct 16, 2006. Glumetza (metformin hydrochloride) extended release tablets, 500 mg and 1000 mg were approved for the treatment of T2DM in June 5, 2005. Janumet® (sitagliptin phosphate and metformin hydrochloride) 50/500 mg and 50/1000 mg, IR tablets were approved on March 30, 2007 for the twice daily treatment of T2DM.

The sponsor, Merck has developed a new formulation for Janumet consisting of an extended release, film-coated tablets for the once daily treatment of T2DM. Three fixed dose combinations (FDC) have been developed for registration: 50/500, 50/1000, and 100/1000 (mg sitagliptin as free base/mg metformin hydrochloride). The proposed dosing regimen is sitagliptin/metformin XR 50 mg/500 mg and 50 mg/1000 mg to be given as 2 tablets once daily and sitagliptin/metformin XR 100 mg/1000 mg to be given as 1 tablet once daily. The clinical development program for this new drug formulation for the proposed indication is based on demonstration of bioequivalence between the new ER product and co-administration of sitagliptin and an approved metformin XR formulation (GLUMETZA®) in order to bridge the existing safety and efficacy data from studies with sitagliptin, metformin XR, and the combination of sitagliptin and metformin IR (from the Januvia and Janumet programs) to the new ER product. Several additional Clinical Pharmacology studies were also conducted to support the registration of MK-0431A XR.

This review will be focused on the acceptability of the biowaiver requests, in vitro alcohol interaction study, and the dissolution method and specifications. The OCP will review the bioequivalence studies.

CHEMISTRY

Drug Substances

Sitagliptin Phosphate

Sitagliptin is formulated as the monohydrate phosphate salt; this salt form was selected and extensively characterized during the JANUVIA® development program. The monohydrate phosphate salt is non-hygroscopic, chemically and physically stable, and highly soluble in aqueous media.

Metformin Hydrochloride

Metformin hydrochloride is a stable, white crystalline powder. It is freely soluble in water and across physiological pHs. There are no known polymorphs, hydrates or solvates formed at room temperature.

Drug Product

Janumet ER tablets are film coated tablets containing an immediate release dose of sitagliptin phosphate and an extended release dose of metformin hydrochloride (core) for once daily use. Three fixed dose combinations (FDC) have been developed for registration: 50/500, 50/1000, and 100/1000 (mg sitagliptin as free base/mg metformin hydrochloride). The Sitagliptin Phosphate (+) Metformin Hydrochloride Extended Release Tablets formulation can be separated into three main components as follows:

1. A (b) (4) release tablet (b) (4) core that provides an extended release profile of metformin hydrochloride.
2. A sitagliptin active coating over the (b) (4) core designed to provide immediate release of sitagliptin.
3. A polymeric film coating over the active coating to (b) (4)



The qualitative and quantitative compositions of Janumet extended-release tablets are shown in Table 1.

Table 1. Final Market Image (FMI) MK-0431A XR Tablet Formulations

Components	Compendial Testing [§]	Function	Unit Strength sitagliptin/metformin		
			50 mg/ 500 mg	50 mg/ 1000 mg	100 mg/ 1000 mg
(b) (4)					
Core Tablet					
Metformin Hydrochloride (b) (4)	USP-NF, Ph.Eur				
Povidone (b) (4)	USP-NF, Ph.Eur				
Hypromellose (b) (4)	USP-NF, Ph.Eur				
Microcrystalline Cellulose	USP-NF, Ph.Eur				
Silicon Dioxide, Colloidal	USP-NF, Ph.Eur				
Sodium Stearyl Fumarate	USP-NF, Ph.Eur				
Core Tablet Weight (b) (4)					
Sitagliptin Phosphate ¹	-----				
Propyl Gallate	USP-NF, Ph.Eur				
Hypromellose (b) (4)	USP-NF, Ph.Eur				
Polyethylene Glycol (b) (4)	USP-NF, Ph.Eur				
Kaolin (b) (4)	USP-NF, Ph.Eur				
(b) (4)					
(b) (4)	USP-NF, Ph.Eur				

Carnauba Wax	USP-NF, Ph.Eur				
Total Tablet Weight					(b) (4)
(b) (4)					

Dissolution Method

The dissolution method and specifications being proposed by the sponsor for Janumet ER tablets is based on the in vitro performance of clinical batches, and stability batches are as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Merformin/sitagliptin	ER Tablets	USP Paddle	75	(50mM Phosphate Buffer, pH 6.8	Sitagliptin: Min. (b)(4) in 45 minutes Metformin: (b)(4) in 1 hour (b)(4) in 3 hours Min. (b)(4) in 10 hours

The proposed method and specifications will be a review issue.

Dissolution method development

This information was not provided. The sponsor is requested to provide this information.

Information Supporting the Waiver's Request for the Intermediate Strength (50/100 mg)

A pivotal bioequivalence study (Protocol 147) was conducted to demonstrate BE between the Sitagliptin Phosphate (+) Metformin Hydrochloride Tablets, 50 mg/500 mg and 100 mg/1000 mg and co-administration of corresponding doses of Januvia and Glumetza (metformin extended release tablets) as monoproducts, and between two (2) Sitagliptin Phosphate (+) Metformin Hydrochloride Tablets, 50 mg/500 mg and a single Sitagliptin Phosphate (+) Metformin Hydrochloride Tablets, 100 mg/1000 mg.

However, a request for a biowaiver of the Sitagliptin Phosphate (+) Metformin Hydrochloride Tablets, 50 mg/1000 mg has been included in the present submission. The justification for the biowaiver is based on the results of the pivotal BE Study (Protocol 147) on the 50 mg/500 mg and 100 mg/1000 mg tablets, and on *in vitro* dissolution profiles in four different media (water and USP buffer at pH 1.2, 4.5, and 6.8) conducted on all tablet potencies ((b)(4)).

A preliminary analysis of this information indicates that for all tablet strengths in all media, the metformin dissolution profiles are similar as determined by an f2 similarity factor of >50. For sitagliptin, the dissolution profiles of the 50 mg/500 mg and 50 mg/1000 mg potencies are considered similar based on an f2 value of >50, however, the 100 mg/1000 mg potency exhibits slower dissolution than the other potencies in all media tested.

Reviewer's Comments

The acceptability of the waiver request will be a review issue.

Data supporting the Waiver Request for Addition of Tablet Debossing

According to the sponsor, the proposed commercial process and formulation is the same as that used for manufacture of the FSS/biobatches with the following exceptions; commercial batches will utilize optimized (b) (4) coating parameters, include debossing and (b) (4) wax than the FSS/biobatches. Multi-media dissolution profiles (water and USP buffer pH 1.2, 4.5, 6.8) were performed comparing the biobatches (50 mg/500 mg and 100 mg/1000 mg)/biowaiver batch (50 mg/1000 mg) and final market image batches (FSD#4) which include debossing.

A preliminary analysis of the data indicate that debossing does not impact the metformin extended release dissolution profile as indicated by f2 values > 50. For sitagliptin, the immediate release component of the formulation, all potencies achieve an $f_2 \geq 50$ in all media except for the 50 mg/500 mg potency in pH 4.5 media. In this media, the comparison between tablets that are debossed and tablets that were not debossed results in an f_2 that is marginally below 50.

Reviewer's Comments

The acceptability of the waiver request supporting the additional tablet debossing will be a review issue.

In vitro Alcohol Interaction Study

The 50mg/1000 mg (sitagliptin/metformin hydrochloride) potency was selected for this evaluation. This potency is considered the worst case scenario for dose-dumping as it contains the lowest level of the rate-controlling polymer, HPMC, and contains the highest amount of drug substance in question of being released prematurely, metformin. The dissolution test parameters used are as follows:

The dissolution test parameters are given below.

Apparatus: USP II (paddle)

Rotation Speed: 75 RPM

Dissolution Medium: 0.1N HCl containing: 0% ethanol, 5% ethanol, and 40% ethanol

Dissolution Volume (Du): 900 mL

Medium Temperature: $37 \pm 0.5^\circ\text{C}$

Sampling Volume: Autosampler: 1.5 mL

Sample Filter: Acrodisc 0.45 μm Nylon Filter

Sampling Time: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2hrs

Sinker: Extra Large Helical Sinker (QLA, 4-spiral, XL)

Replicates: n=12

Preliminary analysis of the data indicate that for Sitagliptin Phosphate (+) Metformin Hydrochloride Extended Release Tablets, 50 mg/1000 mg, the % metformin dissolved in alcohol at 2 hours is less than the % dissolved in alcohol-free media (Figure 1).

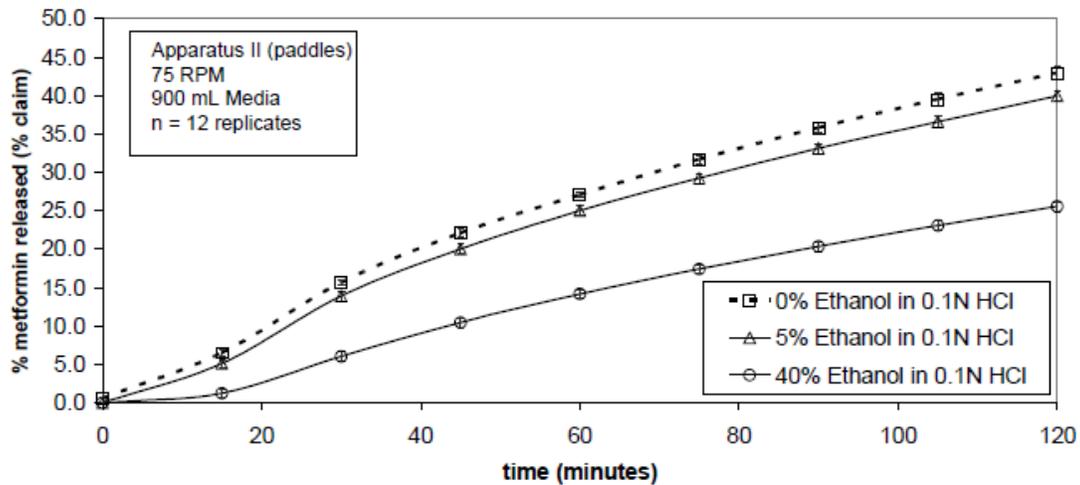


Figure 1. Dissolution Profiles of Sitagliptin Phosphate (+) Metformin Hydrochloride Extended Release Tablets, 50 mg/1000 mg, in Dissolution Media Containing 0%, 5% and 40% Ethanol

Conclusion

The NDA is filable from the biopharmaceutics perspective. The acceptability of the waiver requests, in vitro alcohol interaction study, and dissolution method and specifications will be a review issue.

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/s/

SANDRA SUAREZ
11/15/2010

PATRICK J MARROUM
11/15/2010