CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202343Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM
CLINICAL PHARMACOLOGY REVIEW

NDA	202343
Submission Date(s)	December 3, 2010
Brand Name	Juvisync ™, MK-0431D
Generic Name	Sitagliptin phosphate+simvastatin tablet
Reviewers	Sang M. Chung, Ph.D.
Team Leader	Jayabharathi Vaidyanathan, Ph.D. (Acting)
OCP Division	Clinical Pharmacology II
OND Division	Metabolism and Endocrinology Products (DMEP)
Sponsor	Merck
Submission Type	505(b)(1), Standard
Formulation Strength(s)	100/10, 100/20, and 100/40 (mg sitagliptin / mg simvastatin)
Indication	Treatment with both sitagliptin and simvastatin
Dosage & Administration	Patients switching from co-administered sitagliptin (100 mg) and simvastatin (10, 20, or 40 mg) can initiate JUVISYNC at the doses of sitagliptin and simvastatin already being taken. JUVISYNC can be taken with or without food in the evening.

This addendum is to finalize the pending recommendation in the original Clinical Pharmacology review upon the availability of the Office of Scientific Investigations (OSI) inspection review issued on September 7, 2011. Also provided is the comments on the development of fixed-dose combination with sitagliptin 50 mg from the clinical pharmacology perspective.

Pending Recommendation in the Original Review dated September 1, 2011:
The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 202343 for (b) (4)™ and finds it acceptable provided that 1) the Agency and the sponsor agree on the labeling and 2) there is no significant issue from the review of Office of Scientific Investigation.

Final Recommendation:
The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA 202343 for Juvisync™. Data presented in the submission and the analysis of data indicates that the proposed FDC formulations meet the bioequivalence criteria and the results are acceptable. However, the findings of OSI inspection indicate that there were compliance issues at the clinical study site related to the authenticity of the test and reference formulations. The issues identified are not related to the validity of analytical methods or data presented in the NDA but may be legal or regulatory in nature and are being addressed by the OSI.

Phase IV Commitments:
The sponsor has agreed to develop the FDC with sitagliptin 50 mg to permit dosing of patients with moderate renal impairment. The new strengths needs to be developed and data to support its approval (e.g., *in vivo* and/or *in vitro* study) should be submitted to the Agency per the schedule specified in the approval letter.

Reviewer's Comment:

Comments on the OSI recommendation from the clinical pharmacology perspective
The main issue raised by the OSI was that drug product was not randomly chosen to be administered to the volunteers, but pre-specified by the sponsor, which raised the authenticity question (refer the OSI memo in Attachment 1). To evaluate the impact of this issue, this reviewer looked at additional information available in the NDA as follows:

1. All pivotal studies were open-label and not blinded. Further, reference drug was 2 tablets and test product was 1 tablet. Therefore, it would be obvious if authenticity was being compromised, i.e., the person administering the treatment to volunteers would have known if the treatment is test or a reference.

2. In the NDA, additional pilot BE study (Study 153, Part I, n=24) study had been submitted. The product used in this study was manufactured from the same bulk lot as the pivotal BE study (Study 153, Part II) but different packaging lot (refer the detailed information in Attachment 2). The results from pilot BE study indicated that among the 3 components, sitagliptin and simvastatin acid met the BE criteria. On the other hand, while simvastatin AUC met the BE criteria, its Cmax was marginally outside the BE limits (i.e., upper bound 1.26 instead of 1.25). Therefore both the studies, pilot and pivotal, showed similar results, i.e., the products are BE. The above conclusions are also supported by the following analysis conducted by this reviewer;
    - Means of pharmacokinetic parameters of sitagliptin, simvastatin, and simvastatin acid from Part I are not significantly different ($p>0.05$) compared to those of Part II according to the ANOVA test using SAS 9.2. In addition, variances of those pharmacokinetic parameters from Part I are not significantly different ($p>0.05$) from those of Part II according to Levene's test for homogeneity (equality) of variances using SAS 9.2.

3. All the pharmacokinetic parameters met the BE criteria with tight confidence interval (CI) even though there was significant variability in simvastatin and simvastatin exposure (Table 1 and 2). Therefore, potential difference among kits/packaging lots of the test formulation may not affect the BE conclusion
4. During the drug development, site, equipment and scale changes for the to-be-marketed product was bridged to the biobatch using dissolution comparison data. The difference among packaging lots/kits within the same bulk lot of biobatch would be smaller than the difference between biobatch and to-be-marketed.

Table 1 Summary Statistics and Statistical Comparisons for the Plasma PK Parameters of Sitagliptin, Simvastatin and Simvastatin Acid

P153, Part I

	MK-0431D			Simvastatin + Sitagliptin		
Pharmacokinetic Parameter	**N**	**AM***	**SD (CV%)**	**N**	**AM***	**SD (CV%)**
Sitagliptin						
AUC0-∞ ‡ (nM*hr)	24	7395	1295 (17)	24	7625	1419 (18)
AUC0-last ‡ (nM*hr)	24	7296	1236 (17)	24	7532	1389 (17)
Cmax ‡ (nM)	24	951	321 (31)	24	913	261 (27)
Simvastatin						
AUC0-last ‡ (ng/mL*hr)	24	105.89	53.59 (73)	24	102.45	44.72 (55)
Cmax ‡ (ng/mL)	24	20.34	15.30 (81)	24	19.84	15.97 (81)
Simvastatin Acid						
AUC0-last ‡ (ng/mL*hr)	24	52.07	27.11 (58)	24	57.46	39.08 (61)
Cmax ‡ (ng/mL)	24	4.88	2.81 (58)	24	5.66	5.17 (73)
AM = Arithmetic Mean SD: Standard Deviation CV% = 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale						

P153, Part II

	MK-0431D			Simvastatin + Sitagliptin		
Pharmacokinetic Parameter	**N**	**AM***	**SD (CV%)**	**N**	**AM***	**SD (CV%)**
Sitagliptin						
AUC0-∞ ‡ (nM*hr)	99	7994	1469 (18)	99	8128	1451 (17)
AUC0-last ‡ (nM*hr)	99	7907	1455 (18)	99	8036	1431 (17)
Cmax ‡ (nM)	99	948	268 (28)	99	975	287 (30)
Simvastatin						
AUC0-last ‡ (ng/mL*hr)	99	123.11	70.13 (59)	99	124.7	68.31 (57)
Cmax ‡ (ng/mL)	99	17.46	10.94 (60)	99	18.41	12.45 (68)
Simvastatin Acid						
AUC0-last ‡ (ng/mL*hr)	99	60.70	39.59 (66)	99	55.54	40.61 (69)
Cmax ‡ (ng/mL)	99	4.86	3.14 (65)	99	5.16	3.38 (66)
AM = Arithmetic Mean SD: Standard Deviation CV% = 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale						

Table 2 Summary of statistical analysis on the BE.

PK Parameter	Strength			
	100/80		100/10	
	GMR*	90% CI	GMR	90% CI
Sitagliptin				
AUC0-last (nM*hr)	0.99	(0.98, 1.00)	1.01	(0.99, 1.02)
Cmax (nM)	0.98	(0.94, 1.02)	1.03	(0.98, 1.07)
Simvastatin				
AUC0-last (ng/mL*hr)	0.99	(0.93, 1.05)	1.07	(0.99, 1.16)
Cmax (ng/mL)	0.98	(0.92, 1.06)	1.13	(1.05, 1.21)
Simvastatin Acid				
AUC0-last (ng/mL*hr)	0.93	(0.87, 0.98)	1.03	(0.96, 1.11)
Cmax (ng/mL)	0.95	(0.88, 1.02)	1.04	(0.97, 1.12)

*: geometric mean ratio (FDC / (Simvastatin + Sitagliptin))

Comments on the development program for FDC with sitagliptin 50 mg from the clinical pharmacology perspective

The development of the FDC strengths of sitagliptin/simvastatin 50/10, 50/20 and 50/40 to permit dosing in patients with moderate renal impairment was raised by the FDA in Type C meting on September 30, 2010 (refer the meeting minute in Attachment 3). The sponsor agreed to develop those strengths as Phase IV commitment. (b) (4) The above data indicate that a BE study may not be needed and possible biowaiver request may be submitted as discussed during the Type C meeting. However, if substantial changes need to be made to develop FDC with sitagliptin 50 mg, a BE may be needed.

In conclusion, the new strengths needs to be developed and data to support its approval (e.g., *in vivo* and/or *in vitro* study) should be submitted to the Agency per the schedule in the approval letter.

Table 3 Summary of amount per tablet

	Strength	Amount per tablet (mg)		
		Total	Sitagliptin layer	Simvastatin layer
NDA data	100/10	500	400	100
	100/20*	600	400	200
	100/40*	800	400	400
	(b) (4)			
proposed development	(b) (4)			

*: biowaiver was granted by the ONDQA-Biopharmaceutics review team.

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/s/

SANG M CHUNG
09/16/2011

JAYABHARATHI VAIDYANATHAN
09/16/2011

CHANDRAHAS G G SAHAJWALLA
09/16/2011

CLINICAL PHARMACOLOGY REVIEW

NDA	202343
Submission Date(s)	December 3, 2010
Brand Name	(b) (4)™, MK-0431D
Generic Name	Sitagliptin phosphate+simvastatin tablet
Reviewers	Sang M. Chung, Ph.D.
Team Leader	Jayabharathi Vaidyanathan, Ph.D. (Acting)
OCP Division	Clinical Pharmacology II
OND Division	Metabolism and Endocrinology Products (DMEP)
Sponsor	Merck
Submission Type	505(b)(1), Standard
Formulation Strength(s)	100/10, 100/20, and 100/40 (mg sitagliptin / mg simvastatin)
Indication	Treatment with both sitagliptin and simvastatin
Dosage & Administration	Patients switching from co-administered sitagliptin (100 mg) and simvastatin (10, 20, or 40 mg) can initiate (b) (4) at the doses of sitagliptin and simvastatin already being taken. (b) (4) can be taken with or without food in the evening.

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 202343 for (b) (4)™ and finds it acceptable provided that 1) the Agency and the sponsor agree on the labeling and 2) there is no significant issue from the review of Office of Scientific Investigation.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The sponsor has submitted the NDA 202343 for (b) (4)™, fixed-dose combination (FDC) tablets of sitagliptin and simvastatin as a 505(b)(1), with the indication for whom treatment with both sitagliptin and simvastatin is needed. Sitagliptin and simvastatin have been approved for the treatment of Type 2 diabetes as Januvia™ since October 16, 2006 and for the treatment of dyslipidemia as Zocor™ since December 23, 1991, respectively.

The goal of development program is to demonstrate bioequivalence (BE) of sitagliptin, simvastatin and simvastatin acid exposure following (b) (4)™ administration compared to those of co-administration of sitagliptin and simvastatin (simvastatin+sitagliptin). Simvastatin is an inactive pro-drug and converted to its active form, simvastatin acid, after administration. Therefore, pharmacokinetic (PK) parameters of simvastatin acid should be considered as a primary endpoint for the BE assessment of simvastatin in addition to those of simvastatin. The BE is to bridge to (b) (4)™ from clinical safety and efficacy data of 1) sitagliptin, 2) simvastatin and 3) sitagliptin+simvastatin. The sponsor has not conducted a Phase 3 trial following (b) (4)™ or sitagliptin+simvastatin.

The proposed strengths are 100/10, 100/20 and 100/40 mg (mg sitagliptin / mg simvastatin). The tablet strengths containing 50 mg sitagliptin (i.e., 50/10, 50/20 and 50/40 mg) are currently in development and the sponsor agreed to submit the data by December 2011. Januvia™ has been approved for 100 mg once daily with the dose adjustment to 50 mg for patients with the moderate renal impairment and 25 mg with the severe renal impairment and end stage renal disease. Simvastatin™ dosing range is 5 to 40 mg once daily in the evening and 5 mg/day is recommended as the starting dose for patients with severe renal impairment. The sponsor proposes that (b) (4)™ is not recommended in patients with moderate or severe renal impairment or ESRD because FDC strengths are not available for the specific populations at this time.

A total of eight clinical pharmacology trials were conducted for (b) (4)™ as follows:

- two BE trials - one using the lowest strength (100/10 mg) and the other one using the highest strength (100/80 mg)

- one trial for the food effect on [(b) (4)]™ using the highest strength (100/80 mg)
- two relative bioavailability trials to explore preliminary formulations
- two trials for the drug-drug interaction assessment

Biowaiver was requested for middle strengths (100/20, 100/40) and has been granted by the ONDQA-Biopharmaceutic review team (refer Dr. John Z. Duan's review).

The BE of FDC was concluded referencing Januvia™+Zocor™ because the primary PK parameters (AUC and Cmax) of sitagliptin, simvastatin and simvastatin acid following the FDC met the regulatory BE goal post of 90% confidence interval (90% CI) (Table 1).

Table 1 Summary of statistical analysis on the BE.

	Tablet Strength			
	100/80		100/10	
PK Parameter	GMR*	90% CI	GMR	90% CI
Sitagliptin				
$AUC_{0\text{-last}}$ (nM*hr)	0.99	(0.98, 1.00)	1.01	(0.99, 1.02)
Cmax (nM)	0.98	(0.94, 1.02)	1.03	(0.98, 1.07)
Simvastatin				
$AUC_{0\text{-last}}$ (ng/mL*hr)	0.99	(0.93, 1.05)	1.07	(0.99, 1.16)
Cmax (ng/mL)	0.98	(0.92, 1.06)	1.13	(1.05, 1.21)
Simvastatin Acid				
$AUC_{0\text{-last}}$ (ng/mL*hr)	0.93	(0.87, 0.98)	1.03	(0.96, 1.11)
Cmax (ng/mL)	0.95	(0.88, 1.02)	1.04	(0.97, 1.12)

*: geometric mean ratio (FDC / (Simvastatin + Sitagliptin))

A high-fat breakfast did not affect sitagliptin exposure following [(b) (4)]™ (Table 2). Meanwhile, simvastatin AUC decreased by 24% and its Cmax increased by 20% with the high-fat breakfast. In addition, simvastatin acid AUC and Cmax increased by 37% and 116%, respectively, with the breakfast (Table 2). While, the clinical significance of the above exposure change in simvastatin and simvastatin acid is not known, [(b) (4)]™ is recommended to be taken in the evening as indicated in the simvastatin labeling.

Table 2 Summary of statistical analysis for the effect of food on the exposure of sitagliptin, simvastatin, and simvastatin acid after administration of [(b) (4)]™

	Fed/Fasted	
Pharmacokinetic Parameter	**GMR***	**90% CI**
Sitagliptin		
$AUC_{0\text{-last}}$	1.00	(0.98, 1.02)
Cmax	0.94	(0.87, 1.03)
Simvastatin		
$AUC_{0\text{-last}}$	0.76	(0.64, 0.90)
Cmax	1.20	(0.97, 1.48)
Simvastatin acid		
$AUC_{0\text{-last}}$	1.37	(1.16, 1.63)
Cmax	2.16	(1.84, 2.55)

*: geometric mean ratio

There was no significant drug interaction between sitagliptin and simvastatin. Digoxin exposure was significantly increased by sitagliptin+simvastatin. Patients receiving digoxin should be monitored when (b) (4)™ is co-administered.

The sponsor decided not to market the highest strength (100/80 mg) because simvastatin 80 mg dosing is limited only for patients who are currently taking 80 mg because of significantly higher rhabdomyolysis incidence compared to that of lower doses.

The sponsor submitted a full waiver for the pediatric assessment for the following aspects:

- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested,
- DMEP has not required sponsors of lipid-lowering medications to evaluate drugs' effectiveness in the general pediatric population to satisfy the requirements of PREA. (b) (4)
- Pediatric studies with sitagliptin are ongoing.

PeRC meeting was held on August 17, 2011 and the committee agreed on the above assessments.

Review of the Office of Scientific Investigation (OSI) on the pivotal BE studies is pending at this time.

In conclusion, the clinical pharmacology information of NDA 202343 is acceptable provided that review of OSI finds no significant issue on the pivotal BE studies.

2 Question-Based Review (QBR)

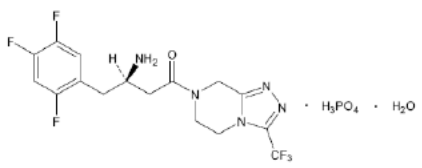
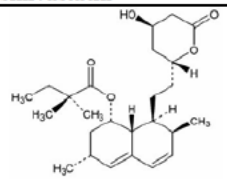
2.1 General Attributes of the Drug and Drug Product

(b) (4)™ is a bi-layer, film coated FDC tablets of sitagliptin and simvastatin. (b) (4)™ is indicated for patients switching from sitagliptin+simvastatin. (b) (4)™ is expected to improve compliance. The proposed strengths are 100/10, 100/20 and 100/40 (sitagliptin-mg/simvastatin-mg) and will submit the developmental tablets data containing 50 mg sitagliptin by December 2011 as agreed at the pre-NDA meeting.

General attributes of drugs

Properties of sitagliptin and simvastatin relevant to the clinical pharmacology are summarized in Table 3 from Januvia™ and Zocor™ labeling.

Table 3 Summary of labeling information related to properties of sitagliptin and simvastatin

	Sitagliptin	simvastatin
Structural formula		
M.W.	523.32	418.57
Solubility / Dissolution	• Soluble in water • ≥85% dissolution at 15 minutes for all tablet strengths at all pHs with or without surfactant	• Practically insoluble in water • Over 60 minutes to be dissolved more than 90%
Mode of action	Dipeptidyl peptidase-4 inhibitor	3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Adjunctive therapy to diet to 1) dyslipidemias except Types I and V and 2) reduction the risk of heart disease mortality
Pharmacokinetics	• Absolute bioavailability=87% • No food effect • Volume of distribution=198 L • Protein binding = 38% • 79% excreted unchanged in the urine • Terminal half-life=12.4 hours • Renal clearance=350 mL/min	• Availability to the general circulation is low (<5%) • Protein binding=95% • 13% and 60% of total radioactivity administered in urine and feces, respectively

FDC formulation development

A bilayer tablet was selected for (b) (4)™ (b) (4) between sitagliptin and simvastatin. Two exploratory (b) (4)™ formulations (MK-0431D D1 and D2) were developed (b) (4) MK-0431D D2 led the final market composition. Clinical pharmacology trials related to the formulation development for MK-0431D are summarized in Table 4.

Table 4 Summary of clinical pharmacology trials related to formulation development for MK-0431D

Study Type	Protocol Number
MK-0431D Tablet Probe Formulation Study • Part I: D1 vs. Januvia+generic simvastatin • Part II: D2 vs. Januvia+generic simvastatin	P154
MK-0431D Tablet Definitive Bioequivalence Study Part I: probe formulation vs. Januvia™+Zocor™ **Part II: definitive bioequivalence study** for 100-mg/80-mg vs. Januvia™+Zocor™	P153
MK-0431D Tablet Food Effect Study	P155
MK-0431D Tablet Definitive Bioequivalence Study for 100-mg/10-mg vs. Januvia™+Zocor™	P255

In addition, the sponsor submitted results of three drug-drug interaction trials as follows:

Effect of sitagliptin 200 mg QD for 5 days on simvastatin 20 mg†	P025
Effect of simvastatin 80 mg QD for 7 days on sitagliptin 100 mg	P168
Effect of co-administration of sitagliptin and simvastatin on digoxin	P169
†: Component of filing with the original sitagliptin (Januvia™) in Dec-2005	

Formulations used to support MK-0431D programs are summarized in Table 5. Components and composition of the final market image of MK-0431D are summarized in Appendix 4.1.

Table 5 Summary of formulations used to support MK-0431D program

Study No.	Protocol Description	Drug[†]	Potency	Formulation Number
P154	Probe BC Study	MK-0431D D2 (sitagliptin/simvastatin)	100-mg/10-mg	WL00032799
		MK-0431D D2 (sitagliptin/simvastatin)	100-mg/80-mg	WL00032800
		MK-0431D D1 (sitagliptin/simvastatin)	100-mg/10-mg	DL00012660
		MK-0431D D1 (sitagliptin/simvastatin)	100-mg/80-mg	DL00012661
		JANUVIA™	100-mg	Mkt. Product Lot#: X4875
		Simvastatin	10-mg	Mkt. Product Lot#: WM0108013
		Simvastatin	80-mg	Mkt. Product Lot#: WM0808008
P153	Probe BC / Definitive BE Study	MK-0431D (sitagliptin/simvastatin)	100-mg/80-mg	WL00033417
		JANUVIA™	100-mg	Mkt. Product WL00032275
		ZOCOR™	80-mg	Mkt. Product WL00034939 (Part I) WL00036141 (Part II)
P255	Low-Dose Definitive BE Study	MK-0431D (sitagliptin/simvastatin)	100-mg/10-mg	WL00033441
		JANUVIA™	100-mg	Mkt. Product WL00037058
		ZOCOR™	10-mg	Mkt. Product WL00038441
P155	Food Effect Study	MK-0431D (sitagliptin/simvastatin)	100-mg/80-mg	WL00033417
P168	DDI Study	JANUVIA™	100-mg	Mkt. Product Lot#: Y1909
		ZOCOR™	80-mg	Mkt. Product Lot#:X5768
P169	Digoxin DDI study	ZOCOR™	80-mg	Mkt. Product Lot#: Y2107
		JANUVIA™	100-mg	Mkt. Product Lot#: Y1911
		Digoxin (Lanoxin®)	0.25-mg	Mkt. Product Lot#: A38580

[†] All MK-0431D formulations refer to MK-0431D D2 formulation, unless otherwise specified.
Mkt.= Marketed

[Sec. 3.3]

2.2 Extrinsic Factors

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

2.2.1.1 Drug-Drug Interaction

Effect of simvastatin on sitagliptin

The effect of simvastatin 80 mg QD for 7 days on sitagliptin 100 mg was evaluated in an open-label, randomized, 2-period, 2-treatment, crossover study design in healthy male (n=5) and female (n=5) subjects (Study P168). The following two treatments were administered after an overnight fasting condition with a minimum 5-day washout:

- Treatment A: sitagliptin 100 mg
- Treatment B: simvastatin 80 mg once daily in the morning Days 1 through 7 and sitagliptin 100 mg on Day 5

Formulations used for the study are as follows:

Drug	Potency	Lot Number	Dosage Form	Expiration Date
Sitagliptin†	100-mg	Y1909	Tablet	Sep-2011
Simvastatin‡	80-mg	X5768	Tablet	Sep-2010
† JANUVIA™ is manufactured by Merck ‡ ZOCOR® is manufactured by Merck				

The primary endpoints were sitagliptin $AUC_{0-\infty}$, AUC_{0-last}, and C_{max}. The effect of simvastatin on sitagliptin was evaluated using the BE approach for the comparability between Treatment A and B. sitagliptin PK parameters and results of statistical analysis are summarized in Table 6. Sitagliptin plasma concentration-time profiles and individual ratios of PK parameters are shown in Figure 1. The results indicate that there is no significant impact of simvastatin 80 mg QD for 7 days on sitagliptin 100 mg.

Table 6 Summary statistics for plasma sitagliptin PK parameters and statistical analysis (P168)

Pharmacokinetic Parameter	Simvastatin + Sitagliptin			Sitagliptin			(Simvastatin + Sitagliptin) / Sitagliptin	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ ‡ (nM hr)	10	7302	(6426, 8297)	10	7217	(6351, 8201)	**1.01**	(0 97, 1 05)
AUC_{0-last} ‡ (nM hr)	10	7222	(6346, 8219)	10	7134	(6269, 8119)	**1.01**	(0 97, 1 05)
C_{max} ‡ (nM)	10	913	(787, 1059)	10	816	(704, 946)	**1.12**	(1 00, 1 26)
T_{max} ‖ (hr)	10	2 5	(0 5, 5 0)	10	2 0	(0 5, 5 0)		
Apparent $t_{1/2}$ § (hr)	10	10 4	1 6	10	11 5	1 2		
‡ Back-transformed least-squares mean and CI from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio ([Simvastatin + Sitagliptin]/Sitagliptin) ‖ Median (min, max) reported for T_{max} § Harmonic mean, jack-knife standard deviation reported for apparent $t_{1/2}$ GM = Geometric Least-Squares Mean; CI: Confidence Interval								

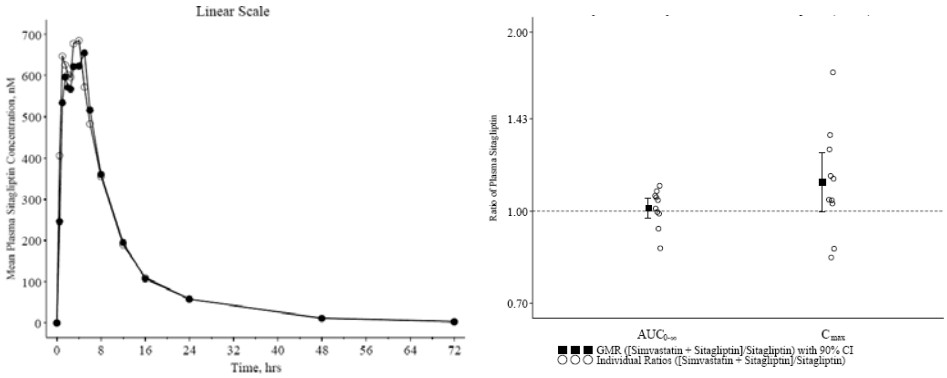


Figure 1 **Mean plasma concentration-time profiles (left) and individual GMR of PK parameters (right)**

Effect of sitagliptin+simvastatin on digoxin

The effect of sitagliptin 100 mg + simvastatin 80 mg QD for 9 days on digoxin 0.5 mg was evaluated in an open-label, randomized, 2-period, 2-treatment, crossover study design in healthy male (n=8) and female (n=6) subjects (Study P169). The following two treatments were administered after an overnight fasting condition with a minimum 5-day washout:

- Treatment A: digoxin 0.5 mg
- Treatment B: sitagliptin 100 mg + simvastatin 80 mg once daily in the morning Days 1 through 9 and digoxin 0.5 mg on Day 5

Formulations used for the study are as follows:

Drug	Potency	Dosage Form	Expiration Date	Lot Number	Manufacturer
Simvastatin (ZOCOR®)	80-mg	Tablet	1-Apr-2011	Y2107	Merck & Co Inc
Sitagliptin (JANUVIA	100-mg	Tablet	1-Sep-2011	Y1911	Merck & Co Inc
Digoxin (Lanoxin®)	0 25-mg	Tablet	1-May-2011	A38580	GlaxoSmithKline

The primary endpoints were digoxin $AUC_{0-\infty}$, AUC_{0-last}, and C_{max}. The effect of simvastatin+sitagliptin on digoxin was evaluated using the BE approach for the digoxin exposure comparability between Treatment A and B. Digoxin PK parameters and results of statistical analysis are summarized in Table 7. Digoxin plasma concentration-time profiles and individual ratios of digoxin PK parameters are shown in Figure 2. The results indicate that sitagliptin 100 mg + simvastatin 80 mg increase digoxin AUC by 26% and Cmax by 41% compared to those of digoxin alone.

The impact of co-administration of sitagliptin and simvastatin on digoxin is greater than that of sitagliptin alone (refer the following Januvia™ labeling on digoxin).

> *Digoxin:* Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of JANUVIA daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C_{max} by 18%.

Therefore, the co-administration should be done with caution in patients with digoxin therapy.

Table 7 Summary statistics for plasma digoxin PK parameters and statistical analysis (P169)

Pharmacokinetic Parameter	Digoxin + Simvastatin + Sitagliptin			Digoxin			(Digoxin + Simvastatin + Sitagliptin) / Sitagliptin	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0\text{-last}}$ ‡ (nM hr)	12	40 10	(35 47, 45 33)	13	31 76	(28 18, 35 79)	**1.26**	(1 13, 1 41)
C_{max} ‡ (nM)	12	3 57	(3 03, 4 21)	13	2 52	(2 15, 2 96)	**1.41**	(1 20, 1 66)
T_{max} ‖ (hr)	12	1 0	(0 5, 2 0)	13	1 0	(1 0, 2 0)		
Apparent $t_{1/2}$ § (hr)	12	34 4	13 5	13	44 9	19 2		

‡ Back-transformed least-squares mean and CI from linear mixed effects model performed on natural log-transformed values;
GMR = Geometric least-squares mean ratio ([Simvastatin + Sitagliptin]/Sitagliptin)
‖ Median (min, max) reported for T_{max}
§ Harmonic mean, jack-knife standard deviation reported for apparent $t_{1/2}$
GM = Geometric Least-Squares Mean;
CI: Confidence Interval
rMSE: Root mean square error on log-scale from linear mixed effect model When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation

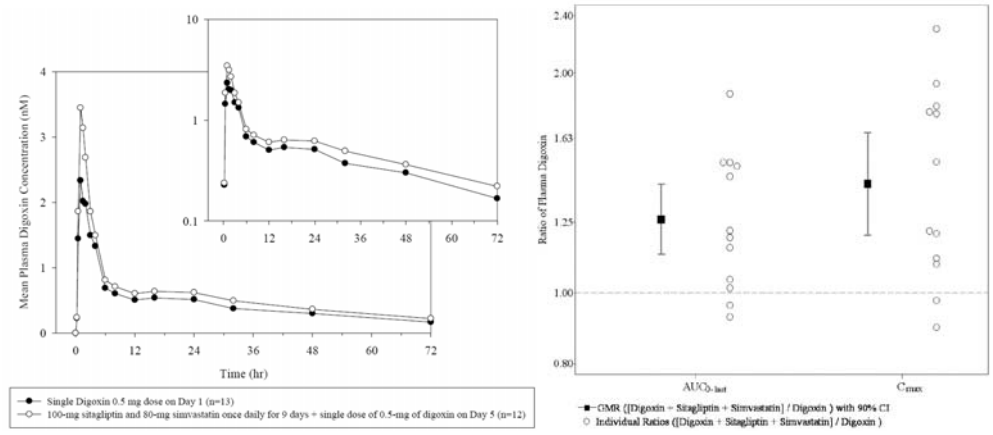


Figure 2 Mean digoxin plasma concentration-time profiles (left) and individual GMR of PK parameters (right)

Reviewer's Comment: The minimum 5 days may not be sufficient washout period considered up to 45 hours digoxin half-life (Table 7). Therefore, the results of statistical analysis may not be reliable. However, labeling on cautions based on the relative digoxin exposure change between treatments seems acceptable.

Effect of sitagliptin on simvastatin

The study results were provided as supplemental information because those were submitted with the sitagliptin original NDA and Januvia™ already had labeling on simvastatin as follows:

> *Simvastatin:* Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, was not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

In brief, the effect of sitagliptin 200 mg as 2x100 mg QD for 5 days on simvastatin 20 mg was estimated in healthy subjects (n=12) (Study P025) and primary results are shown in Table 8. Refer the clinical pharmacology review for the original NDA for the details of study results.

Table 8 Summary statistics for simvastatin PK parameters (N=12) (P025)

Pharmacokinetic Parameters	Geometric Mean†		GMR† (90% CI) or p-Value
	Simvastatin + Sitagliptin	Simvastatin	Simvastatin + Sitagliptin/ Simvastatin
Active HMG-CoA Reductase Inhibitors			
$AUC_{(0\text{-last})}$ (ng-eq hr/mL)	61.14	57.93	1.06 (0.88, 1.26)
C_{max} (ng-eq /mL)	12.23	13.05	0.94 (0.66, 1.34)
T_{max} (hr)	1.8‡	1.8‡	0.663§
Total HMG-CoA Reductase Inhibitors			
$AUC_{(0\text{-last})}$ (ng-eq hr/mL)	161.6	159.6	1.01 (0.80, 1.28)
C_{max} (ng-eq /mL)	46.78	53.06	0.88 (0.59, 1.31)
T_{max} (hr)	1.8‡	1.3‡	0.630§
Simvastatin Acid			
$AUC_{(0\text{-last})}$ (ng·hr/mL)	9.13	8.17	1.12 (0.93, 1.35)
C_{max} (ng/mL)	0.860	0.809	1.06 (0.86, 1.32)
T_{max} (hr)	4.0‡	4.0‡	0.290§
Simvastatin			
$AUC_{(0\text{-last})}$ (ng·hr/mL)	11.56	13.53	0.85 (0.60, 1.22)
C_{max} (ng/mL)	2.940	3.659	0.80 (0.51, 1.26)
T_{max} (hr)	1.5‡	1.0‡	0.639§

† Back-transformed from the log scale.
‡ Median.
§ p-Value: p-Value of between treatment comparison using rank analysis.
GMR=Geometric Mean Ratio;
CI=Confidence Interval.

2.2.1.2 Food Effect

The effect of food on the final market composition (FMC) of fixed-dose combination tablet was evaluated using an open-label, randomized, 2-period, 2-treatment, single-dose, crossover study in healthy subjects (n=18 male and 14 female) (Study P155). The following two treatments were administered with a minimum 5-day washout:

- Treatment A: MK-0431D 100/80 mg administration under fasted condition
- Treatment B: MK-0431D 100/80 mg administration under a standard high-fat breakfast

Formulations used for the study are as follows:

Drug	Potency	Formulation Number	Dosage Form	Control Number	Assay Potency Mean % of Claim (n=2)	
MK-0431D (sitagliptin/simvastatin)	100-mg / 80-mg	WL00033417	Tablet	WL00037796	Sitagliptin	Simvastatin
					95 8	100 2

The primary endpoints were sitagliptin, simvastatin, and simvastatin acid $AUC_{0-\infty}$, AUC_{0-last}, and C_{max}. The effect of food was evaluated using the BE approach for the comparability of exposure between Treatment A and B. Plasma concentration-time profiles of sitagliptin, simvastatin, and simvastatin acid are shown in Figure 3 and their PK parameters with statistical analysis are summarized in Table 9. Individual GMR are shown in Figure 4. The results indicate that there is no significant impact of food on sitagliptin. However, simvastatin AUC decreased by 24% and its Cmax increased by 20% with the high-fat breakfast. In addition, simvastatin acid AUC and Cmax increased by 37% and 116%, respectively, with the breakfast (Table 9). While, the clinical significance of the above exposure change in simvastatin and simvastatin acid is not known, (b) (4)™ is recommended to be taken in the evening as indicated in simvastatin labeling.

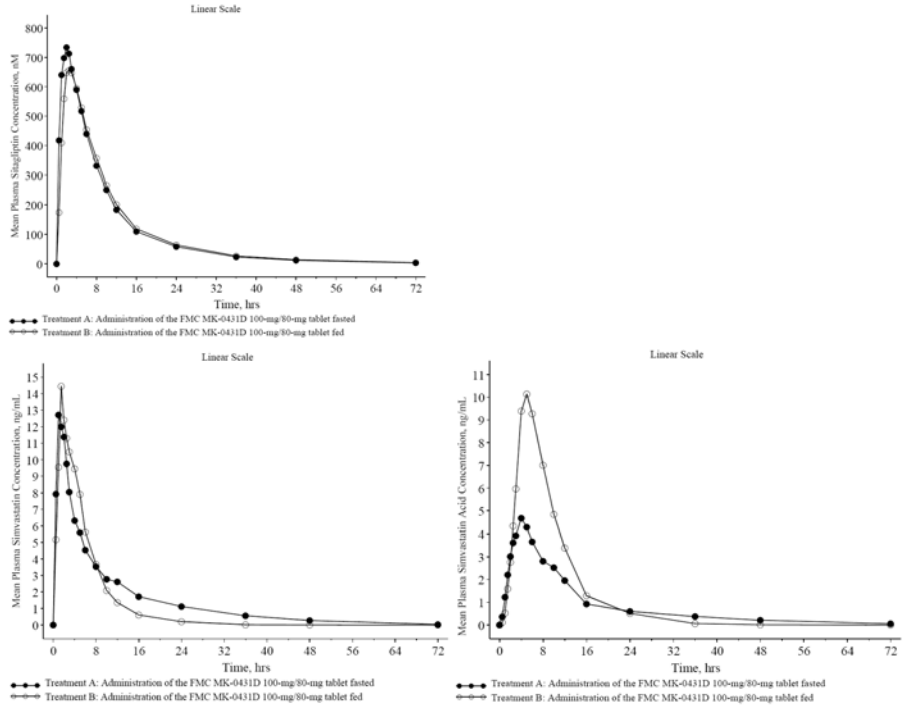


Figure 3 Mean plasma concentration-time profiles: sitagliptin (upper), simvastatin (lower left) and simvastatin acid (lower right)

Table 9 Summary Statistics and Statistical Comparisons of Plasma Sitagliptin, Simvastatin, and Simvastatin Acid Pharmacokinetic Parameters (P155)

	MK-0431D Fed			MK-0431D Fasted			MK-0431D Fed/Fasted	
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ ‡ (nM•hr)	32	7266	(6907, 7643)	32	7263	(6904, 7640)	1 00	(0 98, 1 02)
$AUC_{0\text{-last}}$ ‡ (nM•hr)	32	7163	(6808, 7536)	32	7165	(6810, 7539)	1 00	(0 98, 1 02)
C_{max} ‡ (nM)	32	764	(689, 846)	32	809	(731, 897)	0 94	(0 87, 1 03)
T_{max} ‖ (hr)	32	2 3	(0 5, 6 0)	32	2 0	(0 5, 5 0)		
Apparent Terminal $t_{1/2}$ § (hr)	32	12 9	2 7	32	12 6	2 8		
Simvastatin								
$AUC_{0\text{-last}}$ ‡ (ng/mL•hr)	32	67 39	(55 76, 81 45)	32	88 76	(73 44, 107 27)	0 76	(0 64, 0 90)
C_{max} ‡ (ng/mL)	32	16 89	(13 61, 20 97)	32	14 08	(11 35, 17 48)	1 20	(0 97, 1 48)
T_{max} ‖ (hr)	32	2 0	(0 5, 6 0)	32	1 5	(0 5, 5 0)		
Simvastatin Acid								
$AUC_{0\text{-last}}$ ‡ (ng/mL•hr)	32	67 67	(54 36, 84 23)	32	49 27	(39 58, 61 33)	1 37	(1 16, 1 63)
C_{max} ‡ (ng/mL)	32	9 33	(7 44, 11 70)	32	4 31	(3 44, 5 41)	2 16	(1 84, 2 55)
T_{max} ‖ (hr)	32	5 0	(2 3, 8 0)	32	4 0	(2 0, 12 0)		

† rMSE: Root mean square error on log-scale from linear mixed effect model When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation ‡ Back-transformed least-squares mean and CI from mixed effect model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D Fed/MK-0431D Fasted) ‖ Median (min, max) reported for T_{max} § Harmonic mean, jack-knife standard deviation reported for apparent terminal $t_{1/2}$ GM = Geometric Least-Squares Mean; CI = Confidence Interval

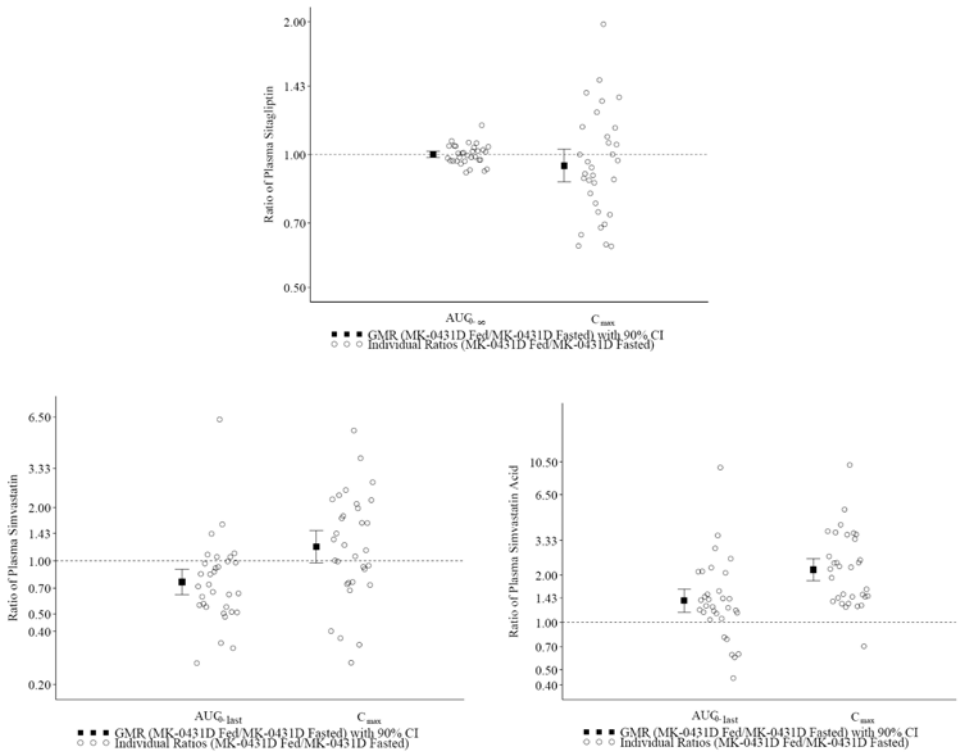


Figure 4 individual GMR of PK parameters; sitagliptin (upper), simvastatin (lower right) and simvastatin acid (lower right)

Reviewer's Comment:
The sponsor concluded that the food effect on simvastatin and simvastatin acid was not clinically significant. The sponsor referred Simcor™ (FDC of niacin extended-release and simvastatin) labeling (see the following table) for their conclusion and its labeling indicates that there is no dose adjustment for up to 84% increase in simvastatin acid Cmax in the drug interaction as shown in the following table.

The sponsor's conclusion is not acceptable as follows:

- The food affected AUCs of simvastatin and simvastatin acid in opposite direction (Table 9) and its clinical impact is not known.
- Statin dose adjustment should be assessed using both statin exposure data and muscle related adverse events data because exposure data of parent compound alone may not be sufficient enough to quantitatively predict myopathy/rhabdomyolysis, the most serious statin adverse events.
- For Simcor™, there was 24-week Phase 3 study to assess the efficacy and safety in addition to the exposure change data.

(part of Table 5 for drug interaction of Simcor™ labeling)

Coadministered Drug or Grapefruit Juice	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Simvastatin	Geometric Mean Ratio (Ratio* with / without coadministered drug) No Effect = 1.00		
				AUC	C_{max}
No dosing adjustments required for the following:					
Fenofibrate	160 mg QD for 14 days	80 mg QD on Days 8-14	simvastatin acid	0.64	0.89
			simvastatin	0.89	0.83
Niacin extended-release[b]	2 g single dose	20 mg single dose	simvastatin acid	1.6	1.84
			simvastatin	1.4	1.08
Propranolol	80 mg single dose	80 mg single dose	total inhibitor	0.79	↓ from 33.6 to 21.1 ng·eq/mL
			active inhibitor	0.79	↓ from 7.0 to 4.7 ng·eq/mL

2.3 General Biopharmaceutics

2.3.1 Is the proposed to-be-marketed fixed dose formulation bioequivalent to the co-administration of sitagliptin and simvastatin formulations?

The sponsor conducted an exploratory BE for FMC of MK-0431D 100/80 mg using a small number of subject (Part I; n=24) before the formal study (Part II). The preliminary results indicate that pharmacokinetics of sitagliptin and simvastatin acid following MK0431D 100/80 mg met the BE criteria compared to those of Januvia™ 100 mg + Zocor™ 80 mg (see the individual study synopsis for PK parameters and statistical analysis in Appendix 4.2) . Meanwhile, simvastatin AUC following MK0431 met the BE criteria, but upper 90% CI of simvastatin Cmax (1.26) was out of the BE goal post (1.25). Lack of statistical power with insufficient number of subject for its variability appears to lead the BE failure for Cmax.

BE demonstration of MK-0431D 100/80 mg

The exposure comparability of sitagliptin, simvastatin and simvastatin acid following the FMC of MK-0431D 100/80 mg tablet was assessed in an open-label, randomized, 2-part, 2-period, 2-treatment, single dose, crossover study referencing that of Januvia™ 100 mg + Zocor™ 80 mg after an overnight fasting condition in healthy subjects (n=61 male, 39 female) (Study P153).

Formulations used for the study are as follows:

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency (%) (n=2) Sitagliptin	Assay Potency (%) (n=2) Simvastatin
MK-0431D	100 mg/80 mg	WL00033417	Tablet	WL00035429	95.8	100.2
Sitagliptin Phosphate	100 mg	WL00032275	Tablet	WL00035431	100.9	-
Simvastatin	80 mg	WL00036141	Tablet	WL00035430	-	100.1

Plasma concentration-time profiles of sitagliptin, simvastatin and simvastatin acid are shown in Figure 5. Their pharmacokinetic parameters are summarized with statistical analysis for the BE assessment in Table 10. Individual GMR for each PK parameters are shown in Figure 6. The results indicate that PK parameters of sitagliptin, simvastatin and simvastatin acid following MK-0431D 100/80 mg met the BE criteria referencing those of Januvia™ 100 mg + Zocor™ 80 mg.

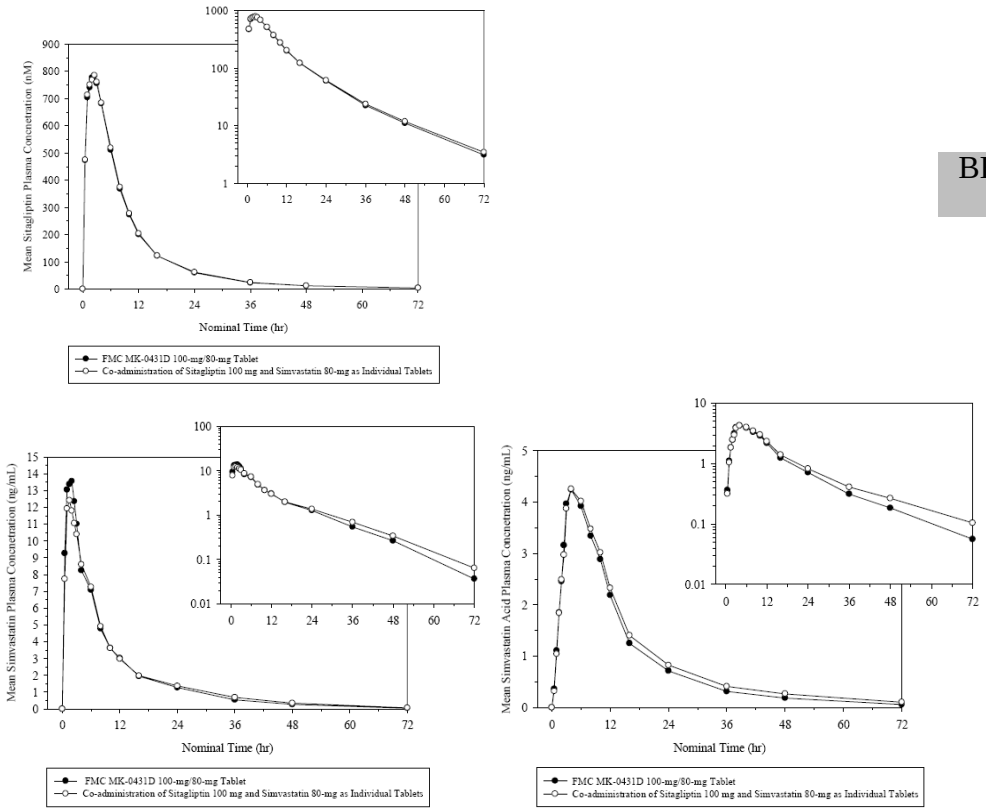


Figure 5 Mean plasma concentration-time profiles: sitagliptin (upper), simvastatin (lower left) and simvastatin acid (lower right)

Table 10 Summary Statistics and Statistical Comparisons for the Plasma PK Parameters of Sitagliptin, Simvastatin and Simvastatin Acid (P153, Part II)

	MK-0431D			Simvastatin + Sitagliptin			MK-0431D / (Simvastatin + Sitagliptin)	
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ ‡ (nM*hr)	99	7882	(7611, 8162)	99	7991	(7716, 8275)	0 99	(0 98, 1 00)
$AUC_{0\text{-last}}$ ‡ (nM*hr)	99	7795	(7527, 8073)	99	7900	(7629, 8181)	0 99	(0 98, 1 00)
C_{max} ‡ (nM)	99	916	(865, 969)	99	934	(882, 988)	0 98	(0 94, 1 02)
T_{max} ‖ (hr)	99	2 0	(0 5, 6 0)	99	2 0	(0 5, 6 0)		
Apparent terminal $t_{1/2}$ § (hr)	99	11 4	3 3	99	12 1	3 3		
Simvastatin								
$AUC_{0\text{-last}}$ ‡ (ng/mL*hr)	99	106 82	(95 93, 118 96)	99	108 04	(97 02, 120 31)	0 99	(0 93, 1 05)
C_{max} ‡ (ng/mL)	99	14 96	(13 31, 16 81)	99	15 19	(13 52, 17 07)	0 98	(0 92, 1 06)
T_{max} ‖ (hr)	99	1 5	(0 5, 12 0)	99	2 0	(0 5, 8 0)		
Simvastatin Acid								
$AUC_{0\text{-last}}$ ‡ (ng/mL*hr)	99	51 15	(45 30, 57 74)	99	55 20	(48 90, 62 32)	0 93	(0 87, 0 98)
C_{max} ‡ (ng/mL)	99	4 08	(3 62, 4 60)	99	4 30	(3 82, 4 84)	0 95	(0 88, 1 02)
T_{max} ‖ (hr)	99	4 0	(2 5, 12 0)	99	4 0	(2 0, 12 0)		

‡ Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D / [Simvastatin + Sitagliptin]) ‖ Median (min, max) reported for T_{max} § Harmonic mean, jack-knife standard deviation reported for apparent terminal $t_{1/2}$ GM = Geometric Least-Squares Mean, CI: Confidence Interval

(ID=448 terminated after treatment B prior period 2 because of a protocol violation with alcohol consumption and ID=478 terminated after treatment A because of positive drug screen prior period 2.)

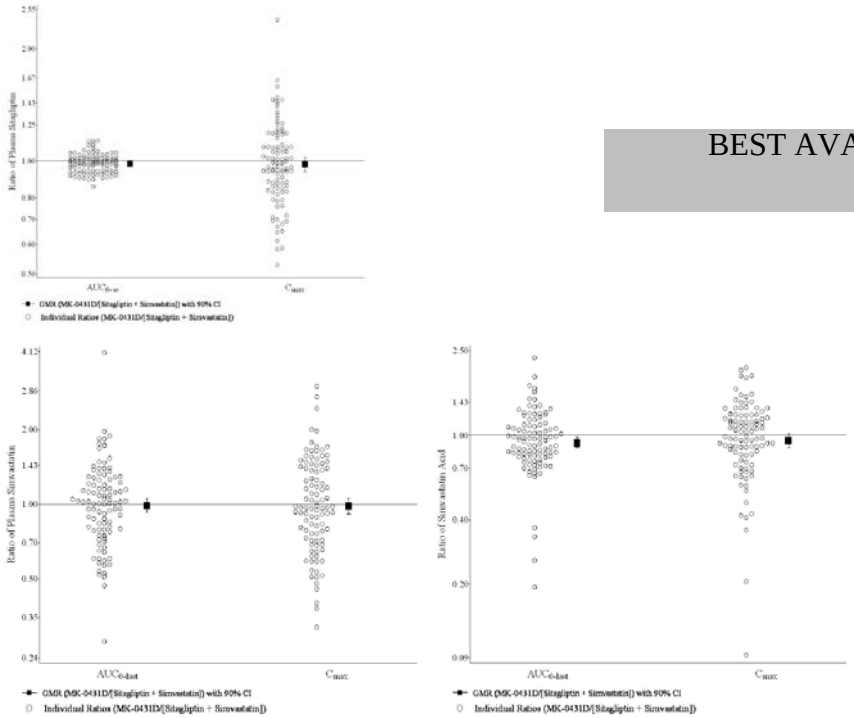


Figure 6 individual GMR of PK parameters: sitagliptin (upper), simvastatin (lower left) and simvastatin acid (lower right)

BE demonstration of 100/10 mg

The exposure comparability of sitagliptin, simvastatin and simvastatin acid following the FMC of MK-0431D 100/10 mg tablet was assessed in an open-label, randomized, 2-part, 2-period, 2-treatment, single dose, crossover study referencing that of Januvia 100 mg + Zocor 10 mg after an overnight fasting condition in healthy subjects (n=41 male, 59 female) (Study P255).

Formulations used for the study are as follows:

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency (Mean % of Claimed) (n=X)†	
					Sitagliptin	Simvastatin
MK-0431D	100-mg/10-mg	WL00033441	Tablet	WL00038476	100.1	100.2
Sitagliptin Phosphate (Januvia)	100-mg	WL00037058	Tablet	WL00038476	100.5	--
Simvastatin (Zocor)	10-mg	WL00038441	Tablet	WL00038476	--	99.4
N=2 for FMX MK-0431D tablet; n=78 for 100-mg sitagliptin tablet, n=2 for simvastatin (Zocor) tabelt						

Plasma concentration-time profiles of sitagliptin, simvastatin and simvastatin acid are shown in Figure 7. Their pharmacokinetic parameters are summarized with statistical analysis for the BE assessment in Table 11 and individual GMR of each PK parameters in Figure 8. The results indicate that pharmacokinetic parameters of sitagliptin, simvastatin and simvastatin acid following MK-0431D 100/10 mg met the BE criteria referencing those of Januvia™ 100 mg + Zocor™ 10 mg.

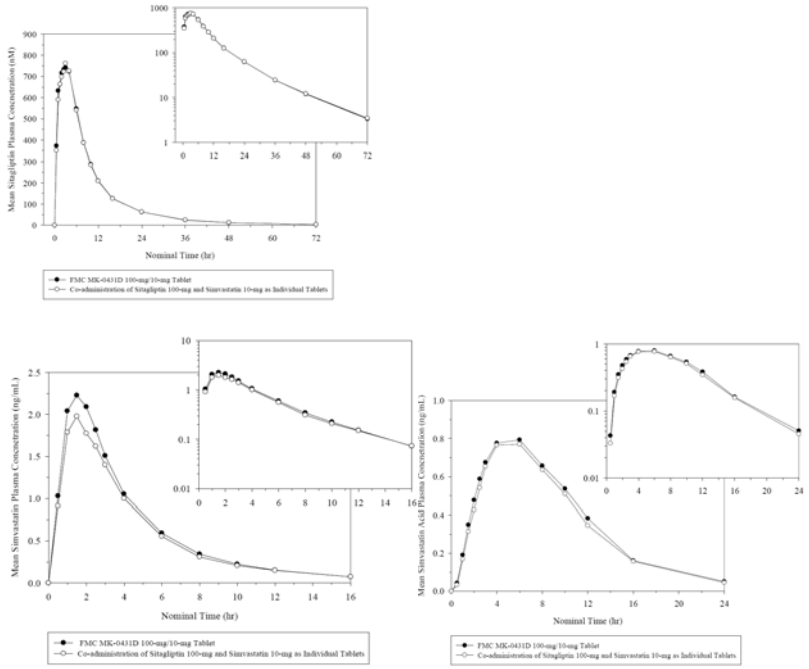


Figure 7 Mean plasma concentration-time profiles: sitagliptin (upper), simvastatin (lower left) and simvastatin acid (lower right)

Table 11 Summary Statistics and Statistical Comparisons for the PK Parameters of Sitagliptin, Simvastatin and Simvastatin Acid (P255)

	MK-0431D			Simvastatin + Sitagliptin			MK-0431D / (Simvastatin + Sitagliptin)	
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ ‡ (nM*hr)	94	8052	(7789, 8324)	97	7978	(7718, 8246)	1 01	(0 99, 1 02)
AUC_{0-last} ‡ (nM*hr)	94	7959	(7698, 8229)	97	7876	(7618, 8142)	1 01	(1 00, 1 03)
C_{max} ‡ (nM)	95	897	(850, 946)	97	872	(827, 920)	1 03	(0 98, 1 07)
T_{max} ‖ (hr)	95	2 5	(0 5, 4 1)	97	2 5	(0 5, 6 0)		
Apparent Terminal $t_{1/2}$ § (hr)	94	11 6	3 2	97	11 7	3 4		
Simvastatin								
AUC_{0-last} ‡ (ng/mL*hr)	95	8 55	(7 49, 9 77)	97	7 98	(6 99, 9 10)	1 07	(0 99, 1 16)
C_{max} ‡ (ng/mL)	95	2 25	(1 98, 2 55)	97	1 99	(1 75, 2 26)	1 13	(1 05, 1 21)
T_{max} ‖ (hr)	95	1 5	(0 5, 6 0)	97	1 5	(0 5, 12 0)		
Simvastatin Acid								
AUC_{0-last} ‡ (ng/mL*hr)	95	7 08	(6 25, 8 03)	97	6 86	(6 06, 7 77)	1 03	(0 96, 1 11)
C_{max} ‡ (ng/mL)	95	0 77	(0 69, 0 87)	97	0 74	(0 66, 0 83)	1 04	(0 97, 1 12)
T_{max} ‖ (hr)	95	6 0	(3 0, 10 0)	97	6 0	(3 0, 12 0)		

‡ Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D / [simvastatin + sitagliptin]) ‖ Median (min, max) reported for T_{max} § Harmonic mean, jack-knife standard deviation reported for apparent terminal $t_{1/2}$ GM = Geometric Least-Squares Mean, CI: Confidence Interval

AN0023 (treatment B only), AN0024 (treatment A only), AN0030 (treatment B only), AN0046 (treatment B only), AN0095 (treatment B only), AN0100 withdrew consent and AN0094 (treatment A only) was removed from the study due to a protocol violation (Positive Urine Drug Screen). GMR was based on the balanced data only.

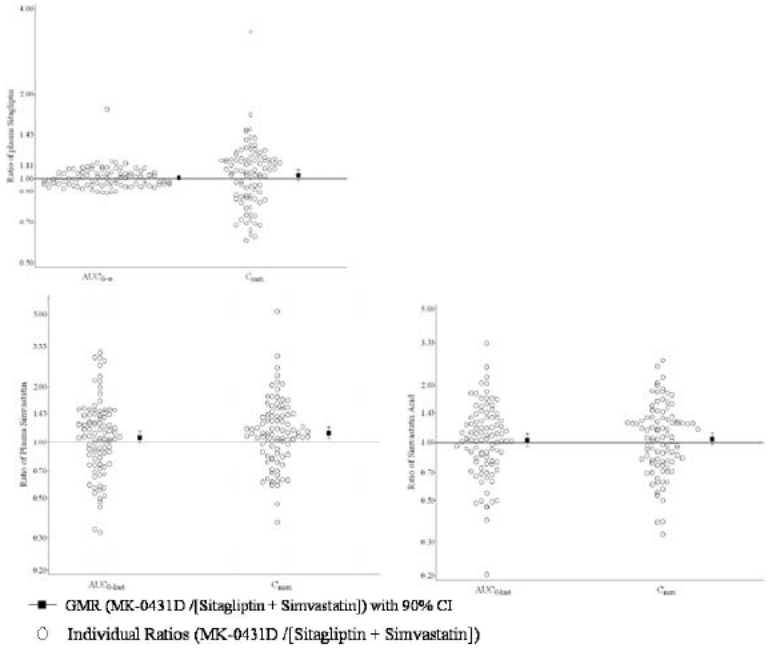


Figure 8 Individual GMR of PK parameters: sitagliptin (upper), simvastatin (upper left) and simvastatin acid (lower right)

Relative bioavailability studies to explore preliminary formulation for MK-0431D

The sponsor assessed *in vivo* performance of two preliminary formulations for MK-0431D; MK-0431D1 (D1) and MK-0431D2 (D2). D1 and D2 formulations contained the (b) (4)

The relative bioavailability of sitagliptin, simvastatin and simvastatin acid following D1 or D2 referencing those of Januvia + generic simvastatin was assessed in a 2-part, open-label, randomized, 4-period, 4-treatment, crossover study with healthy subjects. The following treatments were administered after an overnight fasting condition with a minimum of a 7-day washout interval between treatments:

Part I	
Treatment A	MK-0431D 100-mg/10-mg D1 formulation
Treatment B	sitagliptin 100 mg + generic simvastatin 10 mg
Treatment C	MK-0431D 100-mg/80-mg D1 formulation
Treatment D	sitagliptin 100 mg + generic simvastatin 80 mg
Part II	
Treatment E	MK-0431D 100-mg/10-mg D2 formulation
Treatment F	sitagliptin 100 mg + generic simvastatin 10 mg
Treatment G	MK-0431D 100-mg/80-mg D2 formulation
Treatment H	sitagliptin 100 mg + generic simvastatin 80 mg

Formulations used for the study are as follows:

Drug	Part	Potency	Formulation Number	Assay Potency (%) (n=2) Sitagliptin	Assay Potency (%) (n=2) Simvastatin	Dosage Form	Control Number
MK-0431D D1	I	100-mg /10-mg	DL 00012660	101 1	102 9	Tablet	DL00013087
MK-0431D D1	I	100-mg /80-mg	DL00012661	100	103 4	Tablet	DL00013088
MK-0431D D2	II	100-mg/10-mg	DL00013044	99 8	99 7	Tablet	WL00032799
MK-0431D D2	II	100-mg/80-mg	DL00013045	98 3	100 9	Tablet	WL00032800

Drug	Potency	Lot Number	Dosage Form	Expiration Date	Manufacturer
Simvastatin	80-mg	WM0808008	Tablet	01-Mar-2010	Aurobindo Pharma Limited
Simvastatin	10-mg	WM0108013	Tablet	01-Feb-2010	Aurobindo Pharma Limited
Sitagliptin	100-mg	X4875	Tablet	01-Sep-2010	Merck & Co Inc

Pharmacokinetic parameters of sitagliptin, simvastatin and simvastatin acid are summarized in Table 12 with statistical comparisons. Both preliminary formulation show significantly higher bioavailability for simvastatin and simvastatin acid compared to those of co-administration (Table 12 for D1 and Table 13 for D2). The sponsor suspected that the higher bioavailability of preliminary formulations was related to simvastatin generic formulations. Based on these results, the sponsor selected FMC (D2 formulation) and assessed its BE through the pivotal studies of P153 and P255.

Table 12 Summary Statistics and Statistical Comparisons for the PK Parameters of Sitagliptin, Simvastatin and Simvastatin Acid (P154, Part I)

100-mg/10-mg

	MK-0431D D1			Simvastatin + Sitagliptin			MK-0431D D1/ (Simvastatin + Sitagliptin)	
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
AUC0-∞ † (nM.hr)	16	7869	(7313, 8467)	18	7597	(7069, 8164)	1.04	(1.00, 1.08)
AUC0-last † (nM.hr)	16	7801	(7254, 8389)	18	7534	(7015, 8091)	1.04	(1.00, 1.08)
Cmax † (nM)	16	928	(810, 1064)	18	872	(766, 993)	1.06	(0 95, 1.19)
Tmax ‡ (hr)	16	1.8	(1.0, 6.0)	18	2 5	(1.0, 4.0)	.	
Apparent terminal t1/2 ‖ (hr)	16	12.2	2.3	18	11.3	1.5	.	
Simvastatin								
AUC0-last † (ng/mL.hr)	16	12.93	(10.05, 16.63)	18	9 24	(7.23, 11.80)	1.40	(1 18, 1.65)
Cmax † (ng/mL)	16	3.22	(2.48, 4.17)	18	2.83	(2.21, 3.62)	1.14	(0 90, 1.43)
Tmax ‡ (hr)	16	1.5	(0 5, 4.0)	18	1.0	(0 5, 3.0)		
Simvastatin Acid								
AUC0-last † (ng/mL.hr) Cmax	16	5.08	(3.78, 6.83)	18	4 14	(3.09, 5.54)	1.23	(1.05, 1.44)
† (ng/mL)	16	0.56	(0.43, 0.74)	18	0.44	(0.33, 0.57)	1.29	(1.09, 1.52)
Tmax ‡ (hr)	16	4.0	(3.0, 8.0)	18	4.0	(3.0, 8.1)		

† Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D D1/ [Simvastatin + Sitagliptin]) ‡ Median (min, max) reported for T_{max} ‖ Harmonic mean, jack-knife standard deviation reported for apparent terminal $t_{1/2}$ GM = Geometric Least-Squares Mean, CI: Confidence Interval

100-mg/80-mg

Pharmacokinetic Parameter	MK-0431D D1			Simvastatin + Sitagliptin			MK-0431D D1 / (Simvastatin+Sitagliptin)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
AUC0-∞ † (nM.hr)	17	7727	(7186, 8309)	19	7771	(7236, 8347)	0.99	(0 96, 1 03)
AUC0-last † (nM.hr)	17	7666	(7133, 8238)	19	7702	(7175, 8267)	1.00	(0 96, 1 03)
Cmax † (nM)	17	974	(853, 1113)	19	974	(857, 1106)	1.00	(0 90, 1 12)
Tmax ‡ (hr)	17	2.0	(1.0, 4.0)	19	2.0	(0.5, 3.0)	.	
Apparent terminal t1/2 ‖ (hr)	17	12.1	2.0	19	12.4	3.7	.	
Simvastatin								
AUC0-last † (ng/mL.hr)	17	107.23	(83.63, 137.47)	19	78.51	(61.63, 100.02)	1.37	(1 16, 1 60)
Cmax † (ng/mL)	17	23.39	(18.16, 30 13)	19	16.08	(12.63, 20.49)	1.45	(1 16, 1 82)
Tmax ‡ (hr)	17	1.0	(1.0, 6.0)	19	1.0	(0.5, 2.5)		
Simvastatin Acid								
AUC0-last † (ng/mL.hr)	17	42.95	(32.01, 57.63)	19	30.81	(23.08, 41.14)	1.39	(1 19, 1 63)
Cmax † (ng/mL)	17	4.25	(3.23, 5.58)	19	3.02	(2 31, 3.94)	1.41	(1 20, 1 65)
Tmax ‡ (hr)	17	6.0	(3.0, 10.0)	19	4.0	(2.5, 6.0)		

† Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D D1/ [Simvastatin + Sitagliptin]) ‡ Median (min, max) reported for T_{max} ‖ Harmonic mean, jack-knife standard deviation reported for apparent terminal $t_{1/2}$ GM = Geometric Least-Squares Mean, CI: Confidence Interval

Table 13 Summary Statistics and Statistical Comparisons for the Plasma PK Parameters of Sitagliptin, Simvastatin and Simvastatin Acid (P154, Part II)

100-mg/10-mg

Pharmacokinetic Parameter	MK-0431D D2			Simvastatin + Sitagliptin			MK-0431D D2 / (Simvastatin + Sitagliptin)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ † (nM hr)	17	8386	(7703, 9129)	19	8350	(7677, 9081)	1 00	(0 97, 1 04)
$AUC_{0\text{-last}}$ † (nM hr)	17	8313	(7638, 9047)	19	8256	(7593, 8977)	1 01	(0 97, 1 05)
C_{max} † (nM)	17	992	(863, 1142)	19	965	(842, 1107)	1 03	(0 94, 1 13)
T_{max} ‡ (hr)	17	1 5	(0 5, 4 0)	19	2 0	(1 0, 4 0)		
Apparent terminal $t_{1/2}$ ‖ (hr)	17	11 8	2 9	19	13 7	2 9		
Simvastatin								
$AUC_{0\text{-last}}$ † (ng/mL hr)	17	8 07	(6 38, 10 20)	19	6 51	(5 18, 8 19)	1 24	(1 07, 1 44)
C_{max} † (ng/mL)	17	2 04	(1 61, 2 59)	19	1 82	(1 45, 2 30)	1 12	(0 93, 1 34)
T_{max} ‡ (hr)	17	1 0	(0 5, 6 0)	19	1 5	(0 5, 4 0)		
Simvastatin Acid								
$AUC_{0\text{-last}}$ † (ng/mL hr)	17	6 24	(4 58, 8 50)	19	5 19	(3 83, 7 05)	1 20	(1 03, 1 40)
C_{max} † (ng/mL)	17	0 61	(0 44, 0 85)	19	0 55	(0 40, 0 77)	1 11	(0 92, 1 34)
T_{ma} ‡ (hr)	17	6 0	(3 0, 10 0)	19	4 0	(2 5, 10 0)		

† Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D D2/ [Simvastatin + Sitagliptin]) ‡ Median (min, max) reported for T_{max} ‖ Harmonic mean, jack-knife standard deviation reported for apparent terminal $t_{1/2}$ GM = Geometric Least-Squares Mean, CI: Confidence Interval

100-mg/80-mg

Pharmacokinetic Parameter	MK-0431D D2			Simvastatin + Sitagliptin			MK-0431D D2 / (Simvastatin + Sitagliptin)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ † (nM hr)	19	8436	(7757, 9175)	17	8340	(7661, 9079)	1 01	(0 97, 1 05)
AUC_{0-last} † (nM hr)	19	8360	(7688, 9090)	17	8287	(7614, 9019)	1 01	(0 97, 1 05)
C_{max} † (nM)	19	966	(843, 1108)	17	1097	(954, 1262)	0 88	(0 80, 0 97)
T_{max} ‡ (hr)	19	1 5	(0 5, 4 0)	17	2 0	(0 5, 3 0)		
Apparent terminal $t_{1/2}$ ‖ (hr)	19	13 1	1 9	17	12 4	1 7		
Simvastatin								
AUC_{0-last} † (ng/mL hr)	19	79 39	(63 11, 99 85)	17	54 69	(43 27, 69 13)	1 45	(1 25, 1 68)
C_{max} † (ng/mL)	19	13 25	(10 53, 16 69)	17	10 33	(8 14, 13 09)	1 28	(1 07, 1 54)
T_{max} ‡ (hr)	19	1 0	(0 5, 6 0)	17	1 0	(0 5, 3 0)		
Simvastatin Acid								
AUC_{0-last} † (ng/mL hr)	19	47 49	(34 99, 64 46)	17	31 58	(23 17, 43 03)	1 50	(1 29, 1 75)
C_{max} † (ng/mL)	19	4 15	(2 98, 5 78)	17	2 59	(1 85, 3 63)	1 60	(1 33, 1 92)
T_{max} ‡ (hr)	19	4 0	(3 0, 10 0)	17	4 0	(3 0, 10 0)		

† Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D D2/ [Simvastatin + Sitagliptin]) ‡ Median (min, max) reported for T_{max} ‖ Harmonic mean, jack-knife standard deviation reported for apparent terminal $t_{1/2}$ GM = Geometric Least-Squares Mean, CI: Confidence Interval

2.4 Analytical

2.4.1 Are bioanalytical studies acceptable?

Concentrations of sitagliptin, simvastatin, and simvastatin acid in plasma were determined using liquid chromatography-tandem mass spectrometric detection (LCMS/MS) methods. Bioanalytical methods to general the clinical pharmacology information are summarized as follows:

Summary of the bioanalytical methods for MK-0431D studies

Clinical Study Title	Clinical Study Number	Analytical Protocols	Anticoagulants
Probe formulation comparison and definitive bioequivalence study	153	ANI 9784.01[a] ANI 9287.04[b]	K_2EDTA[c] Sodium Heparin[d]
Probe formulation comparison study	154	ANI 9520.04[a] ANI 9287.04[b]	K_2EDTA[c] Sodium Heparin[d]
Food effect study	155	ANI 9784.01[a] ANI 9287.04[b]	K_2EDTA[c] Sodium Heparin[d]
Simvastatin interaction study	168	ANI 9784.01[a]	K_2EDTA[c]
Digoxin interaction study	169	ANI 9784.01[a]	K_2EDTA[c]

[a] Analytical method for MK-0431D.
[b] Analytical method for simvastatin and simvastatin acid.
[c] The anticoagulant used for sitagliptin sample collection.
[d] The anticoagulant used for Simvastatin/Simvastatin acid sample collection.

Representative data related to the bioanalytical studies are summarized in Table 14 and 15, and the quality of the data is acceptable.

Table 14 Figures of Merit for Sitagliptin; Linear Range: 1-1000 ng/mL

	n	Mean (%)
Intraday Accuracy with Calibration Standards[a]	6	92.92-104.04
Intraday Precision (CV) with Calibration Standards[a]	6	1.31-10.92
Intraday Accuracy with Quality Control Samples[a]	5	91.34-93.49
Intraday Precision (CV) with Quality Control Samples[a]	5	0.58-13.28
Interday Accuracy with Quality Control Samples[a]	30	94.0-94.2
Interday Precision (CV) with Quality Control Samples[a]	30	2.13-5.52
Interday Accuracy with Calibration Standards[b]	34	99.5-100.9
Interday Precision (CV) with Calibration Standards[b]	34	1.7-3.1
Interday Accuracy with Quality Control Samples[b]	45	97.9-102.7
Interday Precision (CV) with Quality Control Samples[b]	45	3.2-5.8
Extraction Recovery of Analytes[a]	6	74.71-85.55
Extraction Recovery of Internal Standard[a]	6	82.58
Accuracy of Dilution Integrity (20X)[a]	3	94.53
Precision (CV) of Dilution Integrity (20X)[a]	3	3.08
Accuracy of Processed Samples after 107 Hours at Room Temperature[a]	5	93.16-93.92
Precision (CV) of Processed Samples after 107 Hours at Room Temperature[a]	5	0.45-5.48
Accuracy of Quality Control Samples after 4 Freeze/Thaw Cycles at -20ºC[a]	5	97.76-100.98
Precision (CV) of Quality Control Samples after 4 Freeze/Thaw Cycles at -20ºC[a]	5	1.00-3.74
Accuracy of Quality Control Samples after 3 Freeze/Thaw Cycles at -80ºC[a]	5	104.06-104.87
Precision (CV) of Quality Control Samples after 3 Freeze/Thaw Cycles at -80ºC[a]	5	0.58-6.46
Accuracy of Samples Assayed after 26 hours at Room Temperature[a]	5	94.30-96.83
Precision (CV) of Samples Assayed after 26 hours at Room Temperature[a]	5	1.15-7.77
Difference (%) for Quality Control Samples Spiked with Concomitant Medications[a]	5	-6.16
Incurred Sample Re-analysis (% within specification)[a]	338	99.1

[a] Data from Assay Validation Report for sitagliptin [Ref. 5.3.1.4: 2159].
[b] Representative data from Study P153 (~4177 samples in 45 analytical runs).

Table 15 Figures of Merit for Simvastatin and Simvastatin Acid; Linear Ranges of 50.00-50000.00 pg /mL and 50.00-10000 pg/mL, respectively

	n	Simvastatin Mean (%)	Simvastatin Acid (Mean (%)
Interday Accuracy with Calibration Standards[a]	6	99.1-100.8	98.4-100.8
Interday Precision (CV) with Calibration Standards[a]	6	1.20-8.51	2.08-8.64
Intraday Accuracy with Quality Control Samples[a]	6	100.7-108.1	99.96-113.31
Intraday Precision (CV) with Quality Control Samples[a]	6	0.77-2.21	0.55-6.89
Interday Accuracy with Quality Control Samples[a]	42	93.7-97.4	95.0-100.4
Interday Precision (CV) with Quality Control Samples[a]	42	4.7-5.7	6.0-7.7
Interday Accuracy with Calibration Standards[b]	38	99.3-100.7	97.8-101.1
Interday Precision (CV) with Calibration Standards[b]	38	2.9-5.4	3.5-6.0
Interday Accuracy with Quality Control Samples[b]	38	95.8-100.5	96.9-103.8
Interday Precision (CV) with Quality Control Samples[b]	38	3.7-6.2	4.7-5.6
Extraction Recovery of Analytes[a]	6	45.03-60.77	43.95-54.65
Extraction Recovery of Internal Standard[a]	6	57.96	52.05
Accuracy of Dilution Integrity (2X)[a]	6	97.32	99.34
Precision (CV) of Dilution Integrity (2X)[a]	6	1.93	1.51
Accuracy of Reinjection Integrity after 68 hours at Room Temperature[a]	6	104.94-109.21	99.31-109.18
Precision (CV) of Reinjection Integrity after 68 hours at Room Temperature[a]	6	2.32-4.96	2.98-9.44
Accuracy of Quality Control Samples after 3 Freeze/Thaw Cycles – Storage at -70ºC[c]	5	90.0 – 104.9	96.2 – 103.6
Precision (CV) of Quality Control Samples after 3 Freeze/ Thaw Cycles – Storage at -70ºC[c]	5	0.8 -6.6	0.5- 6.8
Accuracy of Quality Control Samples Assayed after 4 hours at Room Temperature[c]	5	87.2 - 102.0	99.4 – 102.5
Precision (CV) of Quality Control Samples Assayed after 4 hours at Room Temperature[c]	5	2.2 - 2.8	1.4 - 2.3
Accuracy of Long Term Stability Quality Control Samples[c]	4	97-100.7	96.9 – 99.2
Precision of Long Term Stability Quality Control Samples[c]	4	1.6-3.0	0.6-1.7
Accuracy of Quality Control Samples Spiked with Concomitant Medications[a]	3	92.5 -94.32	93.88 – 99.47
Incurred Sample Re-analysis (% within specification)[b]	338	97.6	95.0

[a] Data from Assay Validation Report for Simvastatin and Simvastatin acid [Ref. 5.3.1.4: 2158]. [b] Representative data from Study P153 (~4036 samples in up to 38 analytical runs). [c] Data from Merck Validation Summary report for Simvastatin/Ezetimibe [Ref. 5.3.1.4: 2185].

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

4 Appendix

4.1 Components and composition of final market image of MK-0431D

100/10 mg

Components	Quality Reference¶	Function	Amount per tablet (mg)
MK-0431 (sitagliptin phosphate) layer			
Sitagliptin phosphate‡	-	Active	128.5‡
Dibasic calcium phosphate	USP-NF or Ph. Eur.		(b) (4)
Microcrystalline cellulose	USP-NF or Ph. Eur.		
Croscarmellose sodium	USP-NF or Ph. Eur.		
Sodium stearyl fumarate	USP-NF or Ph. Eur.		
Magnesium stearate	USP-NF or Ph. Eur.		
Sitagliptin layer tablet weight			(b) (4)
MK-0733 (simvastatin) layer			
Simvastatin (b) (4)	-	Active	10.00
(b) (4)	BP§		(b) (4)
	USP-NF or Ph. Eur.		
Butylated hydroxyanisole (BHA)	USP-NF or Ph. Eur.		
Ascorbic acid	USP-NF or Ph. Eur.		
Citric acid monohydrate	USP-NF or Ph. Eur.		
Lactose monohydrate	USP-NF or Ph. Eur.		
Pre-gelatinized corn starch	USP-NF or Ph. Eur.		
Microcrystalline cellulose	USP-NF or Ph. Eur.		
Magnesium stearate	USP-NF or Ph. Eur.		
Simvastatin layer tablet weight			(b) (4)
Film coating			
(b) (4)			
Total Tablet Weight			518.3

‡ 128.5 mg of sitagliptin phosphate is equal to 100.0 mg of sitagliptin

(b) (4)

§ Also noted in the ZOCOR® NDA as SD3A

¶ Compendial testing will be performed according to at least one of the compendia listed as applicable for the target market.

100/20 mg

Components	Quality Reference¶	Function	Amount per tablet (mg)
MK-0431 (sitagliptin phosphate) layer			
Sitagliptin phosphate‡	-	Active	128.5
Dibasic calcium phosphate	USP-NF or Ph. Eur.		(b) (4)
Microcrystalline cellulose	USP-NF or Ph. Eur.		
Croscarmellose sodium	USP-NF or Ph. Eur.		
Sodium stearyl fumarate	USP-NF or Ph. Eur.		
Magnesium stearate	USP-NF or Ph. Eur.		
Sitagliptin layer tablet weight			(b) (4)
MK-0733 (simvastatin) layer			
Simvastatin (b) (4)	-	Active	20.00
(b) (4)	BP§		(b) (4)
	USP-NF or Ph. Eur.		
Butylated hydroxyanisole (BHA)	USP-NF or Ph. Eur.		
Ascorbic acid	USP-NF or Ph. Eur.		
Citric acid monohydrate	USP-NF or Ph. Eur.		
Lactose monohydrate	USP-NF or Ph. Eur.		
Pre-gelatinized corn starch	USP-NF or Ph. Eur.		
Microcrystalline cellulose	USP-NF or Ph. Eur.		
Magnesium stearate	USP-NF or Ph. Eur.		
Simvastatin layer tablet weight			(b) (4)
Film coating			
(b) (4)			
Total Tablet Weight			622.4

‡ 128.5 mg of sitagliptin phosphate is equal to 100.0 mg of sitagliptin

(b) (4)

§ Also noted in the ZOCOR® NDA as SD3A

¶ Compendial testing will be performed according to at least one of the compendia listed as applicable for the target market.

100/40 mg

Components	Quality Reference¶	Function	Amount per tablet (mg)
MK-0431 (sitagliptin phosphate) layer			
Sitagliptin phosphate‖	-	Active	128.5
Dibasic calcium phosphate	USP-NF or Ph. Eur.		(b) (4)
Microcrystalline cellulose	USP-NF or Ph. Eur.		
Croscarmellose sodium	USP-NF or Ph. Eur.		
Sodium stearyl fumarate	USP-NF or Ph. Eur.		
Magnesium stearate	USP-NF or Ph. Eur.		
Sitagliptin layer tablet weight			(b) (4)
MK-0733 (simvastatin) layer			
Simvastatin (b) (4) (b) (4)	- BP§	Active	40.00 (b) (4)
Butylated hydroxyanisole (BHA)	USP-NF or Ph. Eur.		
Ascorbic acid	USP-NF or Ph. Eur.		
Citric acid monohydrate	USP-NF or Ph. Eur.		
Lactose monohydrate	USP-NF or Ph. Eur.		
Pre-gelatinized corn starch	USP-NF or Ph. Eur.		
Microcrystalline cellulose	USP-NF or Ph. Eur.		
Magnesium stearate	USP-NF or Ph. Eur.		
Simvastatin layer tablet weight			(b) (4)
Film coating			
(b) (4)			
Total Tablet Weight			827.6

‖ 128.5 mg of sitagliptin phosphate is equal to 100.0 mg of sitagliptin

(b) (4)

§ Also noted in the ZOCOR® NDA as SD3A

¶ Compendial testing will be performed according to at least one of the compendia listed as applicable for the target market.

100/80 mg

Components	Quality Reference¶	Function	Amount per tablet (mg)
MK-0431 (sitagliptin phosphate) layer			
MK-0431‖	-	Active	128.5
Dibasic calcium phosphate	USP-NF or Ph. Eur.		(b) (4)
Microcrystalline cellulose	USP-NF or Ph. Eur.		
Croscarmellose sodium	USP-NF or Ph. Eur.		
Sodium stearyl fumarate	USP-NF or Ph. Eur.		
Magnesium stearate	USP-NF or Ph. Eur.		
Sitagliptin layer tablet weight			(b) (4)
MK-0733 (simvastatin) layer			
MK-0733 (b) (4) (b) (4)	- BP§	Active	80.00 (b) (4)
Butylated hydroxyanisole (BHA)	USP-NF or Ph. Eur.		
Ascorbic acid	USP-NF or Ph. Eur.		
Citric acid monohydrate	USP-NF or Ph. Eur.		
Lactose monohydrate	USP-NF or Ph. Eur.		
Pre-gelatinized corn starch	USP-NF or Ph. Eur.		
Microcrystalline cellulose	USP-NF or Ph. Eur.		
Magnesium stearate	USP-NF or Ph. Eur.		
Simvastatin layer tablet weight			(b) (4)
Film coating			
(b) (4)			
Total Tablet Weight			1236

‖ 128.5 mg of sitagliptin phosphate is equal to 100.0 mg of sitagliptin

(b) (4)

§ Also noted in the ZOCOR® NDA as SD3A

¶ Compendial testing will be performed according to at least one of the compendia listed as applicable for the target market.

50 mg

Potencies Sitagliptin (mg)/ Simvastatin (mg)	50/10	50/20	50/40
Ingredient	mg/tab	mg/tab	mg/tab
[redacted]			

(b) (4)

4.2 Pivotal Study Synopsis (P153 and P255)

MK-0431D Prot. No. 153
A Single-Dose Study to Assess the Pharmacokinetics of Sitagliptin and Simvastatin

2. Synopsis

MERCK RESEARCH LABORATORIES MK-0431D simvastatin (+) sitagliptin phosphate, Tablet Type 2 Diabetes	**CLINICAL STUDY REPORT SYNOPSIS**	
PROTOCOL TITLE/NO.: A 2-Part Single-Dose Study to Evaluate a Probe Formulation of MK-0431D and Evaluate Definitive Bioequivalence of MK-0431D and Co-administration of Sitagliptin and Simvastatin		#153
INVESTIGATOR/STUDY CENTER: Emanuel DeNoia, M.D., Healthcare Discoveries LLC d/b/a ICON Development Solutions, San Antonio, TX		
PRIMARY THERAPY PERIOD: Part I: 11-Aug-2009 through 25-Aug-2009 and Part II: 13-Nov-2009 through 20-Dec-2009. The frozen file date was 21-Apr-2010.	**CLINICAL PHASE:**	I
DURATION OF TREATMENT: For Parts I and II of the study and in each treatment period, subjects received a single FMC sitagliptin/simvastatin (MK-0431D) 100-mg/80-mg tablet or co-administration of corresponding doses of sitagliptin and simvastatin innovator product (ZOCOR) as individual tablets. Study drug was administered orally, with 240 mL of water, after an overnight fast of at least 10 hours.		

OBJECTIVES:

Part I

Primary

Objective: To compare the pharmacokinetics of sitagliptin, simvastatin, and simvastatin acid after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator product as individual tablets.

Hypothesis: The $AUC_{0-\infty}$ and C_{max} of sitagliptin after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets will be similar (*i.e.,* the true GMRs (FDC tablet/[sitagliptin + simvastatin]) for $AUC_{0-\infty}$ and C_{max} for sitagliptin will be contained within (0.70, 1.43)).

Hypothesis: The AUC_{0-last} and C_{max} of simvastatin after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets will be similar (*i.e.,* the true GMRs (FDC tablet/[sitagliptin + simvastatin]) for AUC_{0-last} and C_{max} for simvastatin will be contained within (0.70, 1.43)).

Hypothesis: The AUC_{0-last} and C_{max} of simvastatin acid after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets will be similar (*i.e.,* the true GMRs (FDC tablet/[sitagliptin + simvastatin]) for AUC_{0-last} and C_{max} for simvastatin acid will be contained within (0.70, 1.43)).

Secondary

Objective: To assess the safety and tolerability after single dose administration of the FMC MK-0431D 100-mg/80-mg tablet.

Part II

Primary

Objective: To compare the pharmacokinetics of sitagliptin, simvastatin, and simvastatin acid after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets.

MERCK RESEARCH LABORATORIES
MK-0431D
simvastatin (+) sitagliptin phosphate, Tablet
Type 2 Diabetes

CLINICAL STUDY REPORT SYNOPSIS

Hypothesis: The $AUC_{0-\infty}$ and C_{max} of sitagliptin after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets will be bioequivalent (*i.e.,* the true GMRs (FDC tablet/[sitagliptin + simvastatin]) for $AUC_{0-\infty}$ and C_{max} for sitagliptin will be contained within [0.80, 1.25]).

Hypothesis: The AUC_{0-last} and C_{max} of simvastatin after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets will be bioequivalent (*i.e.,* the true GMRs (FDC tablet/[sitagliptin + simvastatin]) for AUC_{0-last} and C_{max} for simvastatin will be contained within [0.80, 1.25]).

Hypothesis: The AUC_{0-last} and C_{max} of simvastatin acid after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets will be bioequivalent (*i.e.,* the true GMRs (FDC tablet/[sitagliptin + simvastatin]) for AUC_{0-last} and C_{max} for simvastatin acid will be contained within [0.80, 1.25]).

Secondary

Objective: To assess the safety and tolerability after single dose administration of the FMC MK-0431D 100-mg/80-mg tablet.

STUDY DESIGN: This was an open-label, randomized, 2-part, 2-period, single dose, crossover study to evaluate the pharmacokinetics of sitagliptin and simvastatin in a probe fashion (Part I) and demonstrate bioequivalence (Part II) after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator product as individual tablets in healthy male and female subjects. There was a minimum of a 7-day washout interval between study drug administration in each treatment period. Part I of the study was a biocomparison study and was completed prior to initiation of Part II. Part II was a definitive bioequivalence study.

SUBJECT DISPOSITION:

	Part I	Part II	Total
RANDOMIZED:	24	100	124
Male (age range)	15 (19 to 47 yrs)	61 (20 to 55 yrs)	77 (19 to 55 yrs)
Female (age range)	9 (21 to 52 yrs)	39 (20 to 55 yrs)	48 (20 to 55 yrs)
COMPLETED:	24	98	122
DISCONTINUED:	0	2	2
Clinical adverse experience	0	0	0
Laboratory adverse experience	0	0	0
Other	0	2[†]	2

[†] AN 0478 was terminated from the study due to a protocol violation (alcohol consumption above the allowable study limit) prior to Period 2. AN 0448 was terminated from the study due to positive drug screen prior to Period 2.

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DOSAGE/FORMULATION NOS.:

Part I Supplies

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency (%) (n=2) Sitagliptin	Assay Potency (%) (n=2) Simvastatin
MK-0431D	100 mg/80 mg	WL00033417	Tablet	WL00035429	95.8	100.2
Sitagliptin Phosphate	100 mg	WL00032275	Tablet	WL00035431	100.9	-
Simvastatin (ZOCOR®)	80 mg	WL00034939	Tablet	WL00035430	-	100.1

Data Source: [Not Applicable]

Part II Supplies

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency (%) (n=2) Sitagliptin	Assay Potency (%) (n=2) Simvastatin
MK-0431D	100 mg/80 mg	WL00033417	Tablet	WL00035429	95.8	100.2
Sitagliptin Phosphate	100 mg	WL00032275	Tablet	WL00035431	100.9	-
Simvastatin (ZOCOR®)	80 mg	WL00036141	Tablet	WL00035430	-	100.1

Data Source: [Not Applicable]

DIAGNOSIS/INCLUSION CRITERIA: A total of 124 healthy, non-smoking, male and female subjects between the ages of 18 and 55 years with a Body Mass Index (BMI) ≤ 28 kg/m^2 participated in this study. Female subjects could not be pregnant or breast-feeding, and female subjects of childbearing potential were required to use specified birth control measures.

EVALUATION CRITERIA:

Pharmacokinetics

The plasma pharmacokinetics (e.g., $AUC_{0-\infty}$ or AUC_{0-last}, as appropriate, C_{max}, apparent $t_{1/2}$, and T_{max}) for sitagliptin, simvastatin and simvastatin acid after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator product as individual tablets were determined.

Safety

The safety of sitagliptin and simvastatin 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, and vital sign determinations. Serum human chorionic gonadotropin (hCG) assays were performed for women of childbearing potential and were confirmed negative prior to study drug administration in each treatment period.

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STATISTICAL PLANNING AND ANALYSIS:

Methods: For each Part of the study, the pharmacokinetic parameter values [AUC ($AUC_{0\text{-last}}$ for simvastatin/simvastatin acid and $AUC_{0\text{-}\infty}$ for sitagliptin) and C_{max}] of sitagliptin, simvastatin, and simvastatin acid following a single dose administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets were compared using separate linear mixed-effect models appropriate for a 2-period crossover design. The linear mixed-effect model contained factors for sequence, period and treatment as fixed effects, and subject within sequence as a random effect. A log transformation was applied to the AUC and C_{max} data. Back-transformed summary statistics and inferential results were reported for pharmacokinetic parameter values. **Part I** The 90% confidence intervals (CIs), based on the t-distribution, were generated from the above mixed effect model for the geometric mean ratios (GMRs, MK-0431D/[sitagliptin+simvastatin]) for AUC and C_{max} of sitagliptin, simvastatin, and simvastatin acid. The 90% CIs were compared to the pre-specified bounds of (0.70, 1.43). If 90% CIs for all the sitagliptin, simvastatin and simvastatin acid AUC and C_{max} GMRs (MK-0431D/[sitagliptin+simvastatin]) were contained within the interval [0.70, 1.43], then the primary hypotheses that pharmacokinetics of sitagliptin, simvastatin, and simvastatin acid after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets were similar would be concluded. **Part II** The 90% confidence intervals (CIs), based on the t-distribution, were generated from the above mixed effect model for the geometric mean ratios (GMRs, MK-0431D/[sitagliptin+simvastatin]) for the AUC and C_{max} of sitagliptin, simvastatin and simvastatin acid. The 90% CIs were compared to the prespecified bounds of [0.80, 1.25]. If 90% CIs for all the sitagliptin, simvastatin and simvastatin acid AUC and C_{max} GMRs (MK-0431D/[sitagliptin+simvastatin]) were contained within the interval [0.80, 1.25], then the primary hypotheses that pharmacokinetics of sitagliptin, simvastatin, and simvastatin acid after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets were bioequivalent would be concluded.

RESULTS: Part I:

Summary statistics for pharmacokinetic parameter values after administration of a single FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets are provided in the table below. The 90% CIs of the observed GMRs (MK-0431D/[sitagliptin+simvastatin]) for the $AUC_{0\text{-}\infty}$ and C_{max} of sitagliptin, and the $AUC_{0\text{-last}}$ and C_{max} of simvastatin and simvastatin acid after administration of a single FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets were all within the pre-specified bounds [0.70, 1.43], supporting the primary hypothesis that one FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets were similar.

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Summary Statistics and Statistical Comparisons for the Plasma Pharmacokinetic Parameters of Sitagliptin, Simvastatin, and Simvastatin Acid after Single Dose Administration of One FMC MK-0431D 100-mg/80-mg Tablet or the Co-administration of Corresponding Doses of Sitagliptin and Simvastatin (Zocor) as Individual Tablets in Healthy Male and Female Subjects

Pharmacokinetic Parameter	MK-0431D			Simvastatin + Sitagliptin			MK-0431D / (Simvastatin + Sitagliptin)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ ‡ (nM*hr)	24	7290	(6771, 7848)	24	7511	(6976, 8087)	0.97	(0.95, 0.99)
AUC_{0-last} ‡ (nM*hr)	24	7198	(6693, 7741)	24	7421	(6900, 7981)	0.97	(0.95, 0.99)
C_{max} ‡ (nM)	24	907	(802, 1025)	24	881	(779, 996)	1.03	(0.95, 1.11)
T_{max} ‖ (hr)	24	2.0	(0.5, 4.0)	24	2.8	(0.5, 4.0)	.	
Apparent $t_{1/2}$ § (hr)	24	10.7	3.2	24	10.4	3.3	.	
Simvastatin								
AUC_{0-last} ‡ (ng/mL*hr)	24	89.63	(69.81, 115.06)	24	91.95	(71.63, 118.04)	0.97	(0.88, 1.07)
C_{max} ‡ (ng/mL)	24	16.07	(11.87, 21.75)	24	15.51	(11.46, 21.00)	1.04	(0.85, 1.26)
T_{max} ‖ (hr)	24	1.3	(0.5, 4.0)	24	1.8	(0.5, 6.0)	.	
Simvastatin Acid								
AUC_{0-last} ‡ (ng/mL*hr)	24	45.69	(36.05, 57.91)	24	48.73	(38.45, 61.77)	0.94	(0.83, 1.05)
C_{max} ‡ (ng/mL)	24	4.24	(3.29, 5.48)	24	4.45	(3.45, 5.75)	0.95	(0.83, 1.10)
T_{max} ‖ (hr)	24	4.0	(2.5, 12.0)	24	6.0	(2.6, 24.0)	.	

‡ Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D / [Simvastatin + Sitagliptin])

‖ Median (min, max) reported for T_{max}

§ Harmonic mean, jack-knife standard deviation reported for apparent $t_{1/2}$

GM = Geometric Least-Squares Mean, CI: Confidence Interval

Part II:
Summary statistics for pharmacokinetic parameter values after administration of a single FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets are provided in the table below. The 90% CIs of the observed GMRs (MK-0431D/[sitagliptin+simvastatin]) for the $AUC_{0-\infty}$ and C_{max} of sitagliptin, and the AUC_{0-last} and C_{max} of simvastatin and simvastatin acid after administration of a single FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets were all within the pre-specified bounds [0.80, 1.25], supporting the primary hypothesis that one FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets were bioequivalent.

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Summary Statistics and Statistical Comparisons for the Plasma Pharmacokinetic Parameters of Sitagliptin, Simvastatin, and Simvastatin Acid after Single Dose Administration of One FMC MK-0431D 100-mg/80-mg Tablet or the Co-administration of Corresponding Doses of Sitagliptin and Simvastatin (Zocor) as Individual Tablets in Healthy Male and Female Subjects

Pharmacokinetic Parameter	MK-0431D			Simvastatin + Sitagliptin			MK-0431D / (Simvastatin + Sitagliptin)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ ‡ (nM*hr)	99	7882	(7611, 8162)	99	7991	(7716, 8275)	0.99	(0.98, 1.00)
AUC_{0-last} ‡ (nM*hr)	99	7795	(7527, 8073)	99	7900	(7629, 8181)	0.99	(0.98, 1.00)
C_{max} ‡ (nM)	99	916	(865, 969)	99	934	(882, 988)	0.98	(0.94, 1.02)
T_{max} ‖ (hr)	99	2.0	(0.5, 6.0)	99	2.0	(0.5, 6.0)	.	
Apparent $t_{1/2}$ § (hr)	99	11.4	3.3	99	12.1	3.3	.	
Simvastatin								
AUC_{0-last} ‡ (ng/mL*hr)	99	106.82	(95.93, 118.96)	99	108.04	(97.02, 120.31)	0.99	(0.93, 1.05)
C_{max} ‡ (ng/mL)	99	14.96	(13.31, 16.81)	99	15.19	(13.52, 17.07)	0.98	(0.92, 1.06)
T_{max} ‖ (hr)	99	1.5	(0.5, 12.0)	99	2.0	(0.5, 8.0)	.	
Simvastatin Acid								
AUC_{0-last} ‡ (ng/mL*hr)	99	51.15	(45.30, 57.74)	99	55.20	(48.90, 62.32)	0.93	(0.87, 0.98)
C_{max} ‡ (ng/mL)	99	4.08	(3.62, 4.60)	99	4.30	(3.82, 4.84)	0.95	(0.88, 1.02)
T_{max} ‖ (hr)	99	4.0	(2.5, 12.0)	99	4.0	(2.0, 12.0)	.	

‡ Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D / [Simvastatin + Sitagliptin])

‖ Median (min, max) reported for T_{max}

§ Harmonic mean, jack-knife standard deviation reported for apparent $t_{1/2}$

GM = Geometric Least-Squares Mean, CI: Confidence Interval

SAFETY

Parts I and II:

Administration of single doses of the FMC MK-0431D 100-mg/80-mg FDC tablets and corresponding doses of sitagliptin and simvastatin as individual innovator tablets was generally well tolerated in healthy male and female subjects. No serious clinical or serious laboratory adverse experiences were reported and no subject discontinued due to an adverse experience. Twenty-eight (28) subjects reported a total of forty-seven (47) non-serious clinical adverse experiences rated mild to moderate in intensity with the exception of one (1) non-serious adverse experience of headache characterized as severe. Seven (7) of the 47 clinical adverse experiences were considered by the investigator to be possibly or probably related to study drug administration and were rated by the investigator to be mild or moderate in intensity. All adverse experiences were transient in nature with the exception of one adverse experience of anemia reported at poststudy, which was characterized as "continuing". The most common clinical adverse experiences (reported by ≥ 2 subjects each) were headache, nausea, dizziness, gastroenteritis, oropharyngeal pain, abdominal pain, fatigue, nasal congestion, upper respiratory tract infection, and viral infection. Two (2) subjects reported two (2) non-serious clinical laboratory adverse experiences in this study, one (1) judged as probably drug related and one (1) judged definitely not drug related by the investigator. There were no consistent treatment-related changes in laboratory, vital signs, or ECG safety parameters.

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CONCLUSIONS:

1) **(Part I)** The FMC MK-0431D 100-mg/80-mg tablet and corresponding doses of innovator sitagliptin and simvastatin, co-administered as individual tablets, are similar with respect to $AUC_{0-\infty}$ and C_{max} of sitagliptin and AUC_{0-last} and C_{max} of simvastatin and simvastatin acid.

2) **(Part II)** The FMC MK-0431D 100-mg/80-mg tablet and corresponding doses of innovator sitagliptin and simvastatin, co-administered as individual tablets, are bioequivalent with respect to $AUC_{0-\infty}$ and C_{max} of sitagliptin and AUC_{0-last} and C_{max} of simvastatin and simvastatin acid.

3) **(Part I and II)** Based on assessment of clinical and laboratory adverse experiences, single doses of the FMC MK-0431D 100-mg/80-mg tablet are generally well tolerated.

AUTHORS:

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MK-0431D Prot. No. 255
MK-0431D Low Dose BE Study

2. Synopsis

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-0431D simvastatin (+) sitagliptin phosphate, Tablet Diabetes & Hyperlipidemia	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Single-Dose Study to Evaluate Definitive Bioequivalence of MK-0431D and Co-administration of Sitagliptin and Simvastatin #255

INVESTIGATOR/STUDY CENTER: Emanuel DeNoia, M.D., Healthcare Discoveries LLC d/b/a ICON Development Solutions, San Antonio, TX

PRIMARY THERAPY PERIOD: 19-May-2010 to 28-Jun-2010 **CLINICAL PHASE:** I

DURATION OF TREATMENT: In each treatment period, subjects received a single FMC MK-0431D 100-mg/10-mg tablet or co-administration of corresponding doses of sitagliptin and simvastatin innovator product (ZOCOR) as individual tablets. Study drug was administered orally, with 240 mL of water, after an overnight fast of at least 8 hours.

OBJECTIVES:

As stated in the protocol:

Primary

Objectives: To compare the pharmacokinetics of sitagliptin, simvastatin, and simvastatin acid after administration of the D2 sitagliptin/simvastatin 100-mg/10-mg fixed-dose combination (FDC) tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets.

Hypothesis: The $AUC_{0-\infty}$ and C_{max} of sitagliptin after administration of the D2 sitagliptin/simvastatin 100-mg/10-mg FDC tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets will be bioequivalent (i.e., the true GMRs (FDC tablet/[sitagliptin + simvastatin]) for $AUC_{0-\infty}$ and C_{max} for sitagliptin will be contained within [0.80, 1.25]).

Hypothesis: The AUC_{0-last} and C_{max} of simvastatin after administration of the D2 sitagliptin/simvastatin 100-mg/10-mg FDC tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets will be bioequivalent (i.e., the true GMRs (FDC tablet/[sitagliptin + simvastatin]) for AUC_{0-last} and C_{max} for simvastatin lactone will be contained within [0.80, 1.25]).

Hypothesis: The AUC_{0-last} and C_{max} of simvastatin acid after administration of the D2 sitagliptin/simvastatin 100-mg/10-mg FDC tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets will be bioequivalent (i.e., the true GMRs (FDC tablet/[sitagliptin + simvastatin]) for AUC_{0-last} and C_{max} for simvastatin acid will be contained within [0.80, 1.25]).

Secondary

Objective: To assess the safety and tolerability after single dose administration of the D2 sitagliptin/simvastatin 100-mg/10-mg FDC tablet.

STUDY DESIGN: This was an open-label, randomized, 2-period, single dose, crossover study to evaluate the pharmacokinetics of sitagliptin and simvastatin and demonstrate bioequivalence after administration of the FMC MK-0431D 100-mg/10-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets in healthy male and female subjects. There was a minimum of 7-day washout interval between study drug administration in each treatment period.

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SUBJECT DISPOSITION:

RANDOMIZED:	100
Male (age range)	41 (19-54)
Female (age range)	59 (18-53)
COMPLETED:	93
DISCONTINUED:	7
Clinical adverse experience	0
Laboratory adverse experience	0
Other	7[†]

[†] AN0023, AN0024, AN0030, AN0046, AN0095, AN0100 withdrew consent and AN0094 was removed from the study due to a protocol violation (Positive Urine Drug Screen).

DOSAGE/FORMULATION NOS.:

Drug	Potency	Formulation Number	Dosage Form	Control Number
MK-0431D	100-mg /10-mg	WL00033441	Tablet	WL00038476
Simvastatin (ZOCOR®)	10-mg	WL00038441	Tablet	WL00038476
Sitagliptin Phosphate (JANUVIA™)	100-mg	WL00037058	Tablet	WL00038476

DIAGNOSIS/INCLUSION CRITERIA: A total of 100 healthy, non-smoking, male and female subjects between the ages of 18 and 55 years with a Body Mass Index (BMI) ≤ 28 kg/m^2 participated in this study. Female subjects could not be pregnant or breast-feeding and female subjects of childbearing potential were required to use specified birth control measures.

EVALUATION CRITERIA:

PHARMACOKINETICS: In each treatment period, blood for determination of plasma sitagliptin and simvastatin concentrations was collected predose and at various time points up to 48 hours postdose for simvastatin and up to 72 hours postdose for sitagliptin. The plasma pharmacokinetics (e.g., $AUC_{0-\infty}$ or AUC_{0-last}, as appropriate, C_{max}, apparent $t_{1/2}$, and T_{max}) for sitagliptin, simvastatin, and simvastatin acid after administration of the FMC MK-0431D 100-mg/10-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets was determined.

SAFETY: The safety of sitagliptin and simvastatin 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, and vital sign determinations. Serum human chorionic gonadotropin (hCG) assays were performed for women of childbearing potential and were confirmed negative prior to study drug administration in each treatment period.

STATISTICAL PLANNING AND ANALYSIS:

Methods: The pharmacokinetic parameter values [AUC (AUC_{0-last} for simvastatin/simvastatin acid and $AUC_{0-\infty}$ for sitagliptin) and C_{max}] of sitagliptin, simvastatin, and simvastatin acid following a single dose administration of the FMC MK-0431D 100-mg/10-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets were compared using a linear mixed

effect models appropriate for a 2-period crossover design. The linear mixed-effect model contained factors for sequence, period and treatment as fixed effects, and subject within sequence as a random effect. A log transformation was applied to the AUC and C_{max} data. Back-transformed summary statistics and inferential results were reported for pharmacokinetic parameter values. The 90% confidence intervals (CIs), based on the t-distribution, were generated from the above mixed effect model for the geometric mean ratios (GMRs, MK-0431D/[sitagliptin + simvastatin]) for AUC and C_{max} of sitagliptin, simvastatin, and simvastatin acid. The 90% CIs were compared to the pre-specified bounds of [0.80, 1.25]. If 90% CIs for all the sitagliptin, simvastatin and simvastatin acid AUC and C_{max} GMRs (MK-0431D / [sitagliptin + simvastatin]) were contained within the interval [0.80, 1.25], then the primary hypotheses that pharmacokinetics of sitagliptin, simvastatin, and simvastatin acid following administration of the FMC MK-0431D 100-mg/10-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual tablet were bioequivalent would be concluded.

RESULTS: Summary statistics for pharmacokinetic parameter values after administration of a single FMC MK-0431D 100-mg/10-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets are provided in the table below. The 90% CIs of the observed GMRs (MK-0431D/[sitagliptin+simvastatin]) for the $AUC_{0-\infty}$ and C_{max} of sitagliptin, and the $AUC_{0\text{-last}}$ and C_{max} of simvastatin and simvastatin acid after administration of a single FMC MK-0431D 100-mg/10-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets were all within the pre-specified bounds [0.80, 1.25], supporting the primary hypothesis that one FMC MK-0431D 100-mg/10-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin as individual innovator tablets were bioequivalent.

Summary Statistics and Statistical Comparisons for the Plasma Pharmacokinetic Parameters of Sitagliptin, Simvastatin, and Simvastatin Acid after Single Dose Administration of One FMC MK-0431D 100-mg/10-mg Tablet or the Co-administration of Corresponding Doses of Sitagliptin and Simvastatin (Zocor) as Individual Tablets in Healthy Male and Female Subjects

Pharmacokinetic Parameter	MK-0431D			Simvastatin + Sitagliptin			MK-0431D / (Simvastatin + Sitagliptin)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ ‡ (nM*hr)	94	8052	(7789, 8324)	97	7978	(7718, 8246)	1.01	(0.99, 1.02)
$AUC_{0\text{-last}}$ ‡ (nM*hr)	94	7959	(7698, 8229)	97	7876	(7618, 8142)	1.01	(1.00, 1.03)
C_{max} ‡ (nM)	95	897	(850, 946)	97	872	(827, 920)	1.03	(0.98, 1.07)
T_{max} ‖ (hr)	95	2.5	(0.5, 4.1)	97	2.5	(0.5, 6.0)	.	
Apparent Terminal $t_{1/2}$ § (hr)	94	11.6	3.2	97	11.7	3.4	.	
Simvastatin								
$AUC_{0\text{-last}}$ ‡ (ng/mL*hr)	95	8.55	(7.49, 9.77)	97	7.98	(6.99, 9.10)	1.07	(0.99, 1.16)
C_{max} ‡ (ng/mL)	95	2.25	(1.98, 2.55)	97	1.99	(1.75, 2.26)	1.13	(1.05, 1.21)
T_{max} ‖ (hr)	95	1.5	(0.5, 6.0)	97	1.5	(0.5, 12.0)	.	
Simvastatin Acid								
$AUC_{0\text{-last}}$ ‡ (ng/mL*hr)	95	7.08	(6.25, 8.03)	97	6.86	(6.06, 7.77)	1.03	(0.96, 1.11)
C_{max} ‡ (ng/mL)	95	0.77	(0.69, 0.87)	97	0.74	(0.66, 0.83)	1.04	(0.97, 1.12)
T_{max} ‖ (hr)	95	6.0	(3.0, 10.0)	97	6.0	(3.0, 12.0)	.	

‡ Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D / [simvastatin + sitagliptin])
‖ Median (min, max) reported for T_{max}
§ Harmonic mean, jack-knife standard deviation reported for apparent terminal $t_{1/2}$
GM = Geometric Least-Squares Mean, CI: Confidence Interval

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-0431D simvastatin (+) sitagliptin phosphate, Tablet Diabetes & Hyperlipidemia	**CLINICAL STUDY REPORT SYNOPSIS** -4-

SAFETY: Administration of single doses of MK-0431D 100-mg/10-mg tablets and corresponding doses of sitagliptin and simvastatin co-administered as individual tablets was generally well tolerated in healthy male and female subjects. No serious clinical or laboratory adverse experiences were reported and no subject discontinued due to an adverse experience. Twenty-four (24) subjects reported a total of (35) non-serious clinical adverse experiences rated mild to moderate in intensity. Seven (7) of the 35 clinical adverse experiences were considered by the investigator to be possibly related to study drug administration and were rated by the investigator to be mild to moderate in intensity. All clinical adverse experiences were transient in nature with the exception of one adverse experience (airborne allergy) reported five (5) days after Period 2, which was characterized as "continuing". The most common clinical adverse experiences (reported by ≥2 subjects each) were headache, and nausea. There was one (1) laboratory adverse experience reported in this study. The single laboratory adverse experience (leukocytosis) was reported at the poststudy visit fifteen (15) days after Period 2, which was characterized as "continuing." There were no consistent treatment-related changes in laboratory, vital signs, or ECG safety parameters.

CONCLUSIONS:

1) The FMC MK-0431D 100-mg/10-mg tablet and corresponding doses of sitagliptin and simvastatin, co-administered as individual tablets, are bioequivalent with respect to $AUC_{0-\infty}$ and C_{max} of sitagliptin and AUC_{0-last} and C_{max} of simvastatin and simvastatin acid.

2) Based on assessment of clinical and laboratory adverse experiences, single doses of the FMC MK-0431D 100-mg/10-mg tablet are generally well tolerated.

AUTHORS:	Michael Cerra, B.S. Assoc. Early Clinical Scientist Clinical Pharmacology	Wen-Lin Luo, Ph.D. Senior Biometrician CBARDS	Matt S. Anderson, Ph.D. Associate Director Clinical Pharmacology
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/s/

SANG M CHUNG
09/01/2011

JAYABHARATHI VAIDYANATHAN
09/01/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**202-343/S-000**
Submission Date:	12/6/10, 4/28/11, 6/22/11, 8/1/11
Drug Name:	Sitagliptin/Simvastatin FDC
Formulation:	Bilayer tablets
Strength:	100/10, 100/20 and 100/40 mg
Sponsor:	Merck
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

MK-0431D is being developed as a fixed-dose combination (FDC) containing sitagliptin and simvastatin, the active components of JANUVIA™ and ZOCOR™, respectively. Both components of this FDC are established medications that have demonstrated benefits for patients with Type 2 Diabetes.

COMMENTS

1. The biowaiver request for the strengths between the highest and the lowest strengths is accepted. An approval for these strengths is recommended if the bioequivalence studies are deemed acceptable.
2. Based on the proposed conditions and the data provided, the following dissolution acceptance criterion for Sitagliptin is recommended and accepted by the sponsor.

   Q (b) (4) at 15 minutes.

3. Based on the proposed conditions and the data provided, the following dissolution acceptance criterion for Sitagliptin is recommended and accepted by the sponsor.

   Q= (b) (4) at 30 minutes

RECOMMENDATION

The applicant accepted the recommended acceptance criteria and updated the NDA. No further action is necessary at this time.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

cc: NDA 202343
Angelica Dorantes, Patrick Marroum, John Duan

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/s/

JOHN Z DUAN
08/03/2011

PATRICK J MARROUM
08/04/2011

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Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	202343	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	II	**Generic Name**	Fixed dose combination of sitagliptin phosphate and simvastatin
Medical Division	DMEP	**Drug Class**	
OCP Reviewer	Sang M. Chung, Ph D.	**Indication(s)**	Type 2 diabetes and dyslipidemia
OCP Team Leader	Sally Choe, Ph.D.	**Dosage Form**	Tablet of 100/10, 100/20, 100/40 (mg sitagliptin/mg simvastatin) In development: 50/10, 50/20, and 50/40
Pharmacometrics Reviewer		**Dosing Regimen**	FDC once a day
Date of Submission	December 3, 2010	**Route of Administration**	Oral
Estimated Due Date of OCP Review		**Sponsor**	Merck
Medical Division Due Date		**Priority Classification**	Standard
PDUFA Due Date	October 7, 2011		

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) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies	**X**			P025: effect of sitagliptin on simvastatin (referenced to the sitagliptin original NDA) P168: effect of simvastatin on sitagliptin P169: effect of sitagliptin+simvastatin on digoxin
In-vivo effects on primary drug:				

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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:				
II. Biopharmaceutics	**X**			Preliminary studies: P154 and P153 (Part I)
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**X**			MK-0431D FDC vs. co-administration of sitagliptin and simvastatin P153 (Part II) P255
traditional design; single / multi dose:	**X**			
replicate design; single / multi dose:				
Food-drug interaction studies	**X**			P155
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies	**7**			

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	✓			FDC vs. co-administration of sitagliptin and simvastatin
2	Has the applicant provided metabolism and drug-drug interaction information?	✓			• Effect of sitagliptin on simvastatin • Effect of simvastatin on sitagliptin • Effect of sitagliptin+simvastatin on digoxin.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	✓			• FDC vs. co-administration of sitagliptin and simvastatin • Food effect study
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	✓			
5	Has a rationale for dose selection been submitted?			✓	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	✓			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	✓			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	✓			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	✓			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			✓	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	✓			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			✓	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			✓	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the			✓	

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	need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			✓	Requested a waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			✓	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	✓			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	✓			DSI inspection
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			✓	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

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

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

Comment to the project manager (Internal)

Request for the DSI inspection on the pivotal BE studies: Study P153 (Part II; highest strength) and P255 (lowest strength). Both studies used the same clinical site and bioanalytical study sites as follows:

Clinical study site

ICON Development Solutions
8307 Gault Lane
San Antonio, TX 78209

Bioanalytical study site

Anapharm, Inc.
2500 rue Einstein
Quebec, P.Q. G1P 0A2
Canada

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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Filing memo (Internal Memo)

The sponsor submitted this NDA for the fixed-dose combination (FDC) tablets of sitagliptin phosphate and simvastatin as a 505(b)(1) application. The sponsor holds the original NDAs for sitagliptin phosphate (Januvia™) and simvastatin (Zocor™). The sponsor's justification for the development of the FDC tablet is to improve convenience for patients and may also improve compliance.

Sitagliptin (Figure 1) is classified as a BCS Class III/borderline Class I compound and simvastatin (Figure 1) data are not available for the BCS classification.

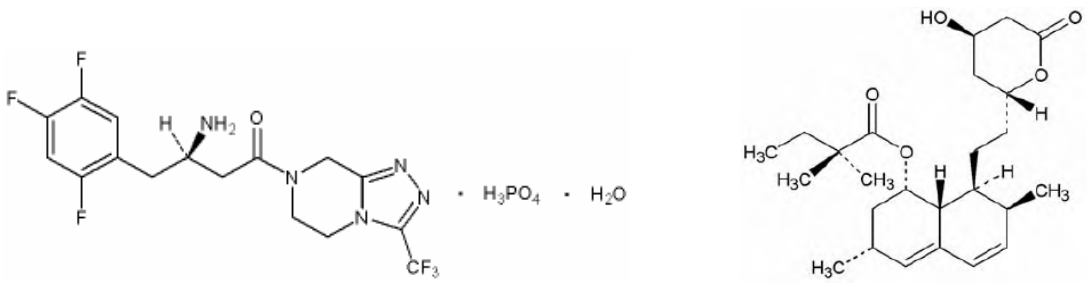

Figure 1 chemical structure of sitagliptin (left) and simvastatin (right)

The proposed FDC formulation (MK-0431D) is a bilayer tablet. It is formed by compressing the separate layers of sitagliptin and simvastatin granulations into a bilayer tablet and then filmcoating the tablet. The components and composition of the FDC are summarized in Table 1.

Table 1 Components and composition of MD-0431D

Components	Compendial Testing	Function	Unit Strength (mg) Sitaglipin/Simvastatin 100 mg/10 mg	100 mg/20 mg	100 mg/40 mg	100 mg/80mg‖
Sitagliptin Layer						
MK-0431	-	Active	128.5	128.5	128.5	128.5
Dibasic calcium phosphate	USP / Ph. Eur.	Diluent	207.5	207.5	207.5	207.5
Microcrystalline cellulose	NF / Ph. Eur.	Compression aid	40.00	40.00	40.00	40.00
Croscarmellose sodium	NF / Ph. Eur.	Disintegrant	8.000	8.000	8.000	8.000
Sodium stearyl fumarate	NF / Ph. Eur.	Lubricant	12.00	12.00	12.00	12.00
Magnesium stearate	NF / Ph. Eur.	Lubricant	4.000	4.000	4.000	4.000
Simvastatin Layer						
MK-0733 (0.01% BHA)	-	Active	10.00	20.00	40.00	80.00
Industrial methylated spirit†	SD3A§	Granulation fluid	---	---	---	---
Purified water†	USP / Ph. Eur.	Granulation fluid	---	---	---	---
Butylated hydroxyanisole (BHA)	NF / Ph. Eur.	Antioxidant	0.0200	0.040	0.080	0.160
Ascorbic acid	USP / Ph. Eur.	Acidifier	2.500	5.000	10.00	20.00
Citric acid monohydrate	USP / Ph. Eur.	Acidifier	1.250	2.500	5.000	10.00
Lactose monohydrate	NF / Ph. Eur.	Diluent	70.73	141.5	282.9	565.8
Pre-gelatinized corn starch 1500	NF / Ph. Eur.	Binder	10.00	20.00	40.00	80.00
Microcrystalline cellulose	NF / Ph. Eur.	Compression aid	5.000	10.00	20.00	40.00
Magnesium stearate	NF / Ph. Eur.	Lubricant	0.5000	1.000	2.000	4.00
Film Coating						
Opadry® II Purple (85F170000)‡	-	Film coat	18.31	22.41	---	36.04
Opadry® II Beige (85F170001)‡		Film coat	---	---	27.59	---
Purified water†	USP / Ph. Eur.	Solvent	---	---	---	---
Total Tablet Weight			518.3	622.4	827.6	1236

† Removed during processing.
‡ OPADRY® II Purple or Beige is purchased from Colorcon and consists of the following ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide , iron oxide yellow, iron oxide red, iron oxide black.
§ Alternatively, alcohol that conforms to USP, BP, or Ph. Eur. may be used.
‖ Will not be marketed.

[Sec. 3.3]

MK-0431D tablets used in the pivotal bioequivalence (BE) studies (P153 Part II and P255) are identical to the final market image (FMI) tablet except for a change in the film coating color, which is not expected to affect the in vivo performance of FMI MK-0431D tablets.

The sponsor conducted a total of 7 clinical pharmacology studies (Table 2). The highest and lowest strengths (100/80 and 100/10) of FDC were bioequivalent to those of sitagliptin+simvastatin. The sponsor proposes a biowaiver for the middle strengths (i.e., 100/40 and 100/20).

Two issues were discussed through the EOP2 and pre-NDA meeting as follows (see the Attachment):

- The pivotal clinical pharmacology studies were conducted using the highest strength (i.e., 100/80). However, the highest strength will not be marketed because of safety issue with 80 mg simvastatin. The Agency concurred that the issue is not related to filing because 1) safety issue with 80 mg simvastatin evolved after the BE study using 100/80 was finished and 2) the situation can be potentially addressed using biowaiver. However, the Agency notified the sponsor that it can be a review issue.
- The sponsor proposed 100 mg sitagliptin strength with proper labeling related to renal impairment because lower strengths (i.e., 50 and 25 mg) of sitagliptin are only for moderate and severe renal impairment. The Agency recommended including the lower strength in the original NDA or providing details of development plan for subsequent supplemental submission. The sponsor provided that the tablet strengths containing 50 mg sitagliptin (i.e., 50/10, 50/20, and 50/40 mg/mg) are currently in development targetting for filing by Dec-2011.

Food effect on FDC (100/80) was consistent to its known effect on individual compounds. Drug interaction between sitagliptin and simvastatin was not clinically significant. The effect of sitagliptin+simvastatin on digoxin exposure was additive of known individual component effect on digoxin.

The sponsor requested a pediatric study waiver because they do not plan to develop MK-0431D for pediatric populations. The sponsor is conducting a pediatric development program for Januvia and Zocor is indicated for the use in adolescent patients with heterozygous familial hypercholesterolemia.

Table 2 Summary of clinical pharmacology studies (Source: \\Cdsesub1\evsprod\NDA202343**)**

Study	Design	Conclusions
P025 (n=12)	This was a single-center, randomized, open-label, two-period, crossover study in healthy male and female subjects (n=12), 18 to 45 years of age, to investigate the effect of multiple doses of sitagliptin 200 mg QD for 5 days on the single dose pharmacokinetics of simvastatin 20 mg.	No statistical or clinically meaningful differences in the plasma AUC0-last, Cmax or Tmax of total HMG-CoA reductase inhibitors, simvastatin, or simvastatin acid were observed after administration of a single oral 20-mg dose of simvastatin with or without co administration of sitagliptin
P168 (n=10)	This was a single-center, open-label, randomized, 2-period, crossover study in healthy male and female subjects (n=10), 18 to 55 years of age, to investigate the effect of multiple-doses of	Multiple-dose administration of simvastatin had no clinically meaningful effect on the single dose pharmacokinetics of sitagliptin.

	simvastatin 80 mg QD for 7 days on the pharmacokinetics of sitagliptin 100 mg.	
P169 (n=13)	This was a single-center, open-label, randomized, 2-period, crossover study in healthy male and female subjects (n=14), 18 to 55 years of age, to determine the effect of co-administration of sitagliptin and simvastatin (to steady state; 100 mg+80 mg QD for 9 days) on the single-dose plasma concentrations of digoxin 0.5 mg.	Relative to digoxin administration alone, the AUC0-last GMR ([sitagliptin + simvastatin + digoxin]/digoxin) was 1.26 with a corresponding 90% CI of (1.13, 1.41), and the Cmax GMR was 1.41 with a corresponding 90% CI of (1.20, 1.66).
P154 (n=20/part)	This was a 2-part, open-label, randomized, 4-period crossover study to evaluate the pharmacokinetics of sitagliptin and simvastatin (generic) after administration of MK-0431D 100-mg/10-mg and 100-mg/80-mg probe formulations and co-administration of corresponding doses of sitagliptin and simvastatin as individual tablets in healthy male and female subjects.	The pharmacokinetics (AUC and Cmax) of sitagliptin and simvastatin after administration of MK-0431D 100-mg/10-mg and 100-mg/80-mg probe formulation D1 and D2 tablets, or co-administration of corresponding doses of sitagliptin and simvastatin, are similar.
P153 (n=24 for Part I, 99 for Part II)	This was an open-label, randomized, 2-part, 2-period, single dose, crossover study to evaluate the pharmacokinetics of sitagliptin and simvastatin in a probe fashion (Part I) and to demonstrate bioequivalence (Part II) after administration of the FMC MK-0431D 100-mg/80-mg tablet and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets in healthy male and female subjects.	**(Part I)** The FMC MK-0431D 100-mg/80-mg tablet and corresponding doses of innovator sitagliptin and simvastatin, co-administered as individual tablets, are similar with respect to AUC0-∞ and Cmax of sitagliptin and AUC0-last and Cmax of simvastatin and simvastatin acid. **(Part II)** The FMC MK-0431D 100-mg/80-mg tablet and corresponding doses of innovator sitagliptin and simvastatin, co-administered as individual tablets, are bioequivalent with respect to AUC0-∞ and Cmax of sitagliptin and AUC0-last and Cmax of simvastatin and simvastatin acid.
P255 (n=94-97)	This was an open-label, randomized, 2-period, single dose, crossover study to demonstrate definitive bioequivalence between the FMI MK-0431D 100-mg/10-mg tablets and co-administration of corresponding doses of sitagliptin and simvastatin innovator products as individual tablets in healthy male and female subjects.	The FMC MK-0431D 100-mg/10-mg tablet and corresponding doses of sitagliptin and simvastatin, co-administered as individual tablets, are bioequivalent with respect to AUC0-∞ and Cmax of sitagliptin and AUC0-last and Cmax of simvastatin and simvastatin acid.
P155 (n=32)	This was an open-label, randomized, two-period, single-dose, crossover study to evaluate the pharmacokinetics of sitagliptin and simvastatin after administration of the FMC MK-0431D 100-mg/80-mg tablet fasted (Treatment A) and after consumption of a highfat breakfast (Treatment B) in healthy male and female subjects.	1) The administration of the FMC MK-0431D 100-mg/80-mg tablet after a standard high-fat meal does not meaningfully affect the AUC0-last of simvastatin and simvastatin acid compared to administration in the fasted state. 2) Administration of the FMC MK-0431D 100-mg/80-mg tablet after a standard high-fat meal increases the Cmax of both simvastatin and simvastatin acid by 20% and 116%, respectively, compared to administration in the fasted state. 3) Administration of the FMC MK-0431D 100-mg/80-mg tablet after a standard high-fat meal does not affect the pharmacokinetics of sitagliptin compared to administration in the fasted state.

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Attachment starts here.

Interactions with FDA

Advice on the MK-0431D development program and concurrence with the Sponsor's plans have been previously obtained from FDA. An End of Phase 2 meeting request was submitted to the IND (103,183) in Sep-2008; the Agency denied the meeting request but did agree to provide responses to questions, which were received in Feb-2009. In that response the Agency agreed with the proposed BE strategy for registration of MK-431D. The Agency also noted that if tablet strengths containing sitagliptin 50 mg were not developed, the lack of those doses would have to be reflected in labeling. On 04-Mar-2010 a teleconference was held to discuss a change in the Agency's position regarding the need for Phase III clinical data; a Phase III trial was now required to examine potential effects of the statin on glycemic control in patients with T2DM taking MK-0431D. However, the Agency agreed that this study could be conducted as a post-approval commitment in this particular case because this new requirement was adopted late during the development of MK-0431D. A pre-NDA meeting was held by teleconference on 24-May-2010. During that meeting the Agency mandated that tablet strengths of 50/10, 50/20, and 50/40 mg/mg be developed in addition to those containing sitagliptin 100 mg, a change from the position taken by the Agency in the End of Phase 2 response. Subsequent teleconferences were held on 11-Jul-2010 and 30-Sep-2010 to discuss the new filing requirements. During these teleconferences, the Agency stated that the 100/80 mg/mg dose would not be approvable because of safety issues associated with the 80-mg dose of simvastatin. The Sponsor pointed out that the 100/80 mg/mg dose had already been used in pivotal BE studies, with FDA concurrence, and asked whether those data could still be acceptable. The Agency agreed in principle but stated that it would be a review issue. FDA also agreed that bridging studies with the 50-mg doses could be performed *in vitro*. The Sponsor proposed to file the 100-mg doses in Dec-2010 with a subsequent submission to register the 50-mg doses no later than Dec-2011. The Agency stated that if the Sponsor choose to submit the NDA without the 50-mg doses, it would be a review issue and asked that the Sponsor clearly convey the development status of the 50-mg doses in the NDA as well as in the 4-month update. The current status of the development of the 50-mg doses is summarized below.

Current Status of the Development of the 50-mg Doses

As previously discussed with the Agency (during teleconferences on 12-Jul-2010 and 30-Sep-2010), the Sponsor is including data to support the registration of the 100/10, 100/20, and 100/40 (mg sitagliptin/mg simvastatin) tablet strengths of MK-0431D in this original NDA. The 50/10, 50/20, and 50/40 (mg sitagliptin/mg simvastatin) MK-0431D tablet strengths are currently in development and will be filed no later than Dec-2011.

Targeted Development Timeline

The targeted development timeline for the 3 tablet strengths of MK-0431D containing 50 mg of sitagliptin, previously submitted to the Agency, is summarized in [Table 2.2: 1].

Table 2.2: 1

Chronology of Key Events for the Development of MK-0431D Tablets Containing 50 mg of Sitagliptin

Date	Key event
Oct-2010-Feb-2011	Commercial scale process verification for MK-0431D tablets containing 50 mg sitagliptin Manufacturing and testing of Formal Stability Study (FSS) batches of 50 mg/10 mg MK-0431D Tablets
Dec-2010	Communication of development status of FDCs containing 50 mg sitagliptin to FDA (in NDA for the 100 mg FDC series)
Mar-Apr-2011	Packaging and initiation of Formal Stability Studies and generation of dissolution bridging data for MK-0431D tablets containing 50 mg sitagliptin
Apr-2011	Communication of development status of FDCs containing 50 mg sitagliptin to FDA (as part of the 4 month safety update to the NDA)
Oct-Nov-2011	Testing of 6 month stability samples and preparation of the submission
Dec-2011	Submission of Prior Approval Supplement for MK-0431D 50 mg/10 mg, 50 mg/20 mg, and 50 mg/40 mg tablet strengths

Current Development Status

Development of the 50/10, 50/20, and 50/40 (mg sitagliptin/mg simvastatin) tablet strengths of MK-0431D is proceeding as planned and is on target for the Dec-2011 filing. Commercial scale process verification and manufacture of pilot scale batches for MK-0431D FDC tablets containing 50 mg sitagliptin have been successfully completed at MSD Ballydine, the proposed commercial manufacturing site. These batches will be utilized to generate in vitro dissolution bridging data to support a biowaiver for the FDC tablets containing 50 mg sitagliptin as agreed to by the Agency during the 30-Sep-2010 teleconference.

In addition, target film coat amounts and colors have been finalized prior to initiation of stability studies; updated tablet formulations are provided in [Table 2.2: 2]. Three pilot scale batches of 50-mg/10-mg tablets will be packaged for registration stability studies in the HDPE bottle configurations and placed on stations on or before the target date (March-April 2011).

Table 2.2: 2

Proposed MK-0431D Tablet Formulations Containing 50 mg Sitagliptin

Potencies Sitagliptin (mg)/ Simvastatin (mg)	50/10	50/20	50/40
Ingredient	mg/tab	mg/tab	mg/tab
Sitagliptin layer			
Sitagliptin phosphate (MK-0431)	64.26[1]	64.26[1]	64.26[1]
Dibasic calcium phosphate	103.8	103.8	103.8
Microcrystalline cellulose	20.00	20.00	20.00
Croscarmellose sodium	4.000	4.000	4.000
Sodium stearyl fumarate	6.000	6.000	6.000
Magnesium stearate	2.000	2.000	2.000
Total sitagliptin layer	200.1	200.1	200.1
Simvastatin layer			
Simvastatin (MK-0733) [0.01% BHA]	10.00	20.00	40.00
Butylated hydroxyanisole (BHA)	0.020	0.040	0.080
Ascorbic acid	2.500	5.000	10.00
Citric acid monohydrate	1.250	2.500	5.000
Lactose monohydrate	70.73	141.5	282.9
Microcrystalline cellulose	5.000	10.00	20.00
Pregelatinized corn starch	10.00	20.00	40.00
Magnesium stearate	0.500	1.000	2.000
Industrial methylated spirit[2]	-	-	-
Water purified[2]	-	-	-
Total simvastatin layer	100.0	200.0	400.0
Film coating			
OPADRY® II Red[3]	14.15	-	23.28
OPADRY® II Orange Beige[3]	-	17.49	-
Water, purified[2]	-	-	-
Total Final Tablet Weight	314.3	417.6	623.4

[1] Equivalent to 50 mg of sitagliptin free base with conversion factor of 1.285.
[2] Removed during processing.
[3] OPADRY Red and OPADRY Orange-Beige are based on the similar compositions of polyvinyl alcohol, talc, macrogrol/PEG and titanium dioxide. OPADRY Red contains the maximum level of iron oxide as compared to the levels used in OPADRY Orange Beige used for 50-mg/20-mg and 100-mg/40-mg and OPADRY Pink-Beige used for 100-mg/10-mg and 100-mg/20-mg tablet strengths.

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/s/

SANG M CHUNG
02/14/2011

SALLY Y CHOE
02/14/2011