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APPLICATION NUMBER:

22-044

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

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

General Information About the Submission

NDA Number	22-044	Brand Name	Janumet™
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Sitagliptin phosphate/Metformin hydrochloride fixed-dose combination
Medical Division	HFD-510	Drug Class	Anti-diabetic
OCPB Reviewer	Xiaoxiong (Jim) Wei	Indication(s)	Type 2 Diabetes
OCPB Team Leader	Hae-Young Ahn	Dosage Form	tablets
		Dosing Regimen	100 mg /1500-2000mg/day
Date of Submission	05-31-2006	Route of Administration	oral
Estimated Due Date of OCPB Review	March 2, 2007	Sponsor	Merck
Division Due Date	March 2, 2007	Priority Classification	S1
PDUFA Due Date	March 30, 2007		

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			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
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 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
Thorough QT Study				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design, single / multi dose:	X	2		
replicate design, single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVVC):				
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		3		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	YES			
Comments sent to firm?	No			
Primary reviewer Signature and Date	Appears This Way On Original			
Secondary reviewer Signature and Date				

Briefing In Content:

Merck submitted this NDA for seeking approval of fixed dose combination drug products of Sitagliptin and Metformin. Sitagliptin phosphate (MK-0431) is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor developed by Merck & Co., Inc. for the treatment of type 2 diabetes mellitus, which is currently with the Agency for review under NDA21-995. Metformin hydrochloride is an approved anti-hyperglycemic agent widely used for the treatment of type 2 diabetes mellitus. The sponsor has developed an immediate release product containing a fixed dose of sitagliptin phosphate and multiple dose levels of metformin hydrochloride for the treatment of patients with type 2 diabetes who are not adequately controlled with either agent alone or patients already being treated with the combination of sitagliptin and metformin. Two dose strengths of a film-coated fixed-dose combination (FDC) tablet have been developed for the U.S. market: sitagliptin/metformin 50/500 mg/mg and 50/1000 mg/mg.

To support this combo drug product, the sponsor submitted three new PK studies, two of which are BE studies, and one of which is PD study. All three studies were conducted in healthy subjects:

1) Study P38 (BE with test formulations)

A 2-Part, Open-Label, Randomized, 3-Period Crossover Study to Evaluate the Pharmacokinetic Profiles of MK-0431 and Metformin After Oral Administration of Single Doses of MK-0431/Metformin Fixed-Dose Combination Tablet Probe Formulations or Coadministration of MK-0431 With Metformin as Individual Tablets to Healthy Adult Subjects

2) Study P48 (BE with commercial formulations)

An Open-Label, Randomized, Two-Part, Two-Period Crossover Study to Demonstrate the Definitive Bioequivalence After Administration of the Final Market Image (FMI) of the MK-0431/Metformin 50/500 mg and 50/1000 mg Fixed-Dose Combination (FDC) Tablet and Concomitant Administration of 50-mg Doses of MK-0431 and 500- or 1000-mg Doses of Metformin as Individual Tablets to Healthy Adult Subjects

3) Study P50 (PD study)

This is 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. The objectives are 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. This study is to assess the effects of sitagliptin and metformin on post-meal incretin hormone (active and total GLP-1 and GIP) 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.

The Sponsor cited many supportive studies in NDA21-995 including drug interaction studies between sitagliptin and metformin.

The sponsor has developed dissolution specification for this combo drug product: no less than — dissolved in 20 min.

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/s/

Xiao-xiong Wei
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Hae-Young Ahn
7/17/2006 02:20:33 PM
BIOPHARMACEUTICS

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CLINICAL PHARMACOLOGY REVIEW

NDA: 22-044	Submission Date(s): 5/31/06
Brand Name	Janumet
Generic Name	Sitagliptin Phosphate and Metformin Hydrochloride Fixed Dose Tablets
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader (Acting)	Jim Wei, Ph.D.
OCP Division	DCP-2
OND Division	Division of Metabolic and Endocrine Products
Sponsor	Merck
Submission Type	505 (b) (2)
Formulation; Strength(s)	50 mg/ 500 mg; 50 mg/ 1000 mg Sitagliptin/metformin Oral tablets administered BID
Indication	Treatment of Type 2 Diabetes Mellitus

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I Executive Summary

Merck has developed fixed-dose combination (FDC) tablets containing sitagliptin and metformin.

The efficacy and safety of the concomitant use of sitagliptin and metformin has previously been evaluated in controlled clinical trials (NDA 21-995). Concomitant administration of the separate commercial sitagliptin and metformin tablets in adult patients with type 2 diabetes was approved by the FDA in October 16, 2006 as a part of the original marketing approval of sitagliptin.

Sitagliptin is approved for once-daily administration at doses of 100 mg. Metformin is available in 500, 850, and 1000 mg tablets and is approved for individualized treatment up to a maximum daily dose of 2550 mg in adults. Typically metformin is administered twice per day with meals.

To aid in the approval of this application the sponsor has submitted one pivotal bioequivalence study (048) and one pharmacodynamic study (058). There were no clinical studies done with the to-be marketed combination product and the bioequivalence study was designed to bridge the proposed combination tablets to the clinical safety and efficacy database supporting the use of sitagliptin in combination with metformin existing under the approved NDA.

A Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed the information provided in the NDA 22-044 for Janumet tablets and finds it *acceptable*. Recommendations and labeling comments should be sent to the sponsor as appropriate.

Clinical Pharmacology briefing was held on 2/21/07 and the attendees were Drs. Chandra Sahajwalla, Suresh Doddapaneni, Ilan Irony, Jim Wei, Jayabharathi Vaidyanathan, Sally Choe, Leena Aljuburi and Qi Liu.

B Phase 4 Commitments

None.

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C Summary of Clinical Pharmacology Findings

The summary of the results from the PK and PD studies are provided below.

Bioequivalence: The results of the study demonstrated that the final market image (FMI) sitagliptin/metformin 50/500 and 50/1000 mg FDC tablets are bioequivalent to concomitant administration of corresponding doses of sitagliptin and metformin as individual tablets. The 90% confidence interval for the geometric mean ratios (FDC/concomitant administration) for the AUC_{inf} and C_{max} for both sitagliptin and metformin fell within the bioequivalence limits of 80-125% for both strengths studied. Demonstration of bioequivalence thus bridges the safety and efficacy data from the clinical studies using co-administration of sitagliptin and metformin to the FDC tablets.

Pharmacodynamics: The 4 hour post-meal mean active glucagon like peptide-1 (GLP-1) concentrations were increased significantly after concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone. The ratio of active to total GLP-1 concentrations increased after administration of sitagliptin alone. On the other hand, glucose dependent insulinotropic peptide (GIP) concentrations were similar following concomitant administration of sitagliptin and metformin versus sitagliptin alone.

The known mechanism of action of metformin is as follows: Decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. The results of the PD study indicates that metformin alone caused an increase in circulating levels of both active and total GLP-1 to a similar extent (about 80%). Therefore, metformin may potentially increase the efficacy of sitagliptin due to at least partially the inhibition of GLP-1 metabolism.

Drug Interaction: Co-administration of multiple twice-daily doses of sitagliptin with metformin, an organic cation transporter (OCT) substrate, did not meaningfully alter the pharmacokinetics of metformin in patients with type 2 diabetes. Therefore, sitagliptin is not an inhibitor of OCT-mediated transport. Also co-administration of multiple doses of metformin with sitagliptin did not alter the pharmacokinetics of sitagliptin in type 2 diabetic patients (From NDA 21-995).

II Question Based Review

A General Attributes

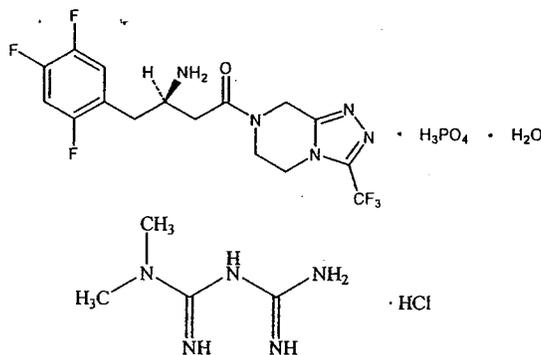
What are the highlights of the chemistry and physico-chemical properties of Janumet?

Janumet tablets contain 2 oral antihyperglycemic drugs used in type 2 diabetes: Sitagliptin phosphate and metformin hydrochloride.

Sitagliptin phosphate is described chemically as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*α*]pyrazine phosphate (1:1) monohydrate. The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32 and is a white to off-white, crystalline, non-hygroscopic powder.

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide, hydrochloride) (Figure 1) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white crystalline powder with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.62.

Figure 1: Chemical structure of Sitagliptin (top) and metformin (bottom).



What is the proposed mechanism (s) of action and therapeutic indication?

Janumet combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: Sitagliptin phosphate, a dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin hydrochloride, a member of the biguanide class.

Sitagliptin is an orally active DPP-4 inhibitor and a member of a new class of drugs intended to treat type 2 diabetes. DPP-4 inhibitors act by enhancing the levels of active incretin hormones. These hormones include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) which are released by the intestine in response to meal and are part of endogenous system involved in maintaining glucose homeostasis.

Metformin hydrochloride is a biguanide antihyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Janumet is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of sitagliptin and metformin or whose diabetes is not adequately controlled with either agent alone.

What is the proposed dose and dosage form?

Janumet is available as immediate release tablets. Based on package insert "The dosage of antihyperglycemic therapy with Janumet should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin.

Janumet should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin.

Dosing Recommendations

The starting dose of Janumet should be based on the patient's current regimen. Janumet should be given twice daily with meals. The following doses are available:

- 50 mg sitagliptin/500 mg metformin hydrochloride
- 50 mg sitagliptin/1000 mg metformin hydrochloride

For patients inadequately controlled on metformin monotherapy

For patients not adequately controlled on metformin alone, the usual starting dose of Janumet should be equal to 100 mg total daily dose (50 mg twice daily) of sitagliptin plus the dose of metformin already being taken.

For patients inadequately controlled on sitagliptin monotherapy

For patients not adequately controlled on sitagliptin alone, the usual starting dose of Janumet is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients may be titrated up to 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily. Patients taking sitagliptin monotherapy dose-adjusted for renal insufficiency should not be switched to Janumet.

For patients switching from sitagliptin co-administered with metformin

For patients switching from sitagliptin co-administered with metformin, Janumet may be initiated at the dose of sitagliptin and metformin already being taken.

No studies have been performed specifically examining the safety and efficacy of Janumet in patients previously treated with other oral antihyperglycemic agents and switched to Janumet. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur."

B General Clinical Pharmacology

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

No clinical studies with the drug product were performed in support of this submission. Consistent with the requirements for a 505 (b) (2) application, the clinical pharmacology studies were performed to demonstrate the bioequivalence of the combined drug product to the commercially available reference products.

Two doses of the sitagliptin/metformin fixed dose tablet (50 mg/500 mg and 50 mg/1000 mg) were evaluated in bioequivalence study. The doses selected for the fixed dose combination tablets were based on the sitagliptin Phase II dose-ranging studies (P010 and P014). Study P014 evaluated sitagliptin 100 mg per day administered as a twice-daily dose (50 mg bid) or a once-daily dose (100 mg qd) and results indicated that both provided similar tolerability and reduction in glycemic endpoints. A Phase II add-on to metformin study (P015) was conducted in parallel to the dose-ranging study and results indicate that dosing of 50 mg bid or 100 mg qd sitagliptin resulted in similar overall drug exposures and comparable efficacy and safety of sitagliptin when administered as 50 mg bid or 100 mg qd in combination with metformin.

4 PK studies were included in the clinical development program for the FDC tablets (2 BE studies, one PD study and one DDI study). A pilot BE study was conducted with probe formulations (P038) and data from this study was used to develop the final market image (FMI) sitagliptin/metformin FDC tablets. A pivotal BE study (P048) was conducted in order to demonstrate bioequivalence between the FMI tablets and co-administration of corresponding doses of sitagliptin and metformin as individual tablets and therefore used to bridge the clinical safety and efficacy data for co-administration of sitagliptin and metformin to the FDC tablets.

Study P050 was conducted to explore the complementary mechanisms of action of sitagliptin and metformin by determining the effect of administration of sitagliptin alone and metformin alone or in combination on active GLP-1 and GIP levels and glucose concentrations.

Study P012 was a drug interaction study between sitagliptin and metformin in type 2 diabetic patients (also submitted with original NDA 21-995 for Januvia).

What is the pharmacodynamic effect resulting from concomitant administration of sitagliptin and metformin?

In order to assess whether concomitant administration of metformin and sitagliptin resulted in enhanced post meal active GLP-1 and/or GIP concentrations compared with administration of sitagliptin alone, metformin alone or placebo, a randomized, placebo-controlled, double-blind, double-dummy, 4-period crossover study was conducted in

healthy adult subjects. The treatments shown below were administered following a overnight fast and with a minimum 7-day washout period.

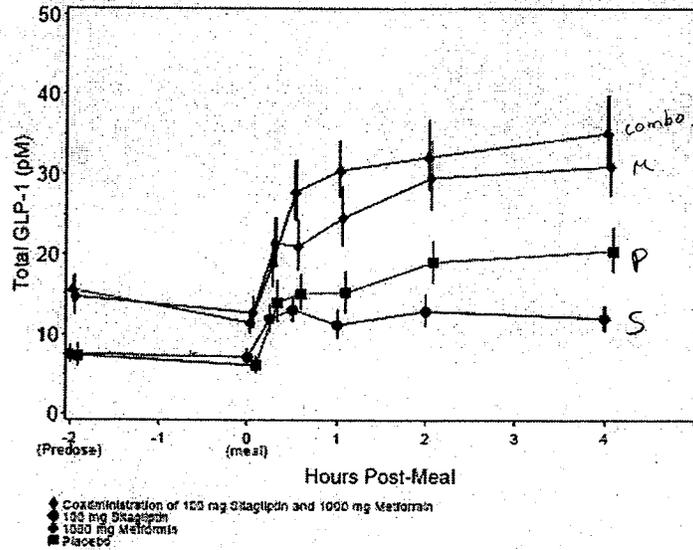
Treatment Group	Treatment	Treatment Details
A	Sitagliptin alone	Day 1: AM (100 mg sitagliptin and placebo to 500 mg metformin) PM (Placebo to 500 mg metformin) Day 2: AM (100 mg sitagliptin and placebo to 1000 mg metformin)
B	Metformin alone	Day 1: AM (Placebo to 100 mg sitagliptin and 500 mg metformin)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

In this study PK analysis was not done. On day 2 of each treatment, blood samples were collected for determination of active GLP-1 and GIP concentrations, plasma glucose concentrations. The primary endpoint was 4h post meal total GLP-1, ratio of active to total GLP-1. GIP concentrations after concomitant administration of sitagliptin and metformin with administration of sitagliptin alone, metformin alone and placebo. DPP-4 inhibitory activity was not assayed.

The total GLP-1 plasma concentrations were determined at Day 2. The geometric means pre-dose (fasting) and post-meal total GLP-1 concentrations (pM) are shown in Figure 2. The 4-h post-meal average GLP-1 concentrations were significantly increased after concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone; while it was similar to that of administration of metformin alone. The 4-h post meal average total GLP-1 concentrations were significantly decreased after administration of sitagliptin alone as compared to placebo and increased following administration after metformin (Figure 2).

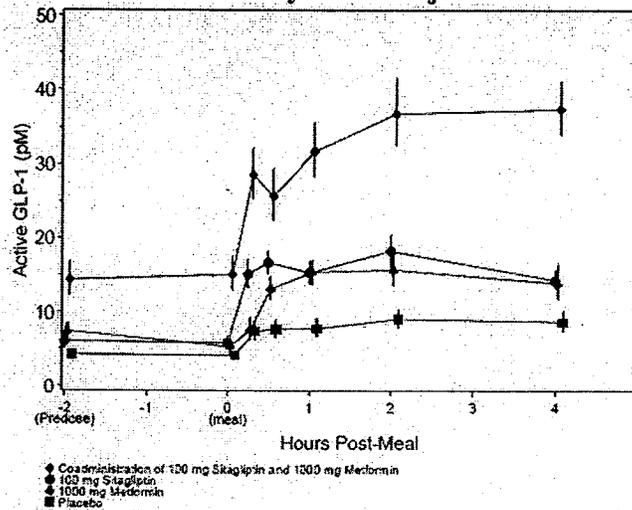
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Figure 2: Total GLP-1 concentrations versus time on Day 2 after concomitant administration of sitagliptin and metformin and after administration of sitagliptin alone, metformin alone and placebo in healthy adult subjects.



Active GLP-1 levels were significantly increased after concomitant administration of sitagliptin and metformin compared with administration of metformin alone or placebo. The 4-h GLP-1 levels were also increased with sitagliptin alone and metformin alone as compared to placebo (Figure 3). Administration of metformin alone increases circulating concentrations of both active and total GLP-1 to similar extent suggesting the effect of metformin is primarily due to increase in total GLP-1 concentrations. Sitagliptin therefore appears to stabilize the active GLP-1 since it increases the active form of GLP-1.

Figure 3: Active GLP-1 levels after concomitant administration of sitagliptin and metformin versus administration of sitagliptin alone, metformin alone and placebo in healthy adult subjects.



The ratio of active to total GLP-1 concentrations after administration of sitagliptin alone is increased by 100%. On the other hand, total GIP concentrations following administration of both metformin and sitagliptin were similar to that when the drugs were given alone. While, active GIP concentrations increased after concomitant administration of sitagliptin and metformin as compared to metformin alone or placebo. The ratio of 4-h post meal average ratio of active to total GIP concentrations after concomitant administration of sitagliptin and metformin compared with sitagliptin alone were similar. The ratio increased slightly with concomitant therapy when compared to metformin alone or placebo.

(Note: The GLP-1 level at the -2 h time point on Day 2 (Figure 2 & 3) is much higher for the concomitant treatment group as compared to the individual drugs and placebo. This could be due to the fact that GLP-1 levels may already have started to rise after Day 1 dose of the 2 drugs.)

Glucose concentrations pre-meal and at 2 h post meal (4 h post-dose) were similar between all active treatments and placebo in this study.

This study indicates that metformin can increase GLP-1 levels. The results of the current study suggest a complimentary and potentially additive effect of the combination therapy with sitagliptin and metformin however the glucose-lowering effects in patients with type 2 diabetes with concomitant administration for longer duration is unknown.

C Intrinsic Factors

The effects of various intrinsic factors (e.g., hepatic, renal, gender, elderly) were provided in the original NDA for each drug.

D Extrinsic Factors

Is there any drug-drug interaction between sitagliptin and metformin?

No.

No drug interaction study was conducted with the fixed-dose combination tablet. Drug-drug interaction between sitagliptin and metformin was conducted under the original NDA submission for Januvia (sitagliptin) and was referred to in this NDA. The conclusions from that study (P012) are as follows:

Co-administration of multiple twice-daily doses of sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin in patients with type 2 diabetes. Therefore, sitagliptin is not an inhibitor of OCT-mediated transport. Also

co-administration of multiple doses of metformin with sitagliptin did not alter the pharmacokinetics of sitagliptin in type 2 diabetic patients. Therefore, sitagliptin and metformin do not have any effect on pharmacokinetics of each other (From Dr. Wei's Clinical Pharmacology review of NDA 21-995, Januvia).

E General Biopharmaceutics

What is the formulation of Janumet tablets?

Two drug strengths were selected for the development, containing 50 mg of sitagliptin phosphate and either 500 mg or 1000 mg of metformin hydrochloride in an immediate-release oral tablet and supplied as a film coated tablet. The compositions for the two dosage forms are shown in Table 1.

Table 1: Composition of Janumet tablets

Components	Compendial Testing	Function	Unit Strength	
			50/500 mg/mg	50/1000 mg/mg
Core Tablet			mg/tablet	mg/tablet
Sitagliptin Phosphate (as monohydrate phosphate)	---	Active	64.25	64.25
Metformin Hydrochloride	USP, Ph. Eur.	Active	500.0	1000
Microcrystalline Cellulose	NF, Ph. Eur.	}		
Polyvinylpyrrolidone ()	USP, Ph. Eur.			
Sodium Stearyl Fumarate	NF, Ph. Eur.			
Sodium Lauryl Sulfate	NF, Ph. Eur.			
Core Tablet Weight	---			
Film Coating Suspension	---			
Film Coated Tablet Weight (mg)	---			

mg of the s equivalent to 50 mg of the free base
 : Removed during processing

Is the dissolution method appropriate for Janumet tablets?

Please refer to Chemistry review for dissolution details.

Bioequivalence Study:

Are the combination tablets of sitagliptin and metformin (50mg/500 mg and 50 mg/1000 mg) bioequivalent to concomitant dosing of sitagliptin 50mg and metformin 500 mg or 1000 mg (50 mg + 500 mg; 50 mg + 1000 mg) commercial tablets in healthy subjects?

Yes.

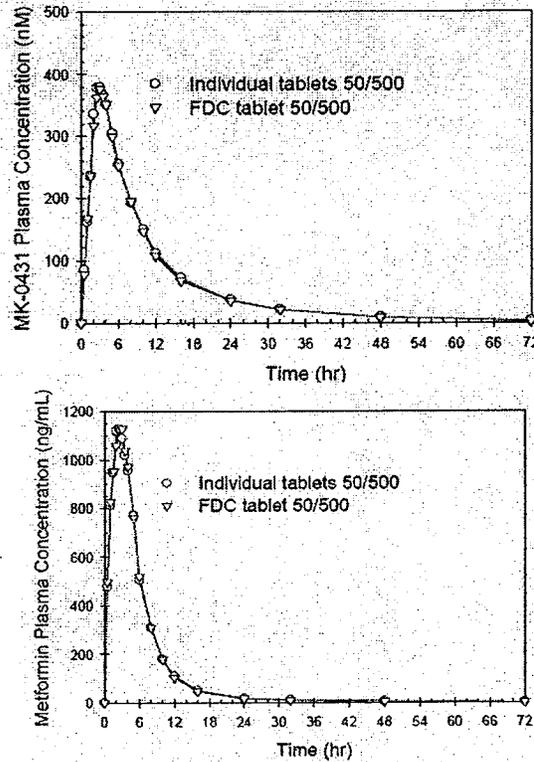
The BE study (P048) was an open-label, randomized, two-period crossover study conducted in two parts: Part I determined the bioequivalence of the FMI sitagliptin/metformin 50/500 mg FDC tablet and concomitant administration of corresponding doses of sitagliptin and metformin as individual tablets and Part II determined the bioequivalence of the FMI sitagliptin/metformin 50/1000 mg FDC tablet and concomitant administration of corresponding doses of sitagliptin and metformin (2 x 500 mg) as individual tablets. Blood samples were collected up to 72 h post-dose for pharmacokinetic analysis (half-life for sitagliptin ~14 h and metformin~ 2-4 h), with 7-days washout between periods. Subjects (N =24; 8 males; 16 females) received all treatments after an overnight fast. The treatments were:

Part I	
Treatment A	A single 50-mg dose of sitagliptin and 500-mg dose of metformin (generic, Apotex), as individual tablets, given concomitantly
Treatment B	A single dose of the FMI sitagliptin/metformin 50/500 mg/mg FDC tablet
Part II	
Treatment C	A single 50-mg dose of sitagliptin and 1000-mg dose of metformin (2 x 500-mg; generic, Apotex), as individual tablets, given concomitantly
Treatment D	A single dose of the FMI sitagliptin/metformin 50/1000 mg/mg FDC tablet
FMI=Final market image. FDC=Fixed-dose combination.	

Part I Results: (FMI sitagliptin/metformin 50/500 mg FDC tablets vs. concomitant administration)

The mean sitagliptin and metformin plasma concentration-time profiles after administration of a single dose of the sitagliptin/metformin 50/500 mg FDC and concomitant administration of individual tablets are shown in Figure 4. As shown the profiles were superimposable.

Figure 4: Mean sitagliptin (top) and metformin (bottom) concentration–time profiles after administration of administration of a single dose of the sitagliptin/metformin 50/500 mg FDC and concomitant administration of individual tablets (50 mg + 500 mg)



The pharmacokinetic parameters for sitagliptin and metformin were also similar following the two treatments. The geometric mean ratios (FDC tablet/concomitant administration) and corresponding 90% confidence interval for the AUC_{inf} and C_{max} of sitagliptin as well as metformin fell within the prespecified bounds of 80-125% indicating bioequivalence (Table 1). Additionally there were no difference observed in T_{max} and apparent t_{1/2} for both components following administration of the two treatments.

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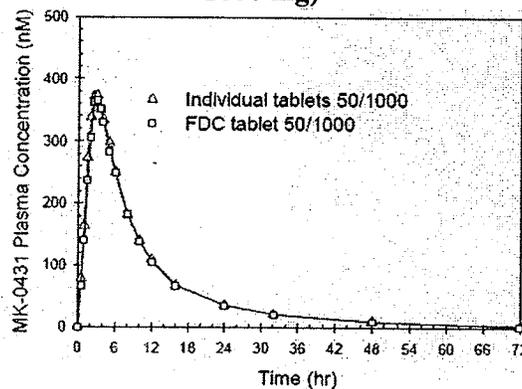
Table 1: Summary statistics of sitagliptin and metformin after administration of administration of a single dose of the sitagliptin/metformin 50/500 mg FDC and concomitant administration of individual tablets (50 mg + 500 mg) (N= 24)

PK Parameter	Sitagliptin			Metformin		
	LS Mean Reference	LS Mean Test	Ratio (90%CI)	LS Mean Reference	LS Mean Test	Ratio (90%CI)
AUCinf (µM. h)	4.085	4.007	98.10 (96.48 – 99.75)	7.261	7.250	99.85 (95.47 – 104.43)
Cmax (nM)	414.73	413.51	99.71 (93.71 – 106.09)	1180.178	1177.330	99.76 (93.67 – 106.24)

Part II Results: (FMI sitagliptin/metformin 50/1000 mg FDC tablets vs. concomitant administration)

The mean sitagliptin and metformin plasma concentration time profiles after administration of the two treatments are presented in Figure 5. As shown the profiles of both components following the two treatments are similar. The summary statistics are provided in Table 2. The 90% confidence interval for AUCinf and Cmax for both sitagliptin and metformin were within the 80-125% range. There were no differences observed in other PK parameters of sitagliptin and metformin between the two treatments.

Figure 5: Mean sitagliptin (top) and metformin (bottom) concentration-time profiles after administration of administration of a single dose of the sitagliptin/metformin 50/1000 mg FDC and concomitant administration of individual tablets (50 mg + 1000 mg)



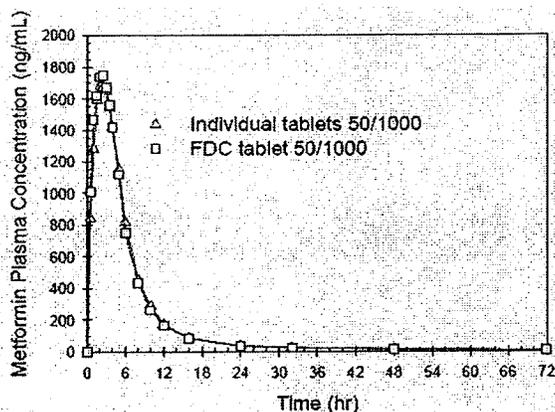


Table 2: Summary statistics of sitagliptin and metformin after administration of administration of a single dose of the sitagliptin/metformin 50/1000 mg FDC and concomitant administration of individual tablets (50 mg + 1000 mg) (N= 24)

PK Parameter	Sitagliptin			Metformin		
	LS Mean Reference	LS Mean Test	Ratio (90%CI)	LS Mean Reference	LS Mean Test	Ratio (90%CI)
AUCinf (µM. h)	4.053	3.938	97.17 (95.00 – 99.39)	11.869	11.868	99.99 (93.55 – 106.87)
Cmax (nM)	423.29	397.172	93.83 (87.51 – 100.61)	1848.044	1870.22	101.20 (93.21 – 109.88)

F Analytical

Have the analytical methods been sufficiently validated?

Sitagliptin

T

L

Table: Mean accuracy and precision of sitagliptin plasma samples analysis

Analyte	Samples	Mean Accuracy*	Mean Precision**

* Accuracy expressed as % bias, relative to theoretical concentration.

** Precision expressed as % coefficient of variation.

Metformin

III Labeling Recommendations

The sponsor's proposed language in the label regarding Pharmacokinetics section is acceptable.

IV Appendix

A Proposed Package Insert

JANUMET™
(sitagliptin phosphate/metformin HCl)
TABLETS



19 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

B Individual Study Synopsis

BE study synopsis

2. Synopsis

MERCK RESEARCH
LABORATORIES

CLINICAL STUDY REPORT
SYNOPSIS

MK-0431A
Metformin hydrochloride (+)
Sitagliptin phosphate
sitagliptin fixed-dose combination
(FDC) tablet
Type 2 diabetes

PROTOCOL TITLE/NO.: An Open-Label, Randomized, Two-Part, Two-Period Crossover Study to Demonstrate the Definitive Bioequivalence After Administration of the Final Market Image (FMI) of the Sitagliptin/Metformin 50/500 mg/mg and 50/1000 mg/mg Fixed-Dose Combination (FDC) Tablet and Concomitant Administration of 50-mg Doses of sitagliptin and 500- or 1000-mg Doses of Metformin as Individual Tablets to Healthy Adult Subjects #048

INVESTIGATOR/STUDY CENTER: Maria J. Gutierrez, M.D., Comprehensive Phase One, Fort Lauderdale, Florida.

PRIMARY THERAPY PERIOD: 05-Dec-2005 to 15-Dec-2005. **CLINICAL PHASE:** I
The frozen file date was 31-Jan-2006.

DURATION OF TREATMENT: Each subject received a single oral dose of the sitagliptin/metformin 50/500 mg/mg or 50/1000 mg/mg fixed-dose combination (FDC) tablet and corresponding doses of sitagliptin and metformin as individual tablets given concomitantly in a 2-period crossover study with a washout interval of at least 7 days between study drug administration in each treatment period. The total duration of treatment for each subject was 2 days.

OBJECTIVES: **Part I:** To demonstrate the definitive bioequivalence after administration of a single dose of the final market image (FMI) sitagliptin/metformin 50/500 mg/mg FDC tablet and concomitant administration of a single 50-mg dose of sitagliptin and a single 500-mg dose of metformin as individual tablets. **Part II:** To demonstrate the definitive bioequivalence after administration of a single dose of the FMI of the sitagliptin/metformin 50/1000 mg/mg FDC tablet and concomitant administration of a single 50-mg dose of and a single 1000-mg dose of metformin as individual tablets.

HYPOTHESES: **Part I: Primary:** The FMI sitagliptin/metformin 50/500 mg/mg FDC tablet and concomitant administration of a 50-mg dose of sitagliptin and a 500-mg dose of metformin as individual tablets will be bioequivalent after administration of single doses based on assessment of the area under the plasma concentration versus time curve ($AUC_{0-\infty}$) for sitagliptin and metformin [i.e., the geometric mean ratio (GMR) for the $AUC_{0-\infty}$ of sitagliptin and metformin after administration of the sitagliptin/metformin 50/500 mg/mg FDC tablet and concomitant administration of a 50-mg dose of sitagliptin and a 500-mg dose of metformin as individual tablets and will be contained within (0.80, 1.25)]. **Secondary:** The maximum concentration of drug in the plasma (C_{max}) of sitagliptin and metformin after administration of single doses of the FMI sitagliptin/metformin 50/500 mg/mg FDC tablet and concomitant administration of a 50-mg dose of sitagliptin and a 500-mg dose of metformin as individual tablets will be similar [i.e., the GMR for the C_{max} of sitagliptin and metformin after administration of the sitagliptin/metformin 50/500 mg/mg FDC tablet and concomitant administration of a 50-mg dose of sitagliptin and a 500-mg dose of metformin as individual tablets will be contained within (0.80, 1.25)]. **Part II: Primary:** The FMI sitagliptin/metformin 50/1000 mg/mg FDC tablet and concomitant administration of a 50-mg dose of sitagliptin and a 1000-mg dose of metformin as individual tablets will be bioequivalent after administration of single doses based on assessment of the $AUC_{0-\infty}$ for sitagliptin and metformin [i.e., the GMR for the $AUC_{0-\infty}$ of sitagliptin and metformin after administration of the sitagliptin/metformin 50/1000 mg/mg FDC tablet and concomitant administration of a 50-mg dose of sitagliptin and a 1000-mg dose of metformin as individual tablets will be contained within (0.80, 1.25)]. **Secondary:** The C_{max} of sitagliptin and metformin after administration of single

MK-0431A
 metformin hydrochloride (+)
 sitagliptin phosphate
 sitagliptin fixed-dose combination
 (FDC) tablet
 Type 2 diabetes

doses of the FMI sitagliptin/metformin 50/1000 mg/mg FDC tablet and concomitant administration of a 50-mg dose of sitagliptin and a 1000-mg dose of metformin as individual tablets will be similar [i.e., the GMR for the C_{max} of sitagliptin and metformin after administration of the sitagliptin/metformin 50/1000 mg/mg FDC tablet and concomitant administration of a 50 mg dose of sitagliptin and a 1000-mg dose of metformin as individual tablets will be contained within (0.80, 1.25)].

STUDY DESIGN: This was an open-label, randomized, two-part, two-period crossover study to demonstrate the definitive bioequivalence after administration of a single dose of the FMI sitagliptin/metformin (50/500 or 50/1000 mg/mg) FDC tablet and concomitant administration of a single dose of sitagliptin (50 mg) and metformin (500 mg or 1000 mg [2 x 500 mg]) as individual tablets in healthy adult subjects. The study was conducted in two parts (Parts I and II) with each part consisting of a two-period, crossover design. Subjects were entered into the study sequentially within each part of the study and each subject participated in only one part of the study (i.e., each subject participated only in Part I or only in Part II). Part I included Treatments A and B, and Part II included Treatments C and D. Each subject received both treatments within each part of the study and the order in which subjects receive treatments was randomly allocated within each part of the study. There was a minimum 7-day washout between study drug administrations in each treatment period within each part of the study. Subjects received all treatments after an overnight fast with 240 mL of water, with water restricted 1 hour prior to and after study drug administration.

Listing of Treatments

Part I	
Treatment A	A single 50-mg dose of sitagliptin and 500-mg dose of metformin (generic, Apotex), as individual tablets, given concomitantly
Treatment B	A single dose of the FMI sitagliptin/metformin 50/500 mg/mg FDC tablet
Part II	
Treatment C	A single 50-mg dose of sitagliptin and 1000-mg dose of metformin (2 x 500 mg; generic, Apotex), as individual tablets, given concomitantly
Treatment D	A single dose of the FMI sitagliptin/metformin 50/1000 mg/mg FDC tablet
FMI=Final market image.	
FDC=Fixed-dose combination.	

Blood for determination of plasma sitagliptin and metformin concentrations was collected at predose and at specified time points up to 72 hours postdose in each treatment period.

SUBJECT DISPOSITION:

	Part 1	Part 2
RANDOMIZED:	24	24
Male (age range)	8 (22-42 years)	9 (21-45 years)
Female (age range)	16 (25-44 years)	15 (21-45 years)
COMPLETED:	24	24
DISCONTINUED:	0	0

DOSAGE/FORMULATION NOS.:

Drug	Potency	Formulation Number	Dosage Form	Control Number
Part I				
Sitagliptin FMI	50 mg	WL00011482	tablet	WP-M604, WP-M607
Sitagliptin/metformin FDC FMI	50/500 mg/mg	WL00014811	tablet	WP-M606
Metformin, generic Apotex	500 mg	WL00016445	tablet	WP-M605, WP-608
Part II				
Sitagliptin FMI	50 mg	WL00011482	tablet	WP-M604, WP-M607
Sitagliptin/metformin FDC FMI	50/1000 mg/mg	WL00014793	tablet	WP-M609
Metformin, generic Apotex	500 mg	WL00016445	tablet	WP-M605, WP-608
FMI=Final market image.				
FDC=Fixed-dose combination.				

Data Source: [Not Applicable]

DIAGNOSIS/INCLUSION CRITERIA: A total of forty-eight healthy adult subjects between the ages of 18 and 45 years participated in this study, with twenty-four different subjects participating in each part of the study.

EVALUATION CRITERIA:

PHARMACOKINETICS: The plasma pharmacokinetics ($AUC_{0-\infty}$, C_{max} , and time to reach C_{max} [T_{max}], and apparent $t_{1/2}$) and apparent $t_{1/2}$ of sitagliptin and metformin after administration of a single dose of the sitagliptin/metformin 50/500 mg/mg or 50/1000 mg/mg FDC tablet and concomitant administration of a single 50-mg dose of sitagliptin and a 500-mg or 1000-mg (2 x 500-mg) dose of metformin as individual tablets was determined.

SAFETY: The safety of sitagliptin and metformin was assessed by clinical evaluation of adverse experiences, medical history and physical examination, routine laboratory safety tests (hematology, serum biochemistry, and urinalysis), 12-lead electrocardiograms (ECGs) and vital sign measurements. Serum β -human chorionic gonadotropin assays were performed for women of child-bearing potential and were confirmed negative prior to study drug administration in both treatment periods for each part of the study.

STATISTICAL PLANNING AND ANALYSIS:

PHARMACOKINETICS: In each part of the study, the pharmacokinetic parameters ($AUC_{0-\infty}$ and C_{max} of sitagliptin and metformin) after oral administration of a single dose of the sitagliptin/ metformin 50/500 mg/mg (Part I) or 50/1000 (Part II) mg/mg FDC tablet and concomitant administration of sitagliptin and metformin as individual tablets were compared using an Analysis of Variance (ANOVA) model appropriate for a 2-period, crossover design. The ANOVA models contained factors for subject (random effect), period, and treatment. A log transformation was applied to the $AUC_{0-\infty}$ and C_{max} data; rank and inverse transformations were applied for T_{max} and $t_{1/2}$, respectively. Ninety percent (90%) confidence intervals (CIs) for the GMRs (FDC tablet/concomitant administration) for $AUC_{0-\infty}$ and C_{max} of sitagliptin and metformin were computed for each part of the study. In each part of the study, to satisfy the primary hypothesis, 90% CIs were calculated for the $AUC_{0-\infty}$ GMRs (FDC tablet/

concomitant administration) of sitagliptin and metformin and compared to the prespecified bounds of [0.80, 1.25]. Similarly, in each part of the study to satisfy the secondary hypothesis, 90% CIs were calculated for the C_{max} GMRs (FDC tablet/concomitant administration) of sitagliptin and metformin and compared to the prespecified bounds of [0.80, 1.25].

SAFETY: Safety information was evaluated by tabulating adverse experiences and by clinical assessment of laboratory safety tests, 12-lead ECG parameters and vital signs measurements. Adverse experiences were evaluated as to their intensity, seriousness and relationship to study drug.

RESULTS:

PHARMACOKINETICS: Summary statistics of pharmacokinetic parameters of sitagliptin and metformin after oral administration of a single dose of the FMI sitagliptin/metformin 50/500 mg/mg or 50/1000 mg/mg FDC tablet and concomitant administration of corresponding doses of sitagliptin and metformin as individual tablets to adult subjects are provided in the tables below. After oral administration of the FMI sitagliptin/metformin 50/500 and 50/1000 mg/mg FDC tablet and concomitant administration of corresponding doses of sitagliptin and metformin as individual tablets, the pharmacokinetic parameter values were similar for both comparisons of sitagliptin concentrations and comparisons of metformin concentrations. The 90% CI of the GMR (FDC tablet/concomitant administration) for the $AUC_{0-\infty}$ and C_{max} of sitagliptin and metformin all were within the prespecified bounds of (0.80, 1.25), demonstrating that the FMI sitagliptin/metformin 50/500 mg/mg and 50/1000 mg/mg FDC tablets are bioequivalent to concomitant administration of the individual tablets of sitagliptin and metformin at the corresponding dose strengths.

Part I: Sitagliptin

Pharmacokinetics of Sitagliptin After Administration of a Single Dose of the Sitagliptin/Metformin 50/500 mg/mg Fixed-Dose Combination Tablet or Concomitant Administration of Corresponding Doses of Sitagliptin 50-mg and Metformin 500-mg as Individual Tablets to Healthy Adult Subjects

Parameter	FMI FDC Tablet	Coadministration of Individual Tablets	GMR ¹ (90% CI)
	Geometric LS Mean N=24	Geometric LS Mean N=24	
$AUC_{0-\infty}$ (uM•hr)	4.01	4.09	0.98 (0.96, 1.00)
C_{max} (nM)	414	415	1.00 (0.94, 1.06)
T_{max} (hr)	2.75 ²	2.50 ²	0.520 ³
Apparent $t_{1/2}$ (hr)	12.6 ⁴	12.3 ⁴	0.572 ⁴

¹ GMR = Geometric LS mean ratio (reference is the coadministration of sitagliptin 50 mg and metformin 500 mg as individual tablets) based on the least-squares means from the ANOVA model.
² Median.
³ p-Value.
⁴ Harmonic Mean.
 CI = Confidence Interval.
 FMI=Final Marker Image.
 FDC=Fixed-Dose Combination.

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Part I: Metformin

Pharmacokinetics of Metformin After Administration of a Single Dose of the Sitagliptin/Metformin 50/500-mg/mg Fixed-Dose Combination Tablet or Concomitant Administration of Corresponding Doses of Sitagliptin 50-mg and Metformin 500-mg as Individual Tablets to Healthy Adult Subjects

Parameter	FMI FDC Tablet	Coadministration of Individual Tablets	GMR [†] (90% CI)
	Geometric LS Mean N=24	Geometric LS Mean N=24	
AUC _{0-∞} (ng/mL·hr)	7.35	7.26	1.00 (0.95, 1.04)
C _{max} (nM)	1180	1180	1.00 (0.94, 1.06)
T _{max} (hr)	2.75 ‡	3.50 ‡	0.781 †
Apparent t _{1/2} (hr)	11.6 §	9.79 †	0.154 †

† GMR = Geometric LS mean ratio (reference is the coadministration of sitagliptin 50 mg and metformin 500 mg as individual tablets) based on the least-squares means from the ANOVA model.
‡ Median.
§ p-Value.
† Harmonic Mean.
CI = Confidence Interval.
FMI=Final Market Image.
FDC=Fixed-Dose Combination.

Part II: Sitagliptin

Pharmacokinetics of Sitagliptin After Administration of a Single Dose of the Sitagliptin/Metformin 50/1000 mg/mg Fixed-Dose Combination Tablet or Concomitant Administration of Corresponding Doses of Sitagliptin 50-mg and Metformin 1000-mg as Individual Tablets to Healthy Adult Subjects

Parameter	FMI FDC Tablet	Coadministration of Individual Tablets	GMR [†] (90% CI)
	Geometric LS Mean N=24	Geometric LS Mean N=24	
AUC _{0-∞} (nM·hr)	3.84	4.05	0.97 (0.93, 0.99)
C _{max} (nM)	397	423	0.94 (0.88, 1.01)
T _{max} (hr)	2.50 ‡	2.50 ‡	0.518 †
Apparent t _{1/2} (hr)	13.7 §	13.1 †	0.467 †

† GMR = Geometric LS mean ratio (reference is the coadministration of sitagliptin 50 mg and metformin 1000 mg as individual tablets) based on the least-squares means from the ANOVA model.
‡ Median.
§ p-Value.
† Harmonic Mean.
CI = Confidence Interval.
FMI=Final Market Image.
FDC=Fixed-Dose Combination.

Part II: Metformin
Pharmacokinetics of Metformin After Administration of a Single Dose of the Sitagliptin/Metformin 50/1000-mg/mg Fixed-Dose Combination Tablet or Concomitant Administration of Corresponding Doses of Sitagliptin 50-mg With Metformin 1000-mg as Individual Tablets to Healthy Adult Subjects

Parameter	FMI FDC Tablet	Coadministration of Individual Tablets	GMR ¹ (90% CI)
	Geometric LS Mean N=24	Geometric LS Mean N=24	
AUC _{0-∞} (ng/mL·hr)	11.9	11.9	1.00 (0.94, 1.07)
C _{max} (nM)	1870	1850	1.01 (0.93, 1.10)
T _{max} (hr)	2.00 ²	2.50 ²	0.143 ³
Apparent t _{1/2} (hr)	13.9 ⁴	13.6 ⁴	0.764 ⁴

¹ GMR = Geometric LS mean ratio (reference is the coadministration of sitagliptin 50 mg and metformin 1000 mg as individual tablets) based on the least-squares means from the ANOVA model.
² Median.
³ p-Value.
⁴ Harmonic Mean.
 CI = Confidence Interval.
 FMI=Final Market Image.
 FDC=Fixed-Dose Combination.

SAFETY:

Administration of single doses of the sitagliptin/metformin 50/500 and 50/1000 mg/mg FDC tablet and concomitant administration of corresponding doses of sitagliptin and metformin as individual tablets were generally well-tolerated. There were no laboratory or serious adverse experiences reported in this study. No subject discontinued from the study due to an adverse experience.

Part I: A total of 3 subjects reported a total of 4 adverse experiences, 3 of which were rated by the investigator to be possibly or probably related to study drug. The 3 drug-related adverse experiences were abdominal pains (2 reports) and headache (1 report) and all were rated as mild in intensity and resolved without treatment.

Part II: A total of 4 subjects reported a total of 5 adverse experiences, none of which were rated by the investigator to be related to study drug.

CONCLUSIONS: (1) The FMI sitagliptin/metformin 50/500 mg/mg and 50/1000 mg/mg FDC tablets are bioequivalent to coadministration of corresponding doses of sitagliptin and metformin as individual tablets. (2) The FMI sitagliptin/metformin 50/500 mg/mg or 50/1000 mg/mg FDC tablets and concomitant administration of sitagliptin and metformin as individual tablets is generally well tolerated.

AUTHORS:

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2) PD study synopsis

2. Synopsis

MERCK RESEARCH
LABORATORIES
Sitagliptin phosphate,
sitagliptin 100 mg; sitagliptin
placebo; metformin 500 mg;
metformin placebo;
Type 2 diabetes

CLINICAL STUDY REPORT
SYNOPSIS

PROTOCOL TITLE/NO.: A Randomized, Placebo-Controlled, Double-Blind, #050
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

INVESTIGATOR(S)/STUDY CENTER(S): Maria J. Gutierrez, M.D., Comprehensive Phase
One, Fort Lauderdale, Florida.

PRIMARY THERAPY PERIOD: 26-Jan-2006 to 3-Mar-
2006. The frozen file date was 27-March-2006.

CLINICAL I
PHASE:

DURATION OF TREATMENT: Each subject participated in four (4) 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.

OBJECTIVE(S): 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: This was a randomized, placebo-controlled, double-blind, double-dummy,
4-period crossover study to assess the effects of sitagliptin and metformin on post-meal
incretin hormone (active and total GLP-1 and GIP) 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.

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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)

On Day 1 of each treatment period, subjects received their randomly assigned study medication in the morning and evening. On Day 2 of each treatment period, subjects received their randomly assigned study medication in the morning and at 2 hours postdose consumed (within 20 minutes) a standardized breakfast (765 calories; 25% fat, 55% carbohydrate, and 20% protein). On Day 2 (only), blood samples for determination of active and total GLP-1 and GIP concentrations and plasma glucose concentrations were collected pre-meal and at specified time points after the postdose meal. Blood samples for possible determination of plasma sitagliptin and metformin concentrations and DPP-4 inhibitory activity were collected and archived at pre-meal and at 2 hours after the postdose meal.

SUBJECT/PATIENT DISPOSITION:

RANDOMIZED:	18
Male (age range)	6 (19-44 years)
Female (age range)	12 (23-49 years)
COMPLETED:	16
DISCONTINUED:	2
Other	2

DOSAGE/FORMULATION NOS.:

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

Data Source: [Not Applicable]

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DIAGNOSIS/INCLUSION CRITERIA: A total of sixteen (16) healthy adult subjects between the ages of 18 and 55 years completed this study.

EVALUATION CRITERIA:

PHARMACOKINETICS: Blood samples were collected and plasma samples archived for possible determination of sitagliptin and metformin concentrations at premeal and at 2 hours after the postdose meal.

PHARMACODYNAMICS: On Day 2 (only) of each treatment period, blood samples were collected for determination of 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 hours after the postdose meal. The primary endpoint was the 4-hour post-meal (meal consumed at 2 hours postdose; at the approximate T_{max} for sitagliptin and metformin) weighted average active GLP-1 concentrations after concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone. Secondary endpoints included, but not limited to, 4-hour post-meal weighted average active GLP-1 concentrations after concomitant 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 concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone, metformin alone and placebo, 4-hour post-meal incremental glucose AUC (glucose AUC_{0-4hr}) and fasting and maximum glucose concentrations (i.e., pre-meal and at 2-hours post-meal, respectively) after concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone, metformin alone and placebo.

SAFETY: The safety of sitagliptin and metformin was assessed by clinical evaluation of adverse events, medical history and physical examination, routine laboratory safety tests (hematology, serum chemistry, and urinalysis), 12-lead electrocardiograms (ECGs) and vital sign measurements. Serum β -human chorionic gonadotropin assays were performed for women of child-bearing potential and were confirmed negative prior to study drug administration in each treatment period.

STATISTICAL PLANNING AND ANALYSIS:

PHARMACOKINETICS: Blood samples were collected and plasma samples archived for possible determination of plasma sitagliptin and metformin concentrations at premeal and at 2 hours after the postdose meal on Day 2 in each treatment period.

PHARMACODYNAMICS: The 4-hour post-meal weighted average active GLP-1 concentrations after concomitant administration of sitagliptin and metformin and after administration of sitagliptin alone on Day 2 were compared using an analysis of variance (ANOVA) model appropriate for a 4-period, crossover design. The ANOVA model included factors for subject, period, and treatment. A log transformation was applied to the weighted average active GLP-1 data. Appropriate linear contrasts from the ANOVA model were used to perform the inferential tests. The geometric mean ratio (GMR) (sitagliptin + metformin/sitagliptin alone), corresponding 95% confidence intervals, and p-values were provided. Back-transformed summary statistics were also provided.

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The above ANOVA model also was used to compare treatment-related effects on the 4-hour post-meal weighted average active GLP-1 concentrations after concomitant administration of sitagliptin and metformin and after administration of metformin alone and placebo. Summary statistics, GMRs and the corresponding 95% confidence intervals were provided.

The 4-hour post-meal weighted average total GLP-1, active and total GIP and ratio of active to total GLP-1 and GIP concentrations after concomitant administration sitagliptin and metformin and after administration of sitagliptin alone, metformin alone and placebo were also evaluated in the same fashion as above. Summary statistics, GMRs and the corresponding 95% confidence intervals were also provided.

For completeness, all pairwise between-treatment differences and comparisons for both active and total GLP-1 and GIP concentrations were provided.

Additionally, the same analyses as described above were conducted for blood glucose concentrations i.e., the 4-hour post-meal incremental glucose AUC (AUC_{0-4hr}). Summary statistics for the fasting or pre-meal (i.e., at 2 hours postdose) and for the 2-hour post-meal (i.e., at 4 hours postdose) glucose concentrations were provided and comparisons were made between treatments as well.

Blood samples were collected and plasma samples archived for possible determination of plasma DPP-4 inhibitory activity at premeal and at 2 hours after the postdose meal on Day 2 in each treatment period.

SAFETY: Safety information was evaluated by tabulating adverse experiences and by clinical assessment of laboratory safety tests, 12-lead ECG parameters and vital signs measurements. Adverse experiences were evaluated as to their intensity, seriousness, and relationship to study drug.

RESULTS:

PHARMACOKINETICS: Blood samples for determination of plasma sitagliptin and metformin concentrations will be analyzed at a future date.

PHARMACODYNAMICS: Summary statistics, geometric mean ratios (GMR) and the corresponding 95% confidence intervals (CI) for the 4-hour post-meal weighted average active, total and ratio of active to total GLP-1 and GIP concentrations and 4-hour post-meal incremental glucose AUC for each active treatments compared with placebo on Day 2 are provided in the following tables. Blood samples for determination of plasma DPP-4 inhibitory activity will be analyzed at a future date.

The GMR (sitagliptin + metformin/sitagliptin) and 95% CI for the 4-hour post-meal weighted average active GLP-1 concentrations is 2.12 (1.73, 2.60); the statistically significant increase in the 4-hour post-meal weighted average active GLP-1 concentrations supports the study primary hypothesis ($p < 0.001$). The results also demonstrated that the 4-hour post-meal weighted average active GLP-1 concentrations were significantly increased after concomitant administration of sitagliptin and

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metformin compared with placebo ($p < 0.001$). With respect to total GLP-1, the 4-hour post-meal weighted average total GLP-1 concentrations were statistically significantly increased (by approximately 120%) after concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone ($p < 0.001$). The 4-hour post-meal weighted average total GLP-1 concentrations after concomitant administration of sitagliptin and metformin compared with administration of metformin alone were similar ($p = 0.134$) and statistically significantly increased after administration of placebo ($p < 0.001$). The 4-hour post-meal weighted average total GLP-1 concentrations were statistically significantly decreased (by approximately 30%) after administration of sitagliptin alone and statistically significantly increased after administration of metformin alone compared with placebo ($p < 0.001$). With respect to ratio of active to total GLP-1, the 4-hour post-meal weighted average ratio of active to total GLP-1 concentrations after concomitant administration of sitagliptin and metformin and administration of sitagliptin alone were similar ($p > 0.200$). The 4-hour post-meal weighted average ratio of active to total GLP-1 concentrations after concomitant administration of sitagliptin and metformin were statistically significantly increased compared with metformin alone and placebo ($p < 0.001$). The 4-hour post-meal weighted average ratio of active to total GLP-1 concentrations were also statistically significantly increased after administration of sitagliptin alone ($p < 0.001$), but were similar after administration of metformin alone compared with placebo ($p > 0.200$).

Summary Statistics for the 4-Hour Post-Meal Weighted Average Active, Total and Ratio of Active to Total GLP-1 After Concomitant Administration of Sitagliptin and Metformin and After Administration of Sitagliptin Alone, Metformin Alone and Placebo in Healthy Adult Subjects

Treatment	N	Geometric LS Means	GMR [†]	95% CI [‡]	p-value
Active GLP-1 (pM)					
Sitagliptin + Metformin	16	34.68	4.12	(3.35, 5.08)	<0.001
Sitagliptin	16	16.37	1.95	(1.58, 2.40)	<0.001
Metformin	16	14.81	1.76	(1.43, 2.17)	<0.001
Placebo	15	8.41			
Total GLP-1 (pM)					
Sitagliptin + Metformin	16	27.82	1.57	(1.29, 1.90)	<0.001
Sitagliptin	16	12.43	0.70	(0.58, 0.85)	<0.001
Metformin	16	32.14	1.81	(1.49, 2.20)	<0.001
Placebo	15	17.77			
Ratio of Active to Total GLP-1					
Sitagliptin + Metformin	16	0.97	2.01	(1.72, 2.34)	<0.001
Sitagliptin	16	0.96	1.96	(1.68, 2.30)	<0.001
Metformin	16	0.47	0.97	(0.83, 1.13)	0.671
Placebo	15	0.49			
† GMR = Ratio of the geometric LS means. Reference is placebo group					
‡ CI = Confidence interval					
LS means = Least-squares means					

The results provided demonstrated that the 4-hour post-meal weighted average active GIP concentrations after concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone were similar ($p = 0.411$). The 4-hour post-meal weighted average active GIP concentrations were significantly increased after concomitant administration of sitagliptin and metformin compared with administration of metformin alone or placebo ($p < 0.001$). The 4-hour post-meal weighted average active GIP concentrations also were statistically significantly increased after administration of sitagliptin alone compared with placebo ($p < 0.001$) and were similar after administration of metformin alone compared with placebo ($p = 0.825$). With respect to total GIP, the 4-hour post-meal weighted average total GIP concentrations after concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone and metformin alone were similar ($p = 0.410$). The 4-hour post-meal weighted average total GIP concentrations were statistically significantly decreased after concomitant administration of sitagliptin and metformin

compared with placebo ($p=0.039$). The 4-hour post-meal weighted average total GI concentrations also were statistically significantly decreased after administration of sitagliptin alone compared with placebo ($p=0.005$) and similar after administration of metformin alone compared with placebo ($p=0.317$). With respect to ratio of active to total GIP, the 4-hour post-meal weighted average ratio of active to total GIP concentrations after concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone were similar ($p=0.710$). The 4-hour post-meal weighted average ratio of active to total GI concentrations were statistically significantly increased after concomitant administration of sitagliptin and metformin compared with administration of metformin alone or placebo ($p<0.001$). The 4-hour post-meal weighted average ratio of active to total GIP concentrations also were statistically significantly increased after administration of sitagliptin alone compared with placebo ($p<0.001$) and similar after administration of metformin alone compared with placebo ($p=0.348$).

Summary Statistics for the 4-Hour Post-Meal Weighted Average Active, Total and Ratio of Active to Total GIP After Concomitant Administration of Sitagliptin and Metformin and after Administration of Sitagliptin Alone, Metformin Alone and Placebo in Healthy Adult Subjects

Treatment	N	Geometric LS Means	GMR [†]	95% CI [‡]	p-value
Active GIP (pM)					
Sitagliptin + Metformin	16	57.18	1.92	(1.50, 2.45)	<0.001
Sitagliptin	16	51.80	1.74	(1.36, 2.22)	<0.001
Metformin	16	29.01	0.97	(0.76, 1.24)	0.825
Placebo	15	29.80			
Total GIP (pM)					
Sitagliptin + Metformin	16	41.75	0.75	(0.58, 0.99)	0.039
Sitagliptin	16	37.49	0.68	(0.52, 0.89)	0.005
Metformin	16	48.38	0.87	(0.67, 1.14)	0.317
Placebo	15	55.31			
Ratio of Active to Total GIP					
Sitagliptin + Metformin	16	0.99	1.80	(1.54, 2.11)	<0.001
Sitagliptin	16	0.96	1.75	(1.49, 2.05)	<0.001
Metformin	16	0.59	1.08	(0.92, 1.26)	0.348
Placebo	15	0.55			
[†] GMR = Ratio of the geometric LS means. Reference is placebo group [‡] CI = Confidence interval LS means = Least-squares means					

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The incremental (i.e., relative to the pre-meal glucose concentration) area under the glucose concentration-time curve (AUC) over a 4 hour post-meal interval (AUC_{0-4hr}) were evaluated for active treatments and placebo. Summary statistics for the incremental glucose AUC_{0-4hr} , the geometric mean ratios (GMR) of the least-squares means and the corresponding 95% confidence intervals (CI) are provided in the following table. These results indicate that there are statistically significant reductions (more than 50%) in the post-meal incremental glucose AUC_{0-4hr} after concomitant administration of sitagliptin and metformin and after administration of sitagliptin alone and metformin alone compared with placebo ($p < 0.001$). The reduction in the post-meal incremental glucose AUC_{0-4hr} after concomitant administration of sitagliptin and metformin compared with administration of either sitagliptin alone or metformin alone were similar ($p > 0.200$). The post-meal incremental glucose AUC_{0-4hr} after administration of sitagliptin alone and metformin alone were similar ($p > 0.200$). It was also shown that the glucose concentrations at pre-meal (fasting; i.e., 2 hours postdose,) and 2 hours post-meal (i.e., 4 hours postdose) were generally similar between all active treatments and placebo.

Summary Statistics for the 4-Hour Post-Meal Incremental Glucose AUC_{0-4hr} (mg-hr/dL) After Concomitant Administration of Sitagliptin and Metformin and After Administration of Sitagliptin Alone, Metformin Alone and Placebo in Healthy Adult Subjects

Treatment	N	Geometric LS Means	GMR [†]	95% CI [‡]	p-value
Sitagliptin + Metformin	16	18.47	0.41	(0.20, 0.83)	0.014
Sitagliptin	16	21.27	0.47	(0.24, 0.94)	0.033
Metformin [§]	15	21.57	0.48	(0.24, 0.95)	0.037
Placebo	15	45.22			

[†] GMR = Ratio of the geometric LS means. Reference is placebo group.
[‡] CI = Confidence interval.
[§] Glucose AUC of 0 mg-hr/dL from AN 0008 in Treatment Period 3 excluded due to calculation of the geometric mean.
 LS means = Least-squares means.

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SAFETY:

A total of 14 subjects reported a total of 38 adverse experiences, 35 of which 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. Two subjects (Allocation Numbers [ANs] 0013 and 0015) were discontinued from the study for compliance issues associated with the study restrictions after completing Treatment Period 1.

CONCLUSIONS: (1) The 4-hour post-meal weighted mean active GLP-1 concentrations were increased by approximately 110% after concomitant 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 concomitant 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.

AUTHORS:


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Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
NDA Number	22-044	Brand Name	Janumet™	
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Sitagliptin phosphate/Metformin hydrochloride fixed-dose combination	
Medical Division	HFD-510	Drug Class	Anti-diabetic	
OCPB Reviewer	Xiaozhong (Jim) Wei	Indication(s)	Type 2 Diabetes	
OCPB Team Leader	Hae-Young Ahn	Dosage Form	tablets	
		Dosing Regimen	100 mg /1500-2000mg/day	
Date of Submission	05-31-2006	Route of Administration	oral	
Estimated Due Date of OCPB Review	March 2, 2007	Sponsor	Merck	
Division Due Date	March 2, 2007	Priority Classification	S1	
PDUFA Due Date	March 30, 2007			
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			
Reference Bioanalytical and Analytical Method:	X			
I. Clinical Pharmacology				
Mass balance:				
Isotopically characterized:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

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hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
Thorough QT Study				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-warrier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics:				
Pediatric development plan				
Literature References				
Total Number of Studies		3		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	YES			
Comments sent to firm?	No			
Primary reviewer Signature and Date	Appears This Way On Original			
Secondary reviewer Signature and Date				

Briefing In Content:

Merck submitted this NDA for seeking approval of fixed dose combination drug products of Sitagliptin and Metformin. Sitagliptin phosphate (MK-0431) is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor developed by Merck & Co., Inc. for the treatment of type 2 diabetes mellitus, which is currently with the Agency for review under NDA21-995. Metformin hydrochloride is an approved anti-hyperglycemic agent widely used for the treatment of type 2 diabetes mellitus. The sponsor has developed an immediate release product containing a fixed dose of sitagliptin phosphate and multiple dose levels of metformin hydrochloride for the treatment of patients with type 2 diabetes who are not adequately controlled with either agent alone or patients already being treated with the combination of sitagliptin and metformin. Two dose strengths of a film-coated fixed-dose combination (FDC) tablet have been developed for the U.S. market: sitagliptin/metformin 50/500 mg/mg and 50/1000 mg/mg.

To support this combo drug product, the sponsor submitted three new PK studies, two of which are BE studies, and one of which is PD study. All three studies were conducted in healthy subjects:

1) Study P38 (BE with test formulations)

A 2-Part, Open-Label, Randomized, 3-Period Crossover Study to Evaluate the Pharmacokinetic Profiles of MK-0431 and Metformin After Oral Administration of Single Doses of MK-0431/Metformin Fixed-Dose Combination Tablet Probe Formulations or Coadministration of MK-0431 With Metformin as Individual Tablets to Healthy Adult Subjects

2) Study P48 (BE with commercial formulations)

An Open-Label, Randomized, Two-Part, Two-Period Crossover Study to Demonstrate the Definitive Bioequivalence After Administration of the Final Market Image (FMI) of the MK-0431/Metformin 50/500 mg and 50/1000 mg Fixed-Dose Combination (FDC) Tablet and Concomitant Administration of 50-mg Doses of MK-0431 and 500- or 1000-mg Doses of Metformin as Individual Tablets to Healthy Adult Subjects

3) Study P50 (PD study)

This is 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. The objectives are 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. This study is to assess the effects of sitagliptin and metformin on post-meal incretin hormone (active and total GLP-1 and GIP) 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.

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The Sponsor cited many supportive studies in NDA21-995 including drug interaction studies between sitagliptin and metformin.

The sponsor has developed dissolution specification for this combo drug product: no less than ~ % dissolved in 20 min.

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Jayabharathi Vaidyanathan
2/22/2007 08:56:35 AM
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Xiao-xiong Wei
2/22/2007 09:54:57 PM
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