

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-995

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

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-995 (000)	Submission Date: 12/16/2005
Brand Name	Januvia™
Generic Name	Sitagliptin
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.
PM Team Leader	Jogarao Gobburu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND division	Division of Metabolic and Endocrine Products (HFD-510)
Sponsor	Merck
Relevant IND(s)	65,495
Submission Type; Code	Original
Formulation; Strength(s)	Tablets; 100 mg, 50mg, 25 mg
Dosing regimen	Once a day
Indication	Type 2 diabetes mellitus

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1 Executive Summary

Merck submitted a 505 (b) (1) NDA for marketing of Januvia™ (Sitagliptin). A total of 33 human Phase 1 and Phase 2 pharmacokinetic and pharmacodynamic studies, bioavailability/bioequivalence studies, in vitro drug metabolism studies and a thorough QT study were submitted to support the section of Clinical Pharmacology and Biopharmaceutics.

Sitagliptin is the first drug of a new class of oral anti-hyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic peptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner.

Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Sitagliptin is also indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a PPAR γ agonist (e.g., thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control. The recommended dose of sitagliptin is 100 mg once daily as monotherapy or as combination therapy.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-2) has reviewed the information provided in the original NDA 21-995 for Januvia™ in the section of human pharmacokinetics and biopharmaceutics. OCP has found the application acceptable. This recommendation and dissolution method and acceptance criterion below should be conveyed to the sponsor as appropriate.

Apparatus	
In vitro dissolution medium	
Volume of dissolution medium	
Medium temperature	
Stirring speed	
Acceptance criterion	

OCP Briefing Notes:

A Required OCP Office Level CPB Briefing was held on August 29, 2006. The following staff were attended: from OCP: Larry Lesko, Shiew-Mei Huang, Chandra Sahajwalla, Mehul Mehta, John Lazor, Atik Rahman, Dennis Bashaw, Hae-Young Ahn, Kelly Reynolds, Jaya Vaidyanathan, Albert Chen, David Lee, Srikanth Nallani, Sandhya Apparaju, Lei Zhang, Partha Roy, Atul Bhattaram; From DMEP: Mary Parks, Ilan Irony, Hylton Joffe, Lina Aljuburi; From ONDQA: Stephen Moore.

During Briefing, the OCP management reached a consensus to recommend a dissolution method as a post approval test method, not disintegration. Speaking for the four OCP division directors present Dr. Bashaw (Division Director, DCP-3), explained that disintegration does not necessarily correlate with solubilization of drug substance. Dissolution testing, on the other hand, incorporates both disintegration and the solubilization of drug substance into the media in its specification. As in the case with this drug, dissolution testing did not discriminate between hardness values as once the tablet disintegrated, the high solubility of the drug substance allowed it to enter the media readily. However, as a general release test, disintegration is not generally considered adequate as there could be formulation changes in the future that would result in decreased solubility (for example, a change in drug substance particle size) that would not be picked up by disintegration testing but would be detected by dissolution testing. Given that the burden of dissolution testing is minimal and is usually automated today, compared to the manual observation required for disintegration testing, it is recommended that a dissolution test be used.

1.2 Phase IV Commitment

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

- Single and multiple dose pharmacokinetics:

After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 $\mu\text{M}\cdot\text{hr}$, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady-state compared to the first dose. The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

- Absolute bioavailability and food effect:

The absolute bioavailability of sitagliptin is approximately 87%. The co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics; sitagliptin may be administered with or without food.

- Dose proportionality:

The power law model of geometric mean $\text{AUC}_{0-\infty}$ values versus dose administered along with the fitted regression line indicated that the slope (90% CI) was 1.00 (0.98, 1.01). The sitagliptin dose adjusted (to 100 mg) $\text{AUC}_{0-\infty}$ geometric least-squares mean ratio (GMR, 400 mg/100 mg) was 1.02 with corresponding 90% CI of (0.99, 1.06). Therefore, sitagliptin $\text{AUC}_{0-\infty}$ increases dose proportionally with increasing dose across the tested dose range. Sitagliptin C_{max} increases in a modestly greater than dose proportional manner with dose.

- Distribution:

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is about 38%.

- Metabolism:

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine. Following a [^{14}C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8. Sitagliptin is a substrate of P-gp.

- Excretion:

Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The renal clearance was approximately 350 mL/min. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3).

- Renal impairment:

Mild renal insufficiency increased sitagliptin AUC by 1.6 fold. An approximately 2-fold or greater increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, and an approximately 4-fold or greater increase was observed in patients with severe renal insufficiency and in patients with ESRD on hemodialysis, as compared to normal healthy control subjects. Sitagliptin was

modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis session starting 4 hours postdose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, 50-mg and 25-mg once a day are recommended for moderately renally impaired and severely renally impaired or ESRD patients, respectively.

- Drug interactions:

In clinical pharmacokinetic studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives. Multiple doses of sitagliptin slightly increased digoxin concentrations.

A single 600-mg oral dose of cyclosporine increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively.

- Pharmacodynamics:

In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal.

- Exposure-response:

The relationship between plasma sitagliptin concentrations and inhibition of plasma DPP-IV activity was explored. No significant hysteresis was observed. Using an Emax model the plasma EC50 was 25.7 nM and the EC80 was approximately 100 nM. In a study of multiple doses of 25 mg to 600 mg sitagliptin in healthy subjects, there was a dose- and concentration-related increase in the percent inhibition of plasma DPP-IV enzyme activity for multiple doses from 25 to 600 mg. Multiple doses of 100 mg once daily or higher were associated with geometric mean values for inhibition of DPP-IV activity at steady-state trough of approximately 80% or higher. These pharmacodynamic data support a once daily dosing regimen for sitagliptin in the treatment of type 2 diabetes.

- Analytical assay:

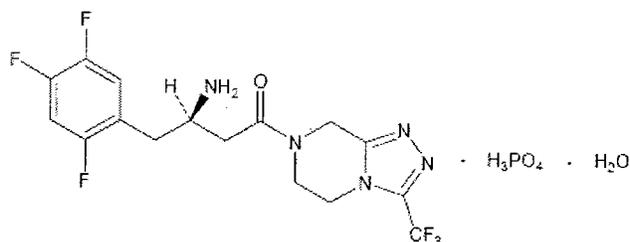
High turbulence liquid chromatography (HTLC) extraction and liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods were used to analyze sitagliptin concentrations in human biological fluids (plasma, urine and dialysate). The lower limit of quantitation (LLOQ) for the plasma assay is 0.500 ng/mL (1.23 nM) and the linear calibration range is 0.500 to 1000 ng/mL (1.23 to 2455 nM). The assays are selective and specific for sitagliptin in human biological fluids. The accuracy of the intra-day analysis (n=5) of quality control (QC) samples did not deviate by more than 10% of the nominal concentrations. The precision (coefficient of variation, CV%) of the intra-day analysis (n=5) of QC samples was less than 10% at each concentration.

2. QUESTION BASED REVIEW (QBR)

2.1 GENERAL ATTRIBUTES OF THE DRUG

2.1.1 *What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulations of the drug product?*

Sitagliptin phosphate is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate. The empirical formula is C₁₆H₁₅F₆N₅O•H₃PO₄•H₂O and the molecular weight is 523.32. The structural formula is as follows:



Sitagliptin phosphate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

2.1.2 What are the mechanism of action, therapeutic indication and dosage recommendations for sitagliptin?

Mechanism of Action

Sitagliptin is the first member of a new class of oral anti-hyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic peptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels lead to lower hemoglobin A1c (A1C) and lower fasting and postprandial glucose concentrations.

Proposed indications:

Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Sitagliptin is also indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a PPAR γ agonist (e.g., thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control.

Proposed dosage recommendation:

The recommended dose of sitagliptin is 100 mg once daily as monotherapy or as combination therapy with metformin or a PPAR γ agonist (e.g., thiazolidinedione). Sitagliptin can be taken with or without food.

Patients with Renal Insufficiency:

For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥ 50 mL/min, approximately corresponding to serum creatinine levels of ≤ 1.7 mg/dL in men and ≤ 1.5 mg/dL in women), no dosage adjustment for sitagliptin is required.

For patients with moderate renal insufficiency (CrCl ≥ 30 to < 50 mL/min, approximately corresponding to serum creatinine levels of > 1.7 to ≤ 3.0 mg/dL in men and > 1.5 to ≤ 2.5 mg/dL in women), the dose of sitagliptin is 50 mg once daily.

For patients with severe renal insufficiency (CrCl <30 mL/min, approximately corresponding to serum creatinine levels of >3.0 mg/dL in men and >2.5 mg/dL in women) or with end-stage renal disease (ESRD) requiring hemodialysis, the dose of sitagliptin is 25 mg once daily. Sitagliptin may be administered without regard to the timing of hemodialysis.

2.1.3 What are the highlights of the formulation of drug product?

Sitagliptin is supplied as a film-coated tablet. Details of the composition are shown in Table 1.

Table 1. Composition of Phase III/ Final Market Image (FMI) Tablets

Component	Phase III/FMI Tablet T13 100 mg /tablet	Phase III/FMI Tablet T10 50 mg /tablet	Phase III/FMI Tablet T5 25 mg /tablet
MK-0431-010X (equivalent free base) [†]			
Calcium Phosphate Dibasic, USP			
Microcrystalline Cellulose NF			
Croscarmellose Sodium NF			
Sodium Stearyl Fumarate NF			
Magnesium Stearate (non-bovine) NF			
Core Tablet Weight			
Total Weight	416.0	208.0	104.0
[†] Conversion factor of _____ used for free base to monohydrate phosphate salt form.			
[†] Removed during processing NA=Not Applicable in this formulation NF =National Formulary USP = United States Pharmacopeia.			

2.2 General Clinical Pharmacology

2.2.1 What are the pharmacokinetic characteristics of a single dose of sitagliptin in healthy subjects and patients with type 2 diabetes?

The sponsor conducted seven single dose pharmacokinetic studies in healthy subjects for 100 mg dose through the drug development. The main pharmacokinetic parameters are summarized in Table 2.

Table 2. Mean pharmacokinetic parameters across Phase I studies following single oral 100-mg doses of sitagliptin administered alone to fasting healthy subjects

Study	Formulation	N	AUC _{0-∞} (μM•hr) [†]	C _{max} (nM) [†]	T _{max} (hr) [‡]	t _{1/2} (hr) [§]	Cl _R (mL/min) [†]	f _{e,0-∞}
P001	Capsule	6	7.76	747	4	10.1	416	0.796
P013	Capsule	6	8.65	959	2	9.56	415	0.878
P027	Phase II tablet	12	8.38	799	2.5	12.2	NA	NA
P027	FMI tablet	12	8.78	856	1.75	12.5	NA	NA
P029	FMI tablet	12	7.90	817	3	11.7	340	0.651
P033	FMI tablet	10	8.52	950	1.3	12.4	350	0.738
P037	FMI tablet	8	7.13	706	4	11.6	366	0.658

[†] Geometric Least-Squares Mean or Geometric Mean.
[‡] Median.
[§] Harmonic Mean for Apparent Terminal t_{1/2}.
^{||} Arithmetic Least-Squares Mean.
 NA=Not applicable, urine was not collected.

In a single dose pharmacokinetic study in patients with type 2 diabetes, 58 drug naïve patients enrolled. Each patient received single oral doses of 25 mg sitagliptin or 200 mg sitagliptin or placebo in the fasted state in a randomized sequence. The PK parameters are summarized in Table 3.

Table 3. Summary statistics of sitagliptin plasma pharmacokinetic parameters following single oral sitagliptin 25-mg and 200-mg doses to patients with type 2 diabetes (P005)

Parameters	25 mg			200 mg		
	N	Mean [†]	SD [‡]	N	Mean [†]	SD [‡]
AUC _{0-24 hr} (μM•hr)	58	1.55	0.292	57	14.1	3.13
AUC _{0-∞} (μM•hr) [§]	7	2.0	0.32	7	15.8	3.75
C _{max} (nM)	58	140	35.1	57	1923	661
C _{24 hr} (nM)	58	22.2	7.46	57	96.3	41.3
T _{max} (hours)	58	4.0	1.1	57	2.0	1.3
Apparent terminal t _{1/2} (hours) [§]	7	13.1	2.58	7	11.0	1.77

[†] Geometric least-squares mean for AUC_{0-24 hr}, AUC_{0-∞}, C_{max}, and C_{24 hr}; median for T_{max}, and harmonic mean for t_{1/2}.
[‡] SD = Between-subject standard deviation; Back-transformed from log scale for AUC_{0-24 hr}, AUC_{0-∞}, C_{max}, and C_{24 hr}; Jackknife standard deviation for t_{1/2}.
[§] AUC_{0-∞} and apparent t_{1/2} were computed for patients with plasma MK-0431 samples collected to 72 hours postdose only.

The pharmacokinetic parameters were generally similar between patients with type 2 diabetes and healthy subjects from the overall comparison.

2.2.1 What are the pharmacokinetic characteristics of multiple doses of sitagliptin in healthy subjects and patients with type 2 diabetes?

In a double-blind, randomized, placebo-controlled, parallel-group, incremental dose study with 7 treatment panels (Panels A, B, C, D, E, F, and G), each consisting of 10 healthy male subjects, Panels A to E, each subject received 25, 50, 100, 200, or 400 mg sitagliptin (n=8) or placebo (n=2) once daily for 10 days (Days 1 to 10). In Panel F, each subject received 800 mg sitagliptin (n=8), or placebo (n=2) on Day 1 and 600 mg sitagliptin (n=8), or placebo (n=2) on Days 3 to 10. In Panel G, each subject received 300 mg sitagliptin (n=8), or placebo (n=2) every 12 hours (twice daily, or b.i.d.) for 10 days (Days 1 to 10). The pharmacokinetics of sitagliptin following multiple doses of sitagliptin, 25 to 600 mg q.d. and 300 mg twice daily are summarized in Table 4.

Table 4. Summary statistics of sitagliptin pharmacokinetic parameters following multiple doses of 25 to 600 mg sitagliptin in healthy young men at steady state (N=8) (P004)

Parameter	25 mg q.d.	50 mg q.d.	100 mg q.d.	200 mg q.d.	400 mg q.d.	600 mg q.d.	300 mg b.i.d.
AUC _{0-∞} , μM·hr [‡]	2.13	3.71	8.48	16.2	29.6	51.1	27.6
C _{max} , nM [†]	172	366	941	2290	3790	7550	4550
C _τ , nM [†]	38.5	56.2	107	151	225	370	956
T _{max} , hr [‡]	2	2.5	3	1	2	2	1
Apparent terminal t _{1/2} , hr [§]	13.6	14.2	14.4	13.3	12.4	11.8	---
f _{e,0-τ} [‡]	0.707	0.698	0.758	0.708	0.492	0.749	0.832
Cl _R [†] , mL/min	337	369	363	354	262	351	428
AUC _{0-τ} ^{SS} / AUC _{0-τ} ^{SD}	1.24	1.29	1.14	1.05	1.07	---	1.40
C _{max} ^{SS} / C _{max} ^{SD}	1.24	1.32	1.07	1.01	1.04	---	1.41
C _τ ^{SS} / C _τ ^{SD}	1.24	1.29	1.34	1.15	1.23	---	1.51
Accumulation t _{1/2} , hr [§]	8.59	10.8	7.77	4.99	4.57	---	6.55

[†] Geometric least-squares mean.
[‡] Median.
[§] Harmonic mean.
^{||} Fraction of dose excreted unchanged in urine extrapolated to infinity.
[¶] Renal Clearance.
AUC_{0-τ} = AUC_{0-24 hr} for once daily doses and AUC_{0-12 hr} for twice daily doses.
f_{e,0-τ} = f_{e,0-24 hr} for once daily doses and f_{e,0-12 hr} for twice daily doses.
C_τ = C₂₄ for once daily doses and C₁₂ for twice daily doses.
SS=Steady-state (Day 10); SD=Single Dose (Day 1).
q.d.=once daily; b.i.d.=twice daily.

The accumulation ratios for 25 mg, 100mg, and 400 mg QD are 1.24 (90% CI: 1.16, 1.32), 1.14 (90% CI: 1.06, 1.21), and 1.07 (90% CI: 1.00, 1.14), respectively. The average accumulation ratio (steady state versus single dose) across the dose range studied for q.d. doses ranged from 1.05 to 1.29. Overall, the multiple-dose data are consistent with that observed following single dose administration of sitagliptin. Plasma AUC_{0-∞} increased approximately dose-proportionally over the range of doses studied (25 to 600 mg q.d.). C_{max} increased in a slightly greater than dose proportional manner and C₂₄ increased in a less than dose proportional manner. There was a trend toward shorter T_{max} with increasing dose. The apparent terminal elimination half-life was 11.8 to 14.4 hours over the dose range of 25 mg q.d. to 600 mg q.d.

2.2.3 What is the absolute bioavailability of sitagliptin and what is food effect on the pharmacokinetics of sitagliptin?

In a 2-Part, randomized, placebo-controlled, intravenous dose escalation study, the pharmacokinetics of rising intravenous doses of sitagliptin and definitive absolute bioavailability/food effect of sitagliptin in healthy adult subjects were evaluated,

Part I was a fixed-sequence design in which rising single intravenous doses of 25-, 50-, and 100-mg sitagliptin (N=8) or matching placebo (N=2) were given in Periods 1, 2, and 3, respectively. The same 2 subjects in each period received placebo. All intravenous doses of sitagliptin were given after an overnight fast. There was at least a 5-day washout between doses. In each period, blood and urine samples were collected at specified time points for determination of sitagliptin concentrations. Continuation of each period was dependent on the tolerability of the previous dose. The pharmacokinetic parameters of intravenous administration of sitagliptin are summarized in Table 5.

Table 5. Mean sitagliptin (SD) pharmacokinetic parameters following administration of 25-, 50- and 100-mg intravenous doses of sitagliptin to healthy adult male and female subjects (N=8)

Parameter	Mean [†] (Between-subject SD [‡])		
	25 mg	50 mg	100 mg
AUC _{0-∞} (μM•hr)	2.47 (0.52)	4.85 (0.58)	9.88 (1.33)
C _{eo1} (nM)	342 (91)	830 (140)	1741 (184)
C _{24 hr} (nM)	20.5 (6.2)	32.8 (5.0)	60.3 (11.1)
Cl _R (mL/min)	249 (168)	340 (124)	279 (126)
Cl _p (mL/min)	414 (88)	421 (50)	413 (56)
Cl _R / Cl _p	0.60 (0.33)	0.81 (0.21)	0.67 (0.22)
V _{d,ss} (L)	262 (44)	234 (28)	198 (30)
MRT (hr)	10.39 (0.82)	9.20 (0.33)	7.92 (0.55)
Apparent Terminal t _{1/2} (hr)	11.7 (1.5)	12.3 (0.7)	10.9 (1.0)
f _{e,0-∞}	0.654 (0.265)	0.828 (0.172)	0.700 (0.193)

[†] Mean = geometric mean for AUC_(0-∞), C_{eo1}, C_{24 hr}, Cl_R, Cl_p and Cl_R/Cl_p, harmonic mean for apparent terminal t_{1/2} and arithmetic mean for V_{d,ss}, MRT and f_{e,0-∞}.

[‡] SD = Standard deviation; back-transformed from log scale for AUC_(0-∞), C_{eo1}, Cl_R, Cl_p and Cl_R/Cl_p, jackknife SD for apparent terminal t_{1/2}.

For Part II, a different group of 12 subjects was randomized and received 3 single doses of sitagliptin in a balanced, 3-period, crossover design: subjects received a 100-mg oral dose of sitagliptin in the fasting state (Treatment A); after completion of a standard breakfast, subjects received a single 100-mg oral dose of sitagliptin in the fed state (Treatment B) and subjects received a 100-mg intravenous dose of sitagliptin infused over 2 hours in the fasting state (Treatment C). All doses of study drug were administered with 240 mL water. There was at least a 5-day washout between doses. The results are summarized in Table 6.

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Table 6. Mean sitagliptin (SD) pharmacokinetic parameters following 100-mg intravenous doses (fasted) and food effect on AUC_{0-∞} (μM•hr) and C_{max} (nM) following 100-mg oral dosing (fasted and fed) of sitagliptin to healthy adult male and female subjects (N=12)

Parameter	Mean [†] (Between-subject SD [‡])			
	100-mg IV Fasted	100-mg Oral Fasted	100-mg Oral Fed	GMR [§] (90% CI) (fed/fasted oral)
AUC _{0-∞} (μM•hr)	9.08 (1.24)	7.90 (1.22)	8.17 (0.97)	1.03 (0.97, 1.11)
C _{max} (nM)	NA	817 (250)	772 (180)	0.94 (0.86, 1.03)
T _{max} (hr)	NA	3.0 (NA) [#]	3.0 (NA) [#]	NA
Apparent terminal t _{1/2} (hr)	10.6 (2.0)	11.7 (2.0)	11.8 (2.0)	NA
Cl _R (mL/min)	249 (168)	340 (124)	NA	NA
f _{e,0-∞}	0.731 (0.159)	0.651 (0.149)	NA	NA

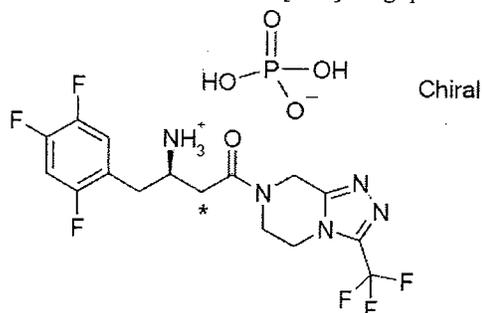
[†] Mean = geometric mean for AUC_{0-∞}, C_{max}, Cl_R, harmonic mean for apparent terminal t_{1/2} and arithmetic mean for f_{e,0-∞}.
[#] Median for T_{max}
[‡] SD = Standard deviation; Back-transformed from log scale for AUC_{0-∞}, C_{max}, Cl_R, and jackknife SD for apparent terminal t_{1/2}.
[§] GMR = geometric mean ratio (fed/fasted oral).
^{||} CI = confidence interval.
 NA = not available.

The absolute bioavailability (AUC_{0-∞} following a 100-mg fasting oral dose / AUC_{0-∞} following a 100-mg fasting IV dose) of sitagliptin was 87% with a corresponding 90% CI of (81%, 93%). The study of food effect showed that the 90% CI for the AUC_{0-∞} GMR (0.97, 1.11) and for the C_{max} GMR (0.86, 1.03) fell within the bounds of (0.80, 1.25). This reviewer agrees with the sponsor that there is an absence of a food effect on sitagliptin bioavailability.

2.2.7 Is the chiral integrity of sitagliptin in human plasma evaluated?

Sitagliptin has one chiral center. The chiral integrity of sitagliptin in clinical plasma samples was evaluated in Study P033. Following 200-mg doses, the samples collected at 2 hours (near T_{max}) and 15 hours were assayed for presence of the enantiomer of sitagliptin. The results of the analysis revealed that the concentration of the enantiomer to sitagliptin at each time point was below the assay limit of quantitation (1.23 nM). Since the C_{max} following the 200-mg dose is approximately 2000 nM, these results indicate that sitagliptin plasma concentrations are at least 1600-fold higher than that of the enantiomer. These results demonstrate that there is negligible chiral inversion of sitagliptin in vivo.

Figure 1. Chemical Structure of [14C] sitagliptin



The asterisk denotes the position of the ¹⁴C label

2.2.7 Is sitagliptin pharmacokinetics dose-proportional?

In a single-center, open-label, randomized, 5-period, balanced crossover study, the dose proportionality of sitagliptin tablets within the 25- to 400-mg dose range was assessed in 10 healthy adult subjects. In each period, the subjects received either a single 25-, 50-, 100-, 200-, or 400-mg dose of sitagliptin in the fasted state. Mean plasma concentration versus time profiles are depicted in Figure 2 and the sitagliptin pharmacokinetic parameters are shown in Table 7.

Figure 2. Mean sitagliptin plasma concentrations following administration of single oral doses of Final Market Image 25, 50, 100, 200, and 400 mg of sitagliptin to healthy male and female subjects (N=10) (P033)

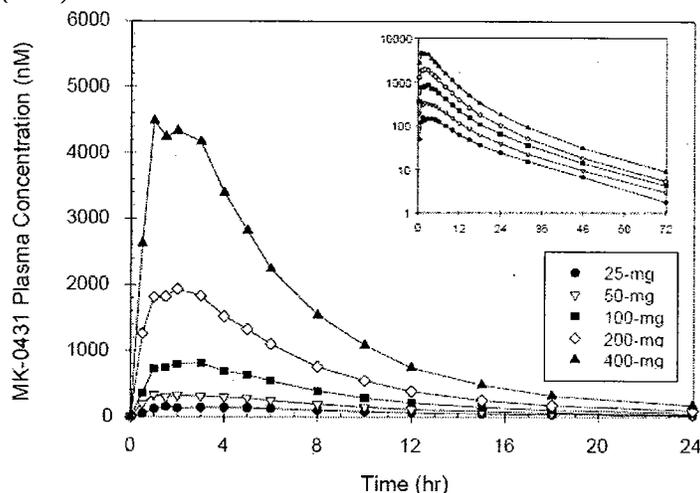


Table 7. Mean sitagliptin pharmacokinetic parameters following single oral doses of Final Market Image tablets to healthy male and female subjects (N=10) (P033)

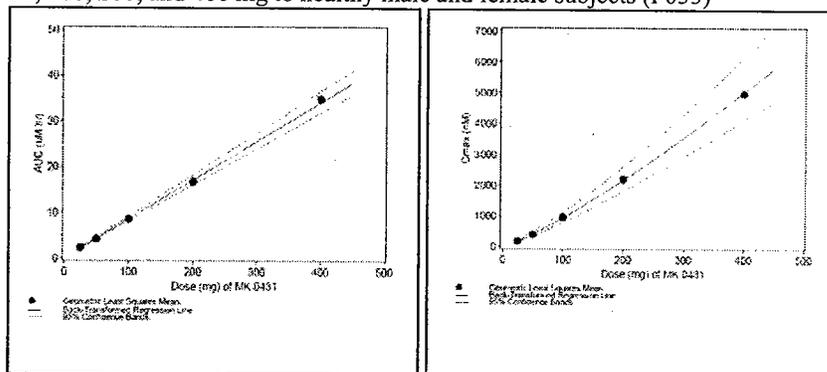
MK-0431 Parameter	LS Mean [†]					Slope (90% CI) [‡]	GMR (90% CI) [§] 400 mg/100 mg
	25 mg	50 mg	100 mg	200 mg	400 mg		
AUC _{0-∞} μM·hr	2.20	4.17	8.52	16.7	34.9	1.00 (0.98, 1.01)	1.02 (0.99, 1.06)
C _{max} nM	177	378	950	2184	4949	1.21 (1.17, 1.26)	1.30 (1.13, 1.50)
C _{24 hr} nM	23.8	38.3	63.5	95.7	170	0.70 (0.67, 0.72)	0.67 (0.62, 0.72)
T _{max} hr	3.5	2.5	1.3	2.0	2.5		
t _{1/2} hr	13.1	13.0	12.4	11.7	11.3		
Cl _R mL/min	325	357	350	342	347		
f _{e, 0-∞} [§]	0.707	0.733	0.738	0.703	0.744		

[†] Geometric least-squares mean, back-transformed from log scale.
[‡] Median.
[§] Arithmetic least-squares mean.
^{||} Harmonic least-squares mean.
^{*} Slope of log[PK parameter] versus log[dose] from power-law model.
[§] Ratio of dose adjusted (to 100 mg) geometric least-squares means (400 mg/100 mg).

A plot of geometric mean AUC_{0-∞} values versus dose administered along with the fitted regression line using the power law model is presented in Figure 3(Left). For AUC_{0-∞}, the slope (90% CI) by the power-law model was 1.00 (0.98, 1.01). The sitagliptin dose adjusted (to 100 mg) AUC_{0-∞} geometric least-squares mean ratio (GMR, 400 mg/100 mg) was 1.02 with a corresponding 90% CI of (0.99, 1.06). Therefore, sitagliptin AUC_{0-∞} increases dose proportionally with increasing dose across the tested dose range.

A plot of geometric mean Cmax values versus dose administered along with the fitted regression line using the power law model is provided in Figure 3(Right). For Cmax, the slope and its 90% CI estimated by the power-law model was 1.21 (1.17, 1.26). These results suggest that sitagliptin Cmax increases in a modestly greater than dose proportional manner with dose.

Figure 3. Sitagliptin AUC_{0-∞} and Cmax versus dose following single oral doses of Final Market Image 25, 50, 100, 200, and 400 mg to healthy male and female subjects (P033)



Based on the nature of drug action, this reviewer agrees that AUC is anticipated to be the most relevant pharmacokinetic parameter for a DPP-IV inhibitor. Sitagliptin PK can be considered as dose proportional.

2.2.10 What is characteristics of sitagliptin metabolism and elimination?

In a mass balance study, 6 healthy male subjects received 83.04 mg ^[14C] sitagliptin followed by collection of plasma, urine, and feces for 7 days. Approximately 100% of the oral radioactivity dose was recovered with 87% in urine and 13% in feces over the 1-week postdose collection interval. Approximately 79% of the sitagliptin dose was excreted unchanged in urine, indicating that the major pathway of elimination of sitagliptin is via urinary excretion. Approximately 16% of the oral radioactivity dose was recovered as metabolites (13% of the dose in urine and 3% of the dose in feces), indicating that metabolism is a minor pathway of elimination of sitagliptin. Parent compound, sitagliptin accounted for the majority of the radioactivity in plasma (74%), as determined by the ratio of sitagliptin AUC and radioactivity AUC.

Six metabolites were detected at trace levels, each representing <8% of the radioactivity in plasma [Figures 4 and 5]. The most abundant metabolites in plasma were M5 (4 to 7% of radioactivity) and M2 (1 to 6%), both of which are formed by oxidative desaturation of the piperazine ring followed by cyclization. Other metabolites included M6 (a group of hydroxylated derivatives; 1 to 4%), M1 (N-sulfate conjugate; 2 to 4%), M4 (carbamoyl glucuronide conjugate; 1%) and M3 (ether glucuronide conjugate of a hydroxylated derivative; <1%). Three of the six metabolites of MK-0431 (M1, M2, and M5) observed in plasma have a known structure and were tested in vitro and shown to have no appreciable plasma DPP-IV inhibitory activity (the other three metabolites were not tested for inhibition of DPP-IV activity). Two of the metabolites not tested for activity (M3 and M4) are glucuronide conjugates. M6 is a very minor metabolite only present in trace levels; the exact structure(s) are not known.

Figure 4. Main Biotransformation Pathways For [¹⁴C]sitagliptin in Humans (P009)

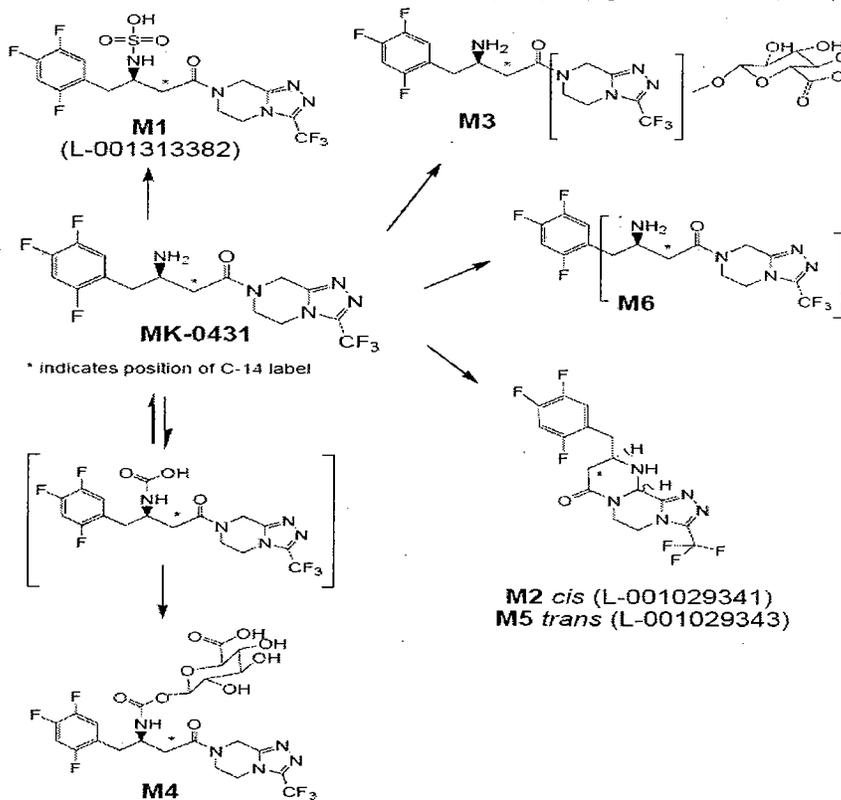
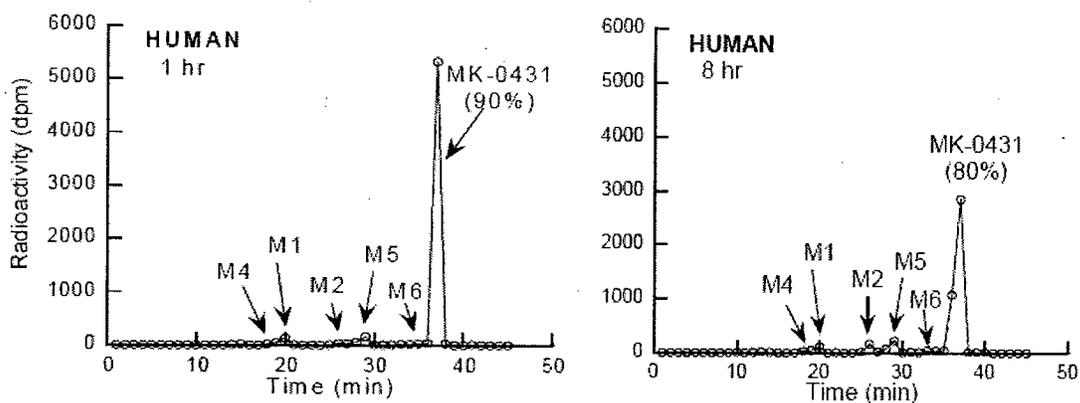


Figure 5. Radiochromatograms of plasma from humans (80 mg) after oral administration of [¹⁴C] sitagliptin



2.2.10 *What are findings from in vitro drug metabolism and transporter studies on sitagliptin?*

The in vitro metabolism of sitagliptin was studied in microsomes and hepatocytes prepared from human livers. The results demonstrated minimal in vitro metabolism of sitagliptin by liver microsomes and hepatocytes. One-hour incubations of 10 μM [^{14}C] sitagliptin with an NADPH-regenerating system and human liver microsomes resulted in no more than 13% turnover. Similarly, less than 15% of 10 μM [^{14}C] sitagliptin was metabolized after 4-hr incubations with human hepatocytes. LC-MS/MS analysis of microsomal and hepatocyte incubation extracts revealed the presence of M2 and M5, and M6 in human liver microsomes, and human hepatocytes.

Sitagliptin was evaluated as a reversible inhibitor of seven human liver microsomal cytochrome P450 (CYP) activities. The IC₅₀ values of sitagliptin for all the CYP activities tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) were >100 μM . Also, sitagliptin was evaluated as a potential pre-incubation time-dependent inhibitor of human liver CYP3A4 (testosterone 6 β -hydroxylase) activity. The results indicated that sitagliptin was not a time-dependent inhibitor of CYP3A4.

The potential of sitagliptin to induce CYP3A4 mRNA expression and enzyme activity in human primary hepatocytes from three organ donors was evaluated. CYP3A4 mRNA expression levels and CYP3A-mediated testosterone 6 β -hydroxylase activity in the hepatocyte cultures were quantified after treatment with sitagliptin (1 and 10 μM) and compared to vehicle and positive (rifampicin, 10 μM) controls. The data indicated that CYP3A4 mRNA expression and activity were not affected meaningfully in response to sitagliptin treatment (1 and 10 μM). The CYP3A4 mRNA levels and activity were within 10 to 30% of the values in solvent-treated hepatocytes, except for the mRNA expression in one of the hepatocyte incubations with 1 μM sitagliptin, which was ~50% lower than the value in the solvent control incubation. The response to the positive control rifampicin (10 μM) was 7.9- to 10-fold increase in CYP3A4 mRNA expression, and 8.4- to 15-fold increase in CYP3A activity. These data suggest that MK-0431 has no potential to induce CYP3A4.

The bi-directional transport of sitagliptin (10 μM) was evaluated in LLC-PK1 cells expressing the human multidrug resistance gene, MDR1. In MDR1 expressing cell lines, sitagliptin exhibited greater basolateral to apical (B \rightarrow A) than apical to basolateral (A \rightarrow B) transport, indicating that sitagliptin is a substrate of the human and mouse P-gp.

The effect of sitagliptin on human MDR1 P-glycoprotein (P-gp)-mediated efflux transport of several known P-gp substrates was evaluated using bi-directional transport studies in LLC-PK1 cells and LLC-PK1 cells stably expressing a human MDR1 cDNA. At concentrations of 0.3 to 500 μM , sitagliptin had no inhibitory effect on the MDR1 P-gp mediated transport of digoxin, verapamil, ritonavir, and vinblastine. Sitagliptin weakly inhibited MDR1 Pgp-mediated transport of quinidine at 500 μM (~30% decrease), but had no effect at 0.3 to 250 μM . On the contrary, cyclosporin A, a known potent P-gp inhibitor, significantly inhibited MDR1 Pgp-mediated transport of sitagliptin with an IC₅₀ of $1.1 \pm 0.3 \mu\text{M}$.

The sponsor conducted in vitro uptake experiments with different cell lines expressing several of the known human renal transporters, namely hOCT2, hOAT1, hOAT3, hOAT4, and hPEPT1. The results indicated that sitagliptin is a low affinity substrate of hOAT3, not a substrate of hOCT2, hOAT1 or hPEPT1. The data on hOAT4 were inconclusive.

Overall, in vitro assays indicated that at clinically relevant concentrations, sitagliptin did not inhibit cytochrome P450s or P-glycoprotein, nor did it induce human CYP3A4. Sitagliptin was shown to be a substrate of the human P-glycoprotein and the human renal organic anion transporter hOAT3.

2.2.8 *What is plasma protein binding for sitagliptin?*

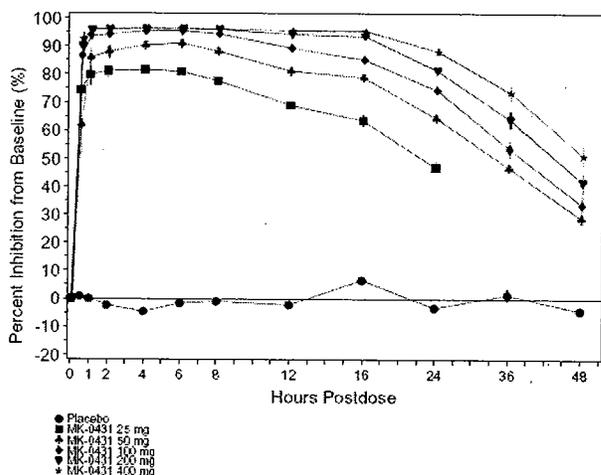
The reversible binding of [^3H] sitagliptin to plasma proteins was determined by ultracentrifugation. The percent of binding was similar in all species tested, with mean values of 32, 33, 32, 33, and 38% in the mouse, rat, rabbit, dog, and human, respectively. Although slightly different concentrations were tested in the different species (concentrations were adjusted based on the clinically relevant levels in each species),

there was no evidence that protein binding was concentration dependent, except possibly in rabbit plasma, where protein binding appeared to decrease from 42% at 0.02 μM to 29% at 0.2 μM , and 24% at 2 μM . Following incubation of [^3H]sitagliptin with a solution of albumin and alpha1-acid glycoprotein at physiologically relevant concentrations of these plasma proteins, 40 and 0.4 mg/mL, respectively, binding was more extensive to albumin (64%) than alpha1-acid glycoprotein (25%).

2.2.9 What is the effect of sitagliptin on the inhibition of DPP-IV activity following single oral doses and multiple doses in healthy subjects and type 2 diabetic patients?

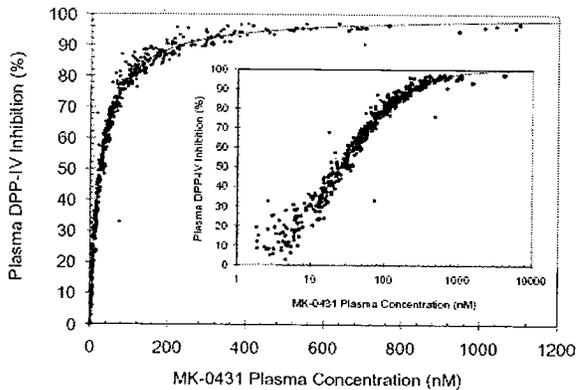
The effect of sitagliptin on pharmacodynamics following single rising doses was investigated in Studies P001, 003, P009. The weighted average inhibition (WAI) of plasma DPP-IV activity over 24 hours was 80% or higher for doses of 100 mg and above relative to placebo (Figure 6). These data support once daily dosing of sitagliptin for the treatment of type 2 diabetes.

Figure 6. Mean percent inhibition (%) of DPP-IV activity from baseline versus time (hours) postdose after single oral doses of sitagliptin in healthy young male subjects (N=6) (P001, P001C1) (Mean \pm SE)



The relationship between plasma sitagliptin concentrations and inhibition of plasma DPP-IV activity was explored. No significant hysteresis was observed; that is, plasma DPP-IV inhibition is dependent on plasma concentration only, and not on time. Using an Emax model the plasma EC₅₀ was 25.7 nM and the EC₈₀ was approximately 100 nM, predicting that plasma sitagliptin concentrations at trough of approximately 100 nM or higher will be associated with near maximal efficacy in glycemic control [Figure 7].

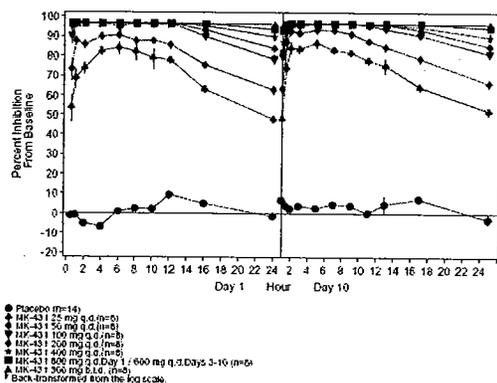
Figure 7. Inhibition of plasma DPP-IV activity versus sitagliptin plasma concentrations following single oral doses of 1.5 to 600 mg to healthy young male subjects (P001, P001C1) (solid line indicates the model fitted curve; inset indicates log scale)



The plasma DPP-IV inhibition time profiles after single oral doses of sitagliptin were studied in elderly male, elderly female, young female and young obese male subjects. The results are generally similar [P003].

There was a dose- and concentration-related increase in the percent inhibition of plasma DPP-IV enzyme activity for multiple doses from 25 to 600 mg [P013]. Multiple doses of 100 mg once daily or higher were associated with geometric mean values for inhibition of DPP-IV activity at steady-state trough of approximately 80% or higher [Figure 8]. These pharmacodynamic data support a once daily dosing regimen for sitagliptin in the treatment of type 2 diabetes. The relationship between sitagliptin plasma concentrations and plasma DPP-IV inhibition was evaluated on Day 1 and Day 10 to determine if this PK/PD relationship was altered with multiple oral doses. Fitting the data to an Emax model, no substantial differences in the EC50 value were observed between Day 1 and Day 10. The EC50 value on Day 10 was approximately 26 nM and the estimated EC80 value was approximately 100 nM. Following the administration of standardized meals at various times postdose, sitagliptin was associated with an increase in post-meal active GLP-1 levels. Following the administration of each standardized meal, doses of 25 mg or higher were associated with approximately 2-fold or greater increases in active GLP-1 levels, and 2- to 3-fold increases in the ratio of active to total GLP-1 levels, as compared to placebo.

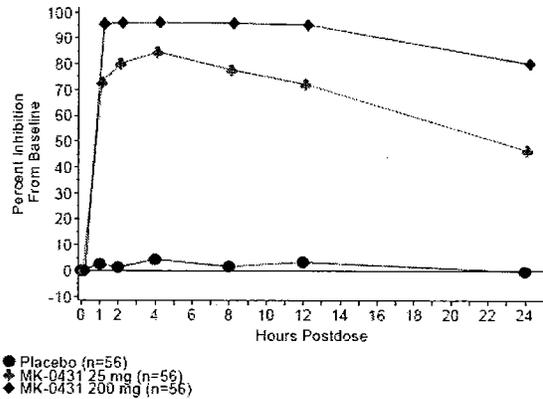
Figure 8. Percent inhibition (%) of DPP-IV activity from baseline (mean \pm standard error) versus time (hours) postdose on Days 1 and 10 after multiple oral doses of sitagliptin in healthy young male subjects



In patients with type 2 diabetes (P005), the 200-mg dose was associated with approximately 95% plasma DPP-IV inhibition through 12 hours postdose falling to approximately 80% inhibition at 24 hours

postdose. The 25-mg dose was associated with peak inhibition of approximately 85% inhibition falling to approximately 50% inhibition at 24 hours postdose (Figure 9).

Figure 9. Plasma DPP-IV percent inhibition from baseline following single oral doses of sitagliptin or placebo in patients with type 2 diabetes (Mean \pm SE)



Therefore, sitagliptin inhibited plasma DPP-IV activity in a dose and concentration-dependent manner.

2.2.10 What is the effect of sitagliptin on pharmacodynamics following single oral doses in type 2 diabetic patients?

In a 3-period crossover study (P005), patients with type 2 diabetes on diet-exercise treatment alone received single oral doses of 25 mg and 200 mg sitagliptin or placebo. Results showed that sitagliptin reduced glycemic excursion following an OGTT (Oral Glucose Tolerance Test) at 2 hours postdose. Both the 25- and 200-mg doses of sitagliptin were associated with significant ($p < 0.001$) reductions in incremental glucose AUC_{0-240 min} compared to placebo by 26% following the 200-mg dose and by 22% following the 25-mg dose. The reduction in incremental glucose AUC following the 200-mg dose was not statistically significantly different from that observed following the 25-mg dose (Figure 10). Following an OGTT at 24 hours postdose in a subset of patients ($n = 19$), incremental glucose AUC_{0-120 min} was reduced by 18% after the 200-mg dose and by 9% after the 25-mg dose (Figure 11).

Figure 10. Plasma glucose (mg/dL) following single oral doses of sitagliptin or placebo and an OGTT at 2 hours postdose in patients with type 2 diabetes (geometric mean \pm SE)

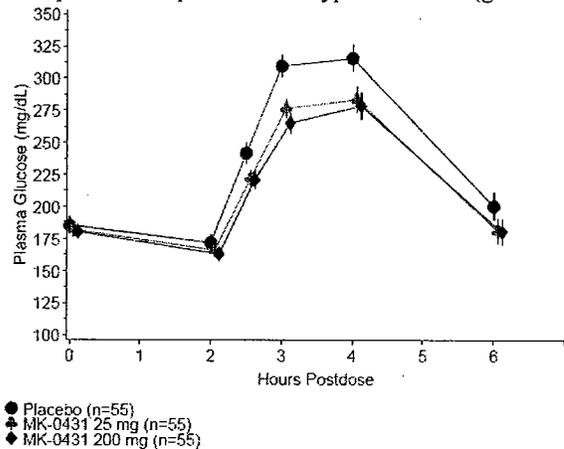
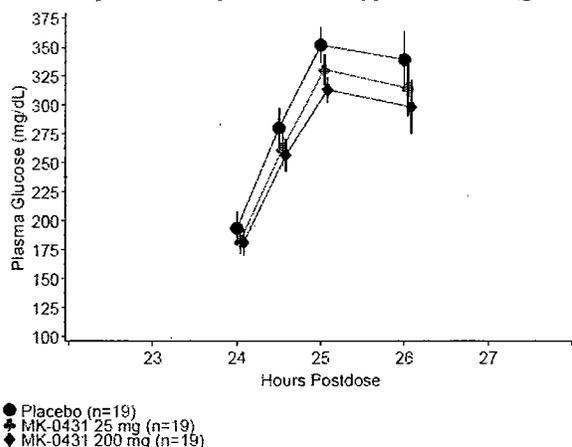


Figure 11. Plasma Glucose (mg/dL) following single oral doses of sitagliptin or placebo and an OGTT at 24 hours postdose in patients with type 2 diabetes (geometric Mean \pm SE)



Following an OGTT at 24 hours postdose, sitagliptin treatment significantly increased active GLP-1 levels, approximately 1.9-fold for the 200-mg dose and approximately 1.3-fold for the 25-mg dose, as compared to placebo. Following the OGTT at 2 hours postdose, the post-OGTT insulin AUC_{0-120 min} GMR (active/placebo) and corresponding 95% CI were 1.21 (1.11, 1.32) and 1.22 (1.12, 1.33) following the 200-mg and 25-mg doses, respectively. The post-OGTT C-peptide AUC_{0-120 min} GMR (MK-0431/placebo) and corresponding 95% CI were 1.21 (1.13, 1.28) and 1.13 (1.07, 1.20) following the 200-mg and 25-mg doses, respectively. The post-OGTT glucagon AUC_{0-120 min} GMR (MK-0431/placebo) and corresponding 95% CI were 0.86 (0.81, 0.92) ($p < 0.001$) and 0.93 [0.87, 0.99] ($p = 0.020$) following the 200-mg and 25-mg doses, respectively.

Therefore, sitagliptin reduced post-OGTT glucose excursion, enhanced active GLP-1 and GIP levels, enhanced post-OGTT C-peptide and insulin levels and reduced post-OGTT glucagon levels in a dose dependent manner.

2.2.11 What is the justification for 100-mg dose once a day regimen?

Pharmacokinetic and pharmacodynamic analyses from the single dose study in patients with type 2 diabetes (P005) suggest that near-maximal reduction of post challenge glucose excursion is associated with sitagliptin plasma concentrations of approximately 100 nM or higher, plasma DPP-IV inhibition of 80% or higher and augmentation of post-challenge active GLP-1 levels of 2-fold or higher. It was reasoned that for optimal chronic glucose lowering in patients with type 2 diabetics, the plasma DPP-IV inhibition should be 80% or greater at trough. These data served as the basis for selecting doses in the Phase II dose range finding studies (P010 and P014).

Four Phase II studies were performed, 2 dose-range finding studies (P010, P014), a metformin combination study (P015), and a study in Japanese patients with T2DM (RC431A201). The 2 dose-range finding studies (P010 and P014) examined doses from 10 to 100 mg per day of sitagliptin in monotherapy use. Results of the studies showed that 100 mg per day, either as 100 mg q.d. (as assessed in P014) or 50 mg b.i.d. (as assessed in P010), provided maximum glucose-lowering; there was no meaningful difference in efficacy with sitagliptin 100 mg administered as 100 mg once-daily or as 50 mg administered twice-daily (as assessed in P014). Thus, these studies supported the selection of the sitagliptin 100 mg dose administered once-daily for further development. Since no clear plateau between 50 and 100 mg per day was established, doses above 100 mg per day were considered to have the potential to provide additional glycemic benefit. For this reason, a dose of 200 mg per day was included in selected Phase III studies (Table 8). Results from these two Phase 3 trials exhibited inconsistent findings since 200-mg showed more efficacy than 100-mg in Study P021V1, but less efficacious in Study P032V1. Therefore, 200 mg did not

demonstrate a better efficacy than 100-mg. This reviewer agrees with sponsor that 100-mg once a day can be recommended for all patients but with renal insufficiency.

Table 8. Analysis of change from baseline in HbA1c (%) at study endpoint all-patients-treated population P021V1, P023V1 Phase III monotherapy studies

Treatment	N	Mean (SD)		Change From Baseline			LS Mean Difference From Placebo (95% CI)
		Baseline	Study Endpoint	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	
P021V1 (Study Endpoint=Week 24)							
MK-0431 100 mg q.d.	229	8.01 (0.88)	7.39 (1.15)	-0.62 (0.07)	-0.61 [†] (0.06)	(-0.74, -0.49)	-0.79 [†] (-0.96, -0.62)
MK-0431 200 mg q.d.	238	8.08 (0.94)	7.31 (1.14)	-0.78 (0.06)	-0.76 [†] (0.06)	(-0.88, -0.64)	-0.94 [†] (-1.11, -0.77)
Placebo	244	8.03 (0.82)	8.20 (1.37)	0.17 (0.07)	0.18 [‡] (0.06)	(0.06, 0.30)	-
P023V1 (Study Endpoint=Week 18)							
MK-0431 100 mg q.d.	193	8.04 (0.82)	7.58 (1.15)	-0.46 (0.06)	-0.48 [†] (0.07)	(-0.61, -0.35)	-0.60 [†] (-0.82, -0.39)
MK-0431 200 mg q.d.	199	8.14 (0.91)	7.81 (1.31)	-0.34 (0.07)	-0.36 [†] (0.06)	(-0.48, -0.23)	-0.48 [†] (-0.70, -0.26)
Placebo	103	8.05 (0.90)	8.21 (1.35)	0.16 (0.09)	0.12 (0.09)	(-0.05, 0.30)	-

[†] p<0.001, [‡] p<0.05.
 CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.

2.2.12 Is there an evidence of dose/concentration response relationship? (by Dr. Atul Bhattaram, PM reviewer)

Yes, there is an evidence of dose-response relationship. Sponsor evaluated the effects of various doses and once-a-day/twice-a-day dosing regimen in Phase II studies (P010, P014). In study P010, patients were randomized in a balanced fashion to one of 6 treatment groups: 4 doses of MK-0431 (5, 12.5, 25 or 50 mg b.i.d) placebo or Glipizide 5-20 mg (elective transition). In study P014, patients were randomized in a balanced fashion to 1 of 5 treatment groups: 3 once-daily doses of MK-0431 (25, 50 or 100 mg) or to a twice-daily dose of MK-0431 (50 mg b.i.d), or to placebo. The studies had 12-week double blind treatment periods. Figure 12 below shows the dose-response relationship from both P010 and P014 studies for the primary endpoint (% change in HbA1c relative to placebo). There was no difference in the primary endpoint when MK-0431 was administered as 50 mg b.i.d or 100 mg q.d. Based on these findings sponsor evaluated the effects of 100 and 200 mg q.d in Phase III studies. The Phase III monotherapy studies (P021V1 and P023V1) were placebo-controlled, double-blind, randomized, parallel group studies. Study P021V1 had a 24-week double-blind treatment period and Study P023V1 had a 18-week double-blind treatment period. Figure 13 shows the time course of changes in HbA1c in the Phase III studies. Overall, the sponsor well identified the intended dose of 100 mg q.d for approval.

Figure 12. Dose-response (placebo subtracted LS Mean Difference in %HbA1c) relationship after various dose(s)/dosing regimens of MK-0431.

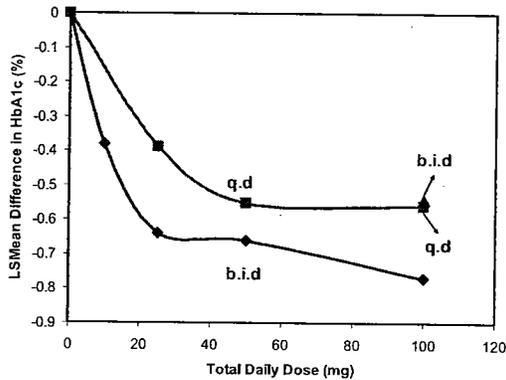
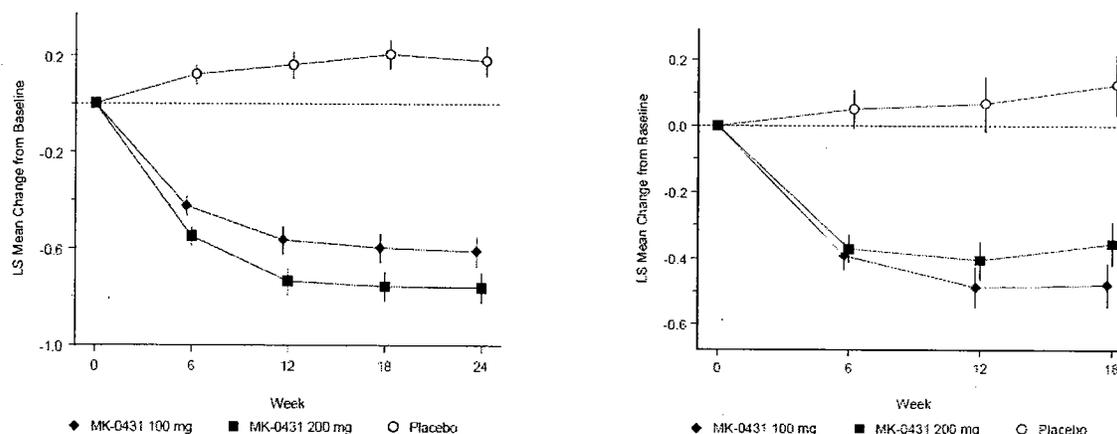


Figure 13. LS Mean change from baseline in HbA1c (%) Over Time (LS Mean \pm SE) by treatment group all-patients-treated population with data carried forward P021V1, P023V1 Phase III monotherapy studies



2.2.13 What is the effect of sitagliptin on QT intervals?

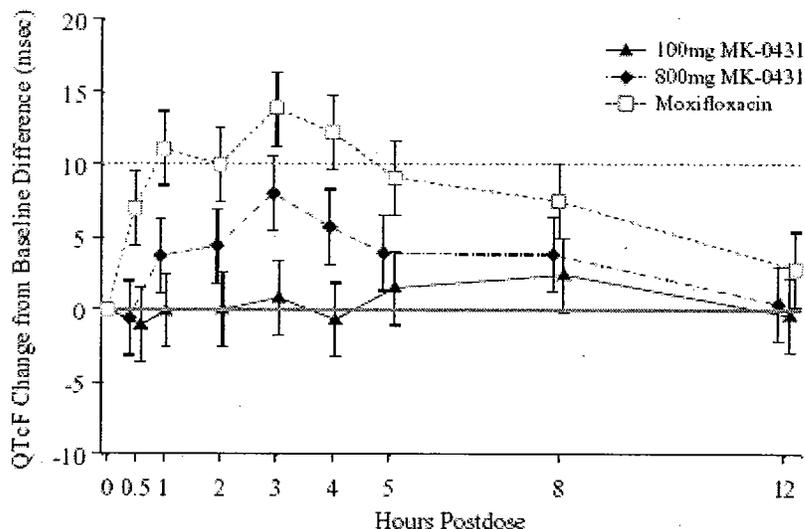
In a 2-center, randomized, double-blind, placebo-controlled, double-dummy, 4-period crossover study in 86 (79 were available for final QTc analysis) healthy subjects, the potential effect of therapeutic and supratherapeutic doses of sitagliptin on QTc interval prolongation was assessed. Each period consisted of a single oral dose of either 400 mg moxifloxacin, 100 mg sitagliptin, 800 mg sitagliptin, or placebo. There was a 7-day washout interval between periods.

The primary endpoint of this study (based upon the draft ICH E14 guidance) was the change in QTcf (Fridericia's correction= $QT/RR^{1/3}$) interval from baseline as measured from digital 12-lead ECGs recorded on a ~~digital~~ digital Holter recorder and subsequently extracted by the core laboratory according to the time points specified in the protocol (baseline predose, 1, 2, 3, 4, 5, 8, and 12 hours postdose). The interpretation of all of the ECGs was done in a blinded fashion by a centralized core laboratory. ECGs for an individual subject were interpreted by the same cardiologist. Five replicates of ECGs were extracted from each time point and the intervals were averaged to reduce the variability of the measurement and to increase precision of the estimate.

The baseline value for QTc interval was defined as the average of 5 replicate baseline QTc intervals from the predose ECGs. The primary hypothesis tested in this study was that the change in QTc interval from baseline compared to placebo will be less than 10 msec at time points that are most likely to correspond to the peak concentration of sitagliptin (3 hours following the 100-mg dose and 1 hour following the 800-mg dose; based on historical data). The change in QTc interval at all of the time points studied was assessed and summarized to identify maximal mean effects on QTcf.

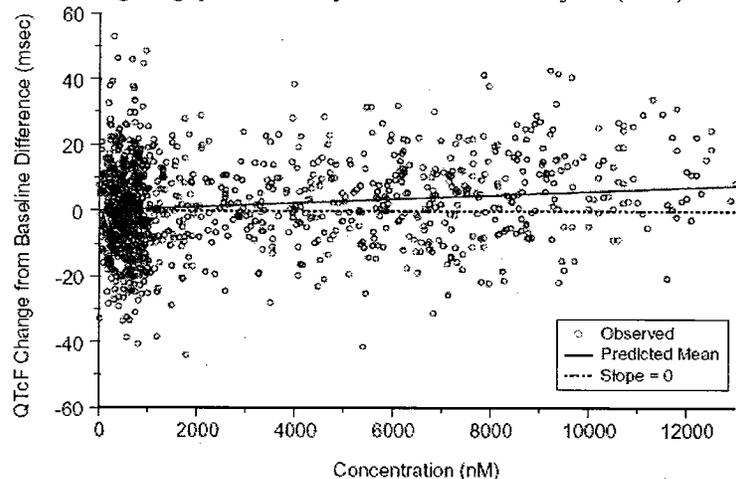
The QTcf change from baseline over time following each dose and after moxifloxacin is indicated in [Figure 14]. Following a dose of 100 mg, there was no statistically significant nor clinically meaningful increase in QTcf observed at any time point. The supratherapeutic sitagliptin 800-mg dose was associated with a small but statistically significant increase in QTcf; the maximum mean increase in the placebo-corrected change in QTc from baseline at 3 hours postdose was 8.0 msec (the upper bound of the one-sided 95% CI was 10.6 msec). At the prespecified time point of 1 hour, the mean change in QTcf from baseline was 3.7 msec (the upper bound of the one-sided 95% CI was 6.2 msec) for the 800-mg dose, supporting the primary hypothesis. There were no extreme values in this study and categorical analysis of the data did not demonstrate any differences in maximum QTcf (>450 msec, >480 msec, and >500 msec), nor any differences in the maximum QTcf change from baseline (>30 msec and >60 ms) across the 2 doses of sitagliptin and placebo.

Figure 14. Mean (90% CI) QTcf change from baseline differences (active –placebo) for sitagliptin and moxifloxacin treatments and by time point following administration of single oral doses of 100-mg and 800-mg sitagliptin and moxifloxacin to healthy male and female subjects (P032)



The sensitivity of the assay to detect modest increases in QTc interval was established with the positive control moxifloxacin. The mean placebo-corrected QTcf change from baseline differences associated with moxifloxacin ranged from 7.0 msec to 13.9 msec. A plot of individual placebo-corrected QTcf change from baseline values versus plasma sitagliptin concentrations and a fitted line based upon a linear model are shown in [Figure 15].

Figure 15. Individual QTcf change from baseline (placebo-corrected) values versus plasma sitagliptin concentration and the fitted linear PK/QTc model following administration of single oral doses of 100-mg and 800-mg sitagliptin to healthy male and female subjects (P032)



The PK/QTc model demonstrated a shallow relationship between the plasma concentration of sitagliptin and the placebo subtracted QTcf change from baseline. Using the 95% upper-one sided confidence limit of the model-based PK-QTc relationship is used (corresponding to a slope of 0.86 msec/1000 nM), the predicted 95% upper CI for the increase in QTcf for a 100-mg dose at C_{max} would be 0.82 msec. The linear model predicts that plasma concentrations up to 8500 nM (approximately 9-fold higher than the anticipated C_{max} of a clinical dose of 100 mg) would result in a mean placebo-corrected

QTcf change from baseline below 5 msec. This reviewer agrees that sitagliptin dose not generate clinically meaningful QTc prolongation at therapeutic doses.

2.3 INTRINSIC FACTORS

2.3.1 Age, Gender, Race:

- ***Do age, gender, body weight and race impact the pharmacokinetics of sitagliptin?***

In a Phase I study (P003), the effects of age, gender, body weight were evaluated preliminarily on the pharmacokinetics of sitagliptin. The results of this study indicated that (1) elderly subjects (>65 years) had slightly higher plasma sitagliptin concentrations as compared to the young (<45 years). Pooled across genders, the AUC_{0-∞} and C_{max} GMRs values (Elderly/ Young) with corresponding 90% CIs were 1.31 (1.19, 1.43) and 1.23 (1.04, 1.46), respectively; (2) female subjects exhibited a similar AUC_{0-∞}, but modestly higher C_{max} values than male subjects. Pooled across age groups, the AUC_{0-∞} and C_{max} GMRs (female/male) with corresponding 90% CIs were 1.07 (0.97, 1.17) and 1.46 (1.23, 1.73), respectively; (3) sitagliptin AUC_{0-∞} was modestly lower while C_{max} was similar for young male obese subjects as compared to the young male non-obese subjects. The AUC_{0-∞} and C_{max} GMR values (obese male/non-obese male) with corresponding 90% CIs were 0.77 (0.69, 0.86) and 0.91 (0.73, 1.14), respectively.

A population pharmacokinetic analysis of Phase I and Phase II data was performed by the sponsor to analyze the effects of demographic factors and special populations on pharmacokinetics of sitagliptin. Please see the pharmacometrics review on this topic.

2.3.2 Renal impairment:

- ***What is the effect of renal impairment on sitagliptin pharmacokinetics?***

The sponsor conducted a multi-center, open-label, 2-part study in 24 patients with renal insufficiency and 6 healthy concurrent control subjects. The primary objectives are to investigate the effect of varying degrees of renal insufficiency on the pharmacokinetics of sitagliptin after administration of a single 50-mg dose in Parts I and II and to investigate the extent to which sitagliptin is removed from plasma by hemodialysis in Part II.

In Part I, 18 patients with renal insufficiency (6 mild, 6 moderate, and 6 severe) and 6 healthy concurrent control subjects received a single 50-mg oral dose of sitagliptin, followed by 96 hours of plasma sampling for sitagliptin levels. Urine for sitagliptin concentrations was also collected for 48 hours postdose.

In Part II Period 1, 6 patients with End-Stage Renal Disease (ESRD) requiring hemodialysis received a single 50-mg oral dose of sitagliptin followed by 96 hours of plasma sampling for sitagliptin levels. In Period 1, these subjects took the drug immediately *following* their normally scheduled hemodialysis. A subsequent hemodialysis session initiated at approximately 48 hours postdose. In addition to plasma sampling, dialysate samples were collected every ½ hour during hemodialysis and at the end of dialysis for sitagliptin assay. Part II Period 2 consisted of the same 6 patients on hemodialysis from Period 1. These subjects received a single oral dose of 50 mg of sitagliptin 4 hours *prior* to their normally scheduled hemodialysis followed by 72 hours of plasma sampling for sitagliptin levels. In addition, pre and post dialysate plasma samples were collected every half hour during hemodialysis. There was a washout interval of at least 1 week between dosing in Periods 1 and 2 of Part II.

The pharmacokinetic parameters from the renal insufficiency patients enrolled in this study were compared to pharmacokinetic parameters obtained from control subjects (with normal renal function) enrolled in this study as well as those obtained from historical healthy controls that received single oral doses of sitagliptin in other studies (001, 002, 003, 006, 008, 013, 017, 027, 029, 033 and 037). The summary PK parameters and statistical analysis are presented in Table 9 and Figure 16.

Table 9. Summary statistics of sitagliptin pharmacokinetic parameters following administration of single oral doses of 50 mg sitagliptin in patients with varying degrees of renal insufficiency and normal healthy subjects

Parameter	Healthy N=82†	Mild N=6		Moderate N=6		Severe N=6		ESRD†† N=6	
	Mean‡	Mean‡	GMR§ [90% CI]	Mean‡	GMR§ [90% CI]	Mean‡	GMR§ [90% CI]	Mean‡	GMR§ [90% CI]
AUC _{0-∞} †† (μM·hr)	4.40	7.09	1.61 (1.43,1.81)	9.96	2.26 (2.02,2.53)	16.6	3.77 (3.37,4.22)	19.8	4.50 (4.03,5.03)
C _{max} (nM)	391	527	1.35 (1.15,1.58)	560	1.43 (1.23,1.67)	684	1.75 (1.51,2.03)	556	1.42 (1.22,1.65)
C ₂₄ (nM)	43.7	83.3	1.91 (1.60,2.28)	129	2.96 (2.50,3.50)	228	5.22 (4.42,6.16)	260	5.95 (5.04,7.02)
T _{max} (hr)	3.0	3.0	p=0.303	3.0	p=0.771 3.5	3.5	p=0.696	5.0	p=0.027
t _{1/2} , (hr)	13.1	16.1	p=0.011	19.1	p<0.001	22.5	p<0.001	28.4	p<0.001
f _{e, 0-∞} ¶	0.76	0.84	0.09 (0.01, 0.16)	0.64	-0.12 (-0.18, -0.05)	0.52	-0.24 (-0.30,-0.17)	NA	NA
Cl _R #, (mL/min)	339	242	0.71 (0.63,0.81)	126	0.37 (0.33,0.42)	60.2	0.18 (0.16,0.20)	NA	NA

† Sample size for AUC_{0-∞} was 151 and 58 for f_{e, 0-∞} and Cl_R. Healthy control data included data from MRL studies 001, 002, 003, 006, 008, 013, 017, 027, 029, 033, and 037.

‡ Geometric least-squares mean for AUC_{0-∞}, C_{max}, C₂₄, and Cl_R; median for T_{max}; harmonic mean for t_{1/2}; arithmetic mean for f_{e, 0-∞}.

§ GMR = Geometric Mean Ratio; CI = Confidence Interval; p-values reported for T_{max} and t_{1/2}; Arithmetic mean difference and 90% confidence intervals reported for f_{e, 0-∞}.

¶ Apparent Terminal t_{1/2}.

Fraction of dose excreted unchanged in urine extrapolated to infinity.

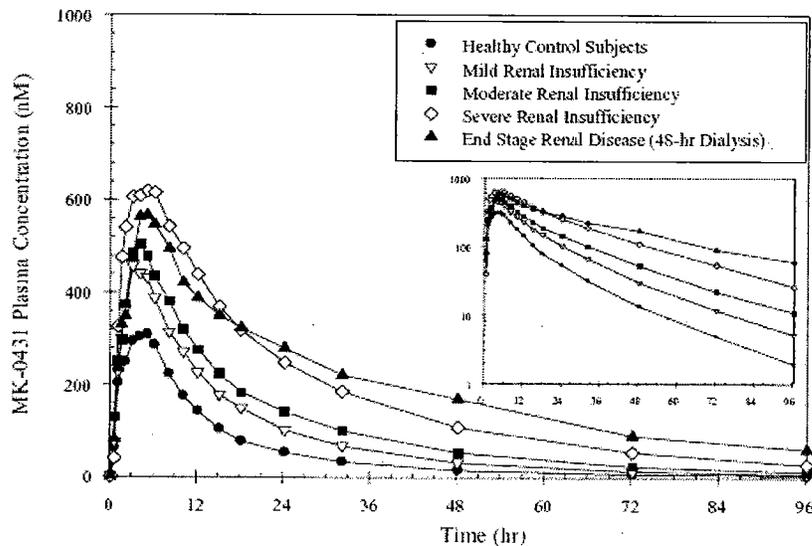
Renal Clearance.

†† Dose-adjusted to 50 mg (single oral doses of 1.5 to 600 mg) for historical controls.

‡‡ For the patients with hemodialysis at 48 hours postdose.

NA=not applicable; urine was not collected for ESRD patients.

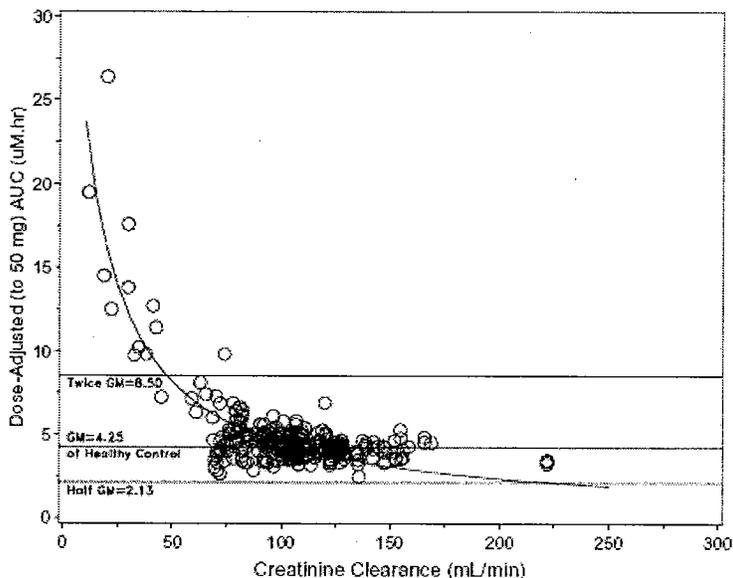
Figure 16. Mean sitagliptin plasma concentrations following administration of single oral 50-mg doses of sitagliptin to patients with varying degrees of renal insufficiency and healthy subjects



A plot of dose-adjusted (to 50-mg) AUC_{0-∞} values versus creatinine clearance is depicted in Figure 17. Data from this study and historical control studies are shown in this figure. The horizontal lines

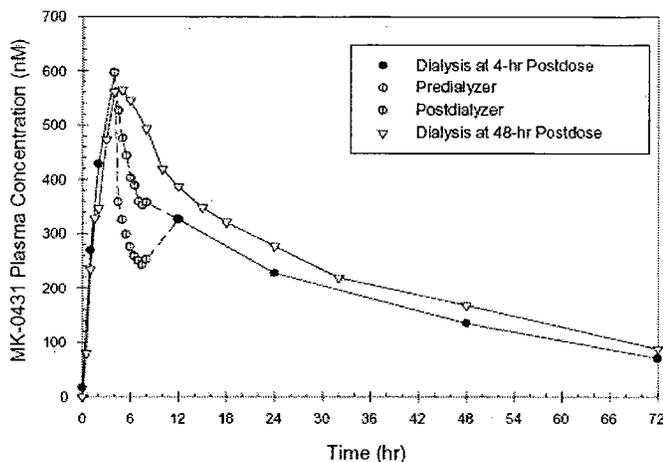
indicate the estimated $AUC_{0-\infty}$ at twice the geometric mean and one-half of the geometric mean $AUC_{0-\infty}$ for control subjects with normal renal function. Examination of the plot indicates a trend for increasing $AUC_{0-\infty}$ with decreasing creatinine clearance.

Figure 17. Sitagliptin plasma $AUC_{0-\infty}$ (Dose-Adjusted to 50 mg) versus creatinine clearance following administration of single oral doses of sitagliptin to patients with varying degrees of renal insufficiency and healthy control subjects



A comparison of mean plasma concentration-time profiles for end stage renal disease (ESRD) patients with hemodialysis administered at approximately 4 or 48 hours postdose is provided in Figure 18. This plot depicts plasma sitagliptin plasma concentrations entering the dialysis machine (pre-dialyzer) and after leaving the dialysis machine (post-dialyzer) for the 4-hr dialysis session as well as mean sitagliptin plasma concentrations from samples taken up to 72 hours postdose. Following the 4-hour dialysis session, the plasma sitagliptin concentrations were slightly lower as compared to plasma concentrations when hemodialysis occurred at 48 hours postdose. Values for $AUC_{0-\infty}$, $AUC_{0-48\text{ hr}}$, and $C_{24\text{ hr}}$ were approximately 21, 19, and 18% lower when hemodialysis occurred at 4 hours postdose as compared to when hemodialysis occurred at 48 hours postdose. The effect of hemodialysis on the sitagliptin apparent terminal $t_{1/2}$ was not statistically significant ($p > 0.050$).

Figure 18. Mean sitagliptin plasma concentrations following single oral 50-mg doses of sitagliptin to end stage renal disease patients undergoing hemodialysis at 4 or 48 hours postdose



This reviewer agrees with the sponsor that since sitagliptin plasma exposure increase less than 2-fold, mild renal insufficiency may not have a clinically meaningful effect on sitagliptin pharmacokinetics. Therefore, no dose adjustment is required for individuals with a creatinine clearance ≥ 50 mL/min/1.73 m². Patients with moderate renal insufficiency should receive 1/2 (half) of the usual clinical dose of sitagliptin since renal insufficiency have an approximately 2-fold higher plasma drug exposure as compared to subjects with normal renal function. Patients with severe renal insufficiency and end stage renal disease (ESRD) requiring hemodialysis have an approximately 4-fold higher plasma drug exposure as compared to subjects with normal renal function. Patients with severe renal insufficiency or ESRD should receive 1/4th (one-fourth) of the usual clinical dose of sitagliptin. Hemodialysis removes sitagliptin by only a modest extent. Sitagliptin can be administered without respect to the timing of hemodialysis in patients with ESRD. This reviewer agrees with these conclusions.

2.3.3 Hepatic impairment,

- *What is the effect of hepatic impairment on sitagliptin pharmacokinetics?*

The sponsor conducted a single-center, open-label study comparing the pharmacokinetics after administration of single 100-mg doses of sitagliptin to patients with moderate hepatic insufficiency with healthy control subjects matched to each patient for race, age, gender, and body mass index (BMI). Ten patients with moderate hepatic insufficiency (a score of 7 to 9 on the Child-Pugh's scale) and ten healthy matched control subjects were enrolled in the study. Blood and urine samples for determination of plasma and urine sitagliptin concentrations were collected predose and at various time points up to 48 hours (urine) and 96 hours (plasma) after the drug administration on Day 1. Sitagliptin pharmacokinetic parameters are summarized in Table 10. AUC_{0-∞} increased by 21% in patients with moderate hepatic insufficiency. Since sitagliptin is primarily renally eliminated and no meaningful effect of moderate hepatic insufficiency was observed, the results of this study can be extrapolated to mild hepatic insufficiency. Therefore, no dosage adjustment is needed for patients with mild or moderate hepatic insufficiency. There is no clinical experience with sitagliptin in patients with severe hepatic insufficiency.

Table 10. Summary statistics of pharmacokinetic parameters after administration of single 100-mg doses of sitagliptin in patients with moderate hepatic insufficiency (N=10) and healthy matched control subjects (N=10)

Parameter	Moderate Hepatic Insufficiency Patients LS Mean¶	Healthy Matched Control Subjects LS Mean¶	Moderate Hepatic Insufficiency Patients/Healthy Matched Controls GMR (90% CI) ††
AUC _{0-∞} (μM·hr)	11.51	9.49	1.21 (1.01, 1.46)
C _{max} (nM)	1186	1046	1.13 (0.91, 1.42)
T _{max} (hr)	1.8†	1.5†	0.726‡
t _{1/2} (hr)	14.4	13.9	0.691‡
fe, _{0-∞}	0.689§	0.681§	0.01 (-0.05, 0.07) #
CL _R (mL/min)	243	292	0.83 (0.68, 1.02)

† Median.
‡ p-Value.
§ Arithmetic LS mean.
|| Harmonic LS mean.
¶ LS Mean = Least-Squares Mean.
Difference of arithmetic LS means (Moderate Hepatic Insufficiency Subjects - Healthy Matched Control Subjects).
†† GMR=Ratio of Least-Squares Means, CI=Confidence Interval.

2.4 Extrinsic Factors:

The effects of sitagliptin on the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, digoxin, warfarin and oral contraceptives (norethindrone/ethinyl estradiol) were assessed. In addition, the effects of metformin and cyclosporine on sitagliptin pharmacokinetics were assessed. All studies were done in healthy volunteers, with the exception of the metformin study, which was conducted in subjects with type 2 diabetes. In addition to the individual studies described here, the effect of concomitant medications on sitagliptin pharmacokinetics using population pharmacokinetic analyses was assessed.

For assessing the clinical relevance of the effect of concomitant medications on sitagliptin pharmacokinetics, the sponsor's pre-specified comparability bounds for lack of a clinically meaningful interaction was that the 90% CI for the sitagliptin AUC_{0-∞} GMR (sitagliptin + other drug/ sitagliptin alone) fell within (0.50, 2.00). This reviewer agrees with the sponsor's 90% CI setting (0.50, 2.00) for lack of clinically meaningful drug interactions since the 200 mg dose was well tolerated in clinical trials.

2.4.1 Does sitagliptin interact with metformin pharmacokinetically?

The sponsor conducted a single-center, randomized, double-blind, double-dummy, placebo-controlled, 3-period, crossover study in 13 type 2 diabetic patients of 18 to 60 years of age on stable monotherapy with metformin, an organic cationic transporter (OCT) substrate to evaluate the effect of concomitant administration of multiple oral doses of sitagliptin and metformin on the pharmacokinetics of sitagliptin and metformin in patients with Type 2 Diabetes.

Following a 1-week run-in period with metformin 1000 mg twice daily, patients were randomized in crossover manner to the order of 3 treatments: (1) multiple oral doses of 50 mg sitagliptin twice daily and 1000 mg metformin twice daily, (2) multiple oral doses of 50 mg sitagliptin twice daily and placebo to metformin twice daily, and (3) multiple oral doses of 1000 mg metformin twice daily and placebo to sitagliptin twice daily for 7 days. Plasma and urine for sitagliptin levels and plasma for metformin levels were collected for up to 12 hours postdose on Day 7 in each treatment period.

Sitagliptin had no meaningful effect on the pharmacokinetics of metformin [Table 11] and is therefore not an inhibitor of OCT-mediated transport. The 90% CI for the metformin AUC_{0-12 hr} GMR

(metformin + sitagliptin /metformin) was contained within the protocol pre-specified similarity bounds of (0.50, 2.00).

Table 11. Summary statistics of metformin pharmacokinetic parameters following multiple-dose administration of 1000 mg metformin with and without 50 mg MK-0431 in male and female Patients with type 2 diabetes (N=13)

Metformin Parameter	Metformin + MK-0431 Geometric LS Mean†	Metformin Geometric LS Mean†	Metformin + MK-0431/ Metformin GMR (90% CI)
AUC _{0-12 hr} (µg·hr/mL)	14.9	14.6	1.02 (0.95, 1.09)
C _{max} (ng/mL)	2050	2130	0.97 (0.89, 1.05)
T _{max} (hr)	2‡	3‡	0.376§

† Back-transformed from log scale.
‡ Median.
§ p-Value.
GMR = Ratio of LS Means; CI = Confidence interval; LS mean = Least-squares mean.

Metformin had no meaningful effect on the pharmacokinetics of sitagliptin [Table 12]. The 90% CI for the sitagliptin AUC_{0-12 hr} GMR (sitagliptin +metformin/ sitagliptin) was contained within the protocol prespecified similarity bounds of (0.50, 2.00).

Table 12. Summary statistics of sitagliptin pharmacokinetic parameters following multiple-dose administration of 50 mg sitagliptin with and without 1000 mg metformin in male and female patients with type 2 diabetes(N=13)

Sitagliptin Parameter	Metformin + Sitagliptin Geometric LS Mean†	Sitagliptin Geometric LS Mean†	Metformin + Sitagliptin / Sitagliptin GMR (90% CI) †
AUC _{0-12 hr} (µM·hr)	4.04	3.95	1.02 (0.97, 1.08)
C _{max} (nM)	522	498	1.05 (0.959, 1.15)
T _{max} (hr)	2‡	3‡	0.285§
Cl _R (mL/min)	343	352	0.98 (0.79, 1.21)
fe _{0-12 hr}	0.694	0.724	-0.029 (-0.162, 0.103) ¶

† Back-transformed from log scale.
‡ Median.
§ p-Value.
|| Arithmetic mean.
¶ Difference and 90% CI.
GMR = Ratio of Geometric LS Means; CI = Confidence interval; LS mean = Least-squares mean.

Therefore, sitagliptin does not interact with metformin pharmacokinetically.

2.4.21 Does sitagliptin administration alters the pharmacokinetics of glyburide?

In a single-center, randomized, open-label, 2-period, crossover study, the effect of oral 200 mg once daily multiple-dose administration of sitagliptin on the single-dose pharmacokinetics of glyburide (1.25 mg DiaBeta™) was evaluated was in healthy male and female subjects. Results are summarized in Table 13.

Table 13. Summary statistics for glyburide pharmacokinetic parameters following a single dose of 1.25 mg glyburide with or without multiple oral once-daily doses of 200 mg sitagliptin to healthy subjects (N=8) (P031)

Glyburide Parameter	Glyburide + MK-0431 Geometric Mean	Glyburide Geometric Mean	Glyburide + MK-0431/ Glyburide GMR (90% CI)
AUC _{0-∞} (ng•hr/mL)	193	177	1.09 (0.96, 1.24)
C _{max} (ng/mL)	32.3	31.9	1.01 (0.84, 1.23)
T _{max} (hr)	5 [†]	5 [†]	0.093 [§]
Apparent t _{1/2} (hr)	8.25 [†]	9.21 [†]	0.602 [§]
[†] Median. [‡] Harmonic Mean. [§] Between Treatment p-value. GMR=Geometric Mean Ratio (glyburide+MK-0431/glyburide); CI=Confidence Interval.			

Results showed that sitagliptin did not meaningfully alter the plasma pharmacokinetics of glyburide.

2.4.1 Does sitagliptin alter the pharmacokinetics of simvastatin?

In a single-center, randomized, open-label, 2-period, crossover study in 12 healthy male and female subjects, subjects were randomized to the sequence order of 2 treatments: Treatment A— a single open-label oral dose of simvastatin 20 mg; Treatment B— open-label once-daily oral doses of 200 mg (2x100-mg tablets) MK-0431 on Days 1 through 5 co-administered with a single open-label oral dose of simvastatin 20 mg on Day 5. Plasma samples were obtained at selected time points for up to 24 hours postdose for determination of active and total HMG-CoA reductase inhibitor concentrations, and concentrations of simvastatin and simvastatin acid. Results are summarized in Table 14.

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Table 14. Summary statistics for the pharmacokinetic parameters of active and total plasma HMG-CoA reductase inhibitors, simvastatin and simvastatin acid following single oral 20-mg doses of simvastatin with or without multiple once-daily oral 200-mg doses of sitagliptin to healthy subjects (N=12) (P025)

Simvastatin Pharmacokinetic Parameters	Simvastatin + MK-0431 Geometric Mean [†]	Simvastatin Geometric Mean [†]	Simvastatin + MK-0431/ Simvastatin GMR [†] (90% CI)
Active HMG-CoA Reductase Inhibitors			
AUC _(0-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-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-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-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 GMR=Geometric Mean Ratio (Simvastatin+MK-0431/Simvastatin); CI=Confidence Interval.			

Sitagliptin did not meaningfully alter the pharmacokinetics of simvastatin. As simvastatin is a CYP3A4 substrate, these results demonstrate that sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

2.4.1 Does sitagliptin alter the pharmacokinetics of rosiglitazone?

In a single-center, open-label, randomized, 2-period, crossover study, the effect of multiple doses of sitagliptin on the single dose pharmacokinetics of rosiglitazone was investigated in healthy male and female subjects. Twelve subjects were randomized to the order of 2 treatments: Treatment A— the subjects received a single oral 4-mg dose of rosiglitazone alone in the fasted state, and Treatment B— the subjects received sitagliptin 200 mg once daily on Days 1 to 5 (totaling 5 doses) with a single oral 4-mg dose of rosiglitazone coadministered with sitagliptin on Day 5. Drug administration on Day 5 was in the fasted state. Plasma samples were obtained at selected time points up to 24 hours postdose for rosiglitazone assay. Results are summarized in Table 15.

Table 15. Summary statistics of rosiglitazone pharmacokinetic parameters following single dose administration of 4 mg rosiglitazone with or without multiple doses of 200 mg once daily sitagliptin in healthy male and female subjects (N=12) (P034)

Rosiglitazone Parameter	Rosiglitazone + MK-0431 LS Mean [†]	Rosiglitazone Only LS Mean [†]	Rosiglitazone + MK-0431/Rosiglitazone GMR (90% CI) [‡]
AUC _{0-∞} (µg·hr/mL)	1.71	1.75	0.98 (0.93, 1.02)
C _{max} (ng/mL)	307	309	0.99 (0.88, 1.12)
T _{max} (hr) [§]	1.0	0.5	0.782 [¶]
Apparent t _{1/2} (hr)	3.98	4.06	0.104 [¶]

[†] Geometric Least-Squares Mean.
[‡] GMR = Geometric Least-Squares Mean Ratio (Rosiglitazone + MK-0431 / Rosiglitazone); CI = Confidence Interval.
[§] Median.
^{||} Harmonic Least-Squares Mean.
[¶] Between-treatment comparison p-Value (Rosiglitazone + MK-0431 versus Rosiglitazone).

Therefore, sitagliptin (at twice the clinical dose) did not meaningfully alter the pharmacokinetics of rosiglitazone.

2.4.1 Does sitagliptin alter the pharmacokinetics of digoxin?

In a two-center, 2-part, double-blind, randomized, placebo-controlled, 2-period, crossover study, the effect of sitagliptin on the plasma concentrations of digoxin was investigated in healthy male and female subjects. Twelve subjects completed Part I and 20 subjects completed Part II. In Part I, 0.25-mg doses of digoxin (Lanoxin™) were given concomitantly with 100-mg doses (2 x 50-mg tablets) of sitagliptin or matching placebo once daily for 10 days whereas in Part II of the study, 0.25-mg doses of digoxin (Lanoxin™) were given concomitantly with 200-mg (4 x 50-mg tablets) doses of sitagliptin or matching placebo to sitagliptin once daily for 10 days to healthy subjects. Results are summarized in Table 16.

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Table 16. Summary statistics for digoxin pharmacokinetic parameters after administration of multiple 0.25-mg doses of digoxin once daily alone or concomitantly with multiple 100-mg (Part I) or 200-mg (Part II) doses of sitagliptin once daily in healthy subjects (N=12 in Part I; N=20 in Part II) P018)

Digoxin Pharmacokinetic Parameters	Digoxin + MK-0431 Geometric LS Mean †	Digoxin Geometric LS Mean †	Digoxin + MK-0431/ Digoxin GMR (90% CI) †
Part I: 0.25-mg Doses of Digoxin Alone or Concomitantly With 100-mg Doses of MK-0431			
AUC _(0-24 hr) (ng•hr/mL)	16.9	15.2	1.11 (1.01, 1.21)
C _{max} (ng/mL)	1.71	1.44	1.18 (1.05, 1.33)
C _{24 hr} (ng/mL)	0.520	0.487	1.07 (0.97, 1.17)
T _{max} (hr)	1.00 [‡]	1.00 [‡]	0.134 [§]
Cl _R (mL/min)	121	112	1.07 (0.89, 1.29)
f _{e, 0-24 hr}	0.514	0.427	0.087 (0.00, 0.17) [¶]
Part II: 0.25-mg Doses of Digoxin Alone or Concomitantly With 200-mg Doses of MK-0431			
AUC _(0-24 hr) (ng•hr/mL)	19.2	16.2	1.18 (1.08, 1.29)
C _{max} (ng/mL)	1.93	1.56	1.24 (1.12, 1.36)
C _{24 hr} (ng/mL)	0.543	0.471	1.15 (1.03, 1.28)
T _{max} (hr)	1.25 [‡]	1.25 [‡]	0.820 [§]
Cl _R (mL/min)	113	98.4	1.15 (0.98, 1.34)
f _{e, 0-24 hr}	0.535	0.418	0.116 (0.05, 0.19) [¶]
[†] Back-transformed from log scale. [‡] Median. [§] p-Value. Arithmetic LS mean. [¶] Difference and 90% CI. LS = Least Squares; GMR= Geometric Least-Squares Mean Ratio (Digoxin+MK-0431/Digoxin); CI = Confidence Interval.			

The results showed that the administration of multiple 0.25-mg doses of digoxin concomitantly with 100-mg or 200-mg (i.e. twice the clinical dose) of sitagliptin had slight effects on the pharmacokinetics of digoxin. This reviewer agrees with the sponsor that no dose adjustment for digoxin or sitagliptin is recommended. However, digoxin use should be monitored appropriately when co-administered with sitagliptin.

2.4.1 Does sitagliptin administration alter the pharmacokinetics of warfarin?

In a single-center, randomized, multiple-dose, open-label, 2-period, crossover study in 12 healthy male and female subjects of non-reproductive potential, subjects were randomized to the order of 2 treatments in Periods 1 and 2: Treatment A-a single open-label dose of 30 mg warfarin (COUMADIN™, BMS) on Day 5 during 11 days of once-daily open-label dosing with 200 mg sitagliptin; Treatment B-a single open-label dose of 30 mg warfarin on Day 1. Blood was collected over 168 hours postdose following warfarin administration in both periods for the assay of R(+) and S(-) enantiomers of warfarin as well as for International Normalized Ratio (INR) analysis. Given the therapeutic index of warfarin, the prespecified comparability bounds for lack of a clinically meaningful interaction was that the 90% CI for the warfarin AUC_{0-∞} GMR (warfarin + sitagliptin /warfarin) fell within (0.80, 1.25). Results are summarized in Table 17.

Table 17. Summary statistics for the pharmacokinetic parameters of S(-) and R(+) warfarin and the pharmacodynamic parameters of warfarin following administration of 30 mg warfarin with and without 200 mg sitagliptin in healthy young male and female subjects (N=12) (P022)

	Warfarin + MK-0431 Least-Squares Mean [†]	Warfarin Least-Squares Mean [†]	Warfarin + MK-0431/ Warfarin GMR [†] (CI)
Pharmacokinetic Parameters			
S(-) Warfarin			
AUC _(0-∞) [‡] (µg·hr/mL)	70.7	74.1	0.95 (0.90, 1.02) [‡]
C _{max} (ng/mL)	1958	2198	0.89 (0.86, 0.92) [‡]
T _{max} (hr)	1.0 [§]	1.0 [§]	0.508 ^{**}
Apparent terminal t _{1/2} [#] (hr)	34.6	34.8	0.919 ^{**}
R(+) Warfarin			
AUC _(0-∞) [‡] (µg·hr/mL)	102.6	103.3	0.99 (0.95, 1.03) [‡]
C _{max} (ng/mL)	1917	2144	0.89 (0.86, 0.93) [‡]
T _{max} (hr)	1.0 [§]	1.0 [§]	0.506 ^{**}
Apparent terminal t _{1/2} [#] (hr)	46.0	44.6	0.248 ^{**}
Pharmacodynamic Parameters			
INR AUC _(0-168hr) [‡]	260	257	1.01 (0.96, 1.06) [¶]
INR _{max}	2.27	2.10	1.08 (1.00, 1.17) [¶]
[*] Back-transformed from the log scale. [‡] 90% CI [§] Median Harmonic Mean [¶] 95% CI [#] N=11 as AUC(0-∞) and apparent terminal t _{1/2} could not be calculated for AN0009 in Period 2. ^{**} p-Value INR=International Normalized Ratio GMR= Geometric Least-Squares Mean Ratio (Warfarin+MK-0431/Warfarin); CI=Confidence Interval			

Therefore, sitagliptin did not meaningfully alter the plasma pharmacokinetics or pharmacodynamics of warfarin. The AUC_{0-∞} GMR (warfarin + sitagliptin /warfarin) 90% CI for R(+) and S(-) warfarin fell within the prespecified bounds of (0.80, 1.25).

2.4.2 Does sitagliptin alter the pharmacokinetics of oral contraceptive?

In a single-center, randomized, placebo-controlled, 2-period, crossover study, the effect of sitagliptin on the pharmacokinetics of ethinyl estradiol (EE2) and norethindrone (NET) in 18 healthy women was evaluated after coadministration of ORTHONOVUM™ 7/7/7 once daily for 28 days (Days 1 to 28) with 200-mg doses (2 x 100-mg tablets) of sitagliptin once daily for 21 days (Days 1 to 21). In each treatment period, subjects received ORTHO-NOVUM™ 7/7/7 once daily on Days 1 to 28 (21 days of active contraception, Days 1 to 21; 7 days of placebo, Days 22 to 28) and 200-mg doses (2 x 100-mg tablets) of MK-0431 or matching placebo once daily on Days 1 to 21. Blood samples for determination of plasma EE2 and NET concentrations were collected at predose on Days 1 and 21 and at specified time points up to 24 hours postdose on Day 21. Given the therapeutic index, the prespecified comparability bounds for lack of a clinically meaningful interaction was that the 90% CI for the EE2 and NET AUC_{0-∞} and C_{max} GMR (ORTHO-NOVUM™ 7/7/7 + MK-0431/ ORTHO-NOVUM™ 7/7/7) fell within (0.80, 1.25). Results are summarized in Table 18.

Table 18. Summary statistics for ethinyl estradiol (EE2) and norethindrone (NET) pharmacokinetic parameters after coadministration ORTHO-NOVUM™ 7/7/7 and 200-mg doses of sitagliptin or matching placebo once daily for 21 days to healthy female subjects (N=18) (P026)

Ortho-Novum 7/7/7™ Parameter	ORTHO-NOVUM™ 7/7/7 + MK-0431 Geometric LS Mean†	ORTHO-NOVUM™ 7/7/7 + Placebo Geometric LS Mean†	ORTHO-NOVUM™ 7/7/7 + MK-0431/ ORTHO-NOVUM™ 7/7/7 + Placebo GMR (90% CI)‡
Ethinyl Estradiol (EE₂)			
AUC _{0-24 hr} (pg·hr/mL)	1116	1129	0.99 (0.93, 1.06)
C _{max} (pg/mL)	122.9	126.5	0.97 (0.86, 1.10)
T _{max} (hr)	1.00‡	1.00‡	0.702§
Norethindrone (NET)			
AUC _{0-24 hr} (ng·hr/mL)	137	133	1.03 (0.97, 1.09)
C _{max} (ng/mL)	18.6	19.0	0.98 (0.89, 1.07)
T _{max} (hr)	1.00‡	1.00‡	0.665§
† Back-transformed from log scale. ‡ Median. § p-Value. GMR = Ratio of geometric LS means (ORTHO-NOVUM™ 7/7/7 + MK-0431/ORTHO-NOVUM™ 7/7/7 + Placebo); CI = Confidence interval; LS mean = Least-squares mean.			

Sitagliptin did not meaningfully alter the plasma pharmacokinetics of EE2 or NET, the active components of ORTHO-NOVUM™ 7/7/7. The results indicate that combination estrogen and progestin oral contraceptives, such as ORTHO-NOVUM™ 7/7/7, can be co-administered with sitagliptin.

2.4.3 What is the effect of cyclosporine on the pharmacokinetics of sitagliptin?

In a single-center, open-label, randomized, 2-period, crossover study, 8 healthy male subjects were randomized to the sequence order of 2 treatments: Treatment A— a single oral dose of 600 mg cyclosporine A (NEORAL™) with a single oral dose of 100 mg sitagliptin; Treatment B— a single oral dose of 100 mg sitagliptin alone. Plasma and urine sitagliptin concentrations were obtained up to 72 hours postdose in each period. Although the cyclosporine A dose given in this study is higher than that typically given to patients, this dose was chosen to maximize the effect of cyclosporine as a P-gp inhibitor. Results are summarized in Table 19.

Table 19. Summary statistics for sitagliptin pharmacokinetic parameters following a single oral dose of sitagliptin (100-mg) with or without a single oral dose of cyclosporine A (600 mg) in young, healthy, male subjects (N=8) (P037)

MK-0431 Pharmacokinetic Parameter	MK-0431 + Cyclosporine A Geometric LS Mean†	MK-0431 Geometric LS Mean†	MK-0431 + Cyclosporine A/MK-0431 GMR (90% CI)‡
AUC ₀₋₂₄ (µM·hr)	9.17	7.13	1.29 (1.24, 1.34)
C _{max} (nM)	1185	706	1.68 (1.36, 2.08)
C _{24 hr} (nM)	61.1	63.5	0.96 (0.88, 1.05)
Cl _R (mL/min)	371	366	1.01 (0.87, 1.18)
T _{max} (hr)	2.25‡	4.00‡	0.401§
Apparent t _{1/2} (hr)	10.6‡	11.6‡	0.011§
f _{e,0-24}	0.838	0.658	0.016§
† Back-transformed from log scale. ‡ Median. § Between treatment p-value. ‡ Harmonic Mean. GMR = Ratio of geometric LS means (MK-0431+cyclosporine A/MK-0431). CI = Confidence interval; LS mean = Least-squares mean.			

Overall, co-administration of a single oral cyclosporine A dose with a single dose of sitagliptin modestly increased maximal plasma concentrations of sitagliptin. This reviewer agrees with the sponsor that no dosage adjustment for sitagliptin is recommended when co-administered with cyclosporine A.

2.4 General Biopharmaceutics

Three different formulations were used in the sitagliptin development program: (1) the Phase I capsule formulation using the phosphate salt form of sitagliptin (Phase I formulation); (2) the Phase IIB film-coated tablet formulation using the phosphate salt form of sitagliptin (Phase II formulation) and (3) the Phase III/final market image (FMI) film-coated tablet formulation using the monohydrate salt form of sitagliptin (Phase III/FMI formulation). The compositions of representative Phase II and III tablets are listed in Table 20.

Table 20. Compositions of formulations of Phase II and Phase III/ Final Market Image (FMI) Tablets

Component	Phase II Tablet T11 100 mg/tablet	Phase III/FMI Tablet T13 100 mg/tablet
MK-0431-010X (equivalent free base) [†]		
MK-0431-006F (equivalent free base) [*]		
Calcium Phosphate Dibasic, USP		
Microcrystalline Cellulose NF		
Croscarmellose Sodium NF		
Sodium Stearyl Fumarate NF		
Magnesium Stearate (non-bovine) NF		
Core Tablet Weight		
Total Weight		

[†] Removed during processing
 NA=Not Applicable in this formulation
 NF =National Formulary
 USP = United States Pharmacopeia.

The 100-mg tablets used in Phase III studies differed from each other only with respect to color additives in the film coating, and this difference in these low level insoluble ingredients would not be expected to impact in vivo performance.

All Phase III supplies were produced at least 1/10th the size of the planned commercial batch size, and some of the Phase III supplies were produced using the proposed commercial process. The 100-mg Phase III/FMI tablet formulation was found to be bioequivalent to the 100-mg phase II tablet formulation (Study P027).

2.5.1 Are they bioequivalent among the Phase I capsules, Phase II tablets and the Phase III/commercial tablets?

The phase I capsules and Phase IIB tablets were tested in an in vivo bioequivalent study. This was an open-label, randomized, 2-period, crossover study in which 12 male and female subjects were randomized to the sequence of treatment in which they received 50 mg (1 x 50 mg) of sitagliptin as either the tablet formulation or the capsule formulation, separated by a washout interval of 7 days

between doses. Each single-dose administration was followed by collection of blood samples through 72 hours postdose in each period. The results revealed that The AUC_{0-∞} GMR (tablet/capsule) following single oral doses of 50 mg of either tablet (used in Phase IIB) or capsule (used in Phase I) was 1.04 with a 90% CI of (1.02, 1.07). The C_{max} for the tablet formulation (used in Phase IIB) was slightly elevated (approximately 20%) and the tablet formulation had a marginally statistically significant shorter T_{max} compared to the capsule formulation used in Phase I. Since 90% CI of GMR for AUC 0-∞ is remained within BE criteria, these two formulations (Phase I capsules and Phase 2 tablets) are similar though not bioequivalent.

To demonstrate a bioequivalence between Phase IIB tablets and Phase III/FMI, an open-label, randomized, 2-period, balanced, crossover trial was conducted in 12 healthy subjects received single oral doses of 2 different tablet formulations of sitagliptin 100 mg (1 x 100-mg tablet): the  form used in the Phase IIB program, and the monohydrate (FMI) form used in the Phase III program and the final market image (FMI) tablets. A single oral dose of each formulation was administered in each of the 2 treatment periods with 240 mL of water at approximately the same time in each period. In each period, blood samples were collected at specified times through 72 hours postdose for plasma sitagliptin concentrations. There was at least a 7-day washout interval after drug administration in Period 1 before the Period 2 dose was administered. The PK analysis showed that the monohydrate (FMI) tablet formulation (used in Phase III) was found to be bioequivalent to the  tablet formulation (used in Phase IIB) of sitagliptin, as assessed by plasma AUC_{0-∞} and C_{max}. The AUC_{0-∞} and C_{max} GMRs (monohydrate (FMI)/anhydrous) and corresponding 90% CIs were 1.05 (1.02, 1.07) and 1.07 (0.94, 1.22), respectively.

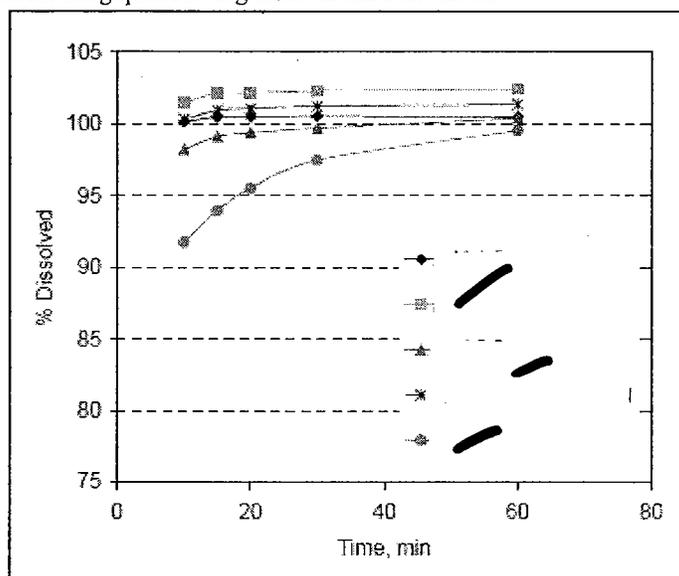
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2.5.2 What are dissolution profiles and proposed post approval in vitro specifications?

The sponsor has proposed an acceptance criterion for disintegration of 15 minutes at release only for sitagliptin tablets. The sponsor described that consistent with ICH Q6A criteria for disintegration, sitagliptin is highly soluble across the physiological pH and the tablets are rapidly dissolving (more than 85% released in 15 minutes at pH 1.2, 4.5 and 6.8, Figure 19).

Both dissolution and disintegration tests were used to assess the performance of the product throughout the product development program. Figure 19 shows the dissolution profiles for 100 mg developmental formulation similar to the proposed commercial formulation in three different media using

Figure 19. Dissolution for sitagliptin 100 mg tablet in different media



The dissolution profiles across the development program, including stability studies, have been consistent with more than 85% released in 15 minutes. Experiments on development and commercial scale tablets have consistently shown rapid dissolution profiles, independent of variations in the formulation composition or manufacturing processing parameters. The sponsor indicated that fast nondiscriminating dissolution results were observed for a range of 100 mg tablet formulations of the same composition of the commercial formulation and manufactured with different hardness. However, disintegration testing seems

Disintegration data have been generated at release and during the formal stability studies of sitagliptin tablets. The data were evaluated in order to establish a meaningful disintegration acceptance criterion for this product in lieu of dissolution testing.

Reviewer's comments:

Based on ICH-Q6A guidance- decision tree #7 for setting acceptance criteria for drug product dissolution, in order to use disintegration as post-approval in vitro release test, it must meet the following four conditions: (1) the drug dosage form is not modified releases form, (2) the drug is soluble at 37°C throughout the physiological pH range (pH 1.2 – 6.8), (3) the drug dosage form is dissolved > 80% in 15 minutes at pH 1.2, 4.8, and 6.8 and (4) a relationship between dissolution and disintegration is established. The sponsor used the hardness experiments to rationalize a disintegration method is more sensitive than dissolution methods. From the stability data, each strength has three different batches. Each batch contains both test results for dissolution and disintegration methods. A preliminary analysis of the correlation between % dissolved in 15 min vs. disintegration time has revealed that there is no relationship between dissolution and disintegration. Thus, based on Decision Tree #7, if relationship between dissolution and disintegration was not established, generally single-point dissolution criteria with lower limit are acceptable. Therefore, the following in vitro dissolution method and acceptance criterion for sitagliptin are recommended:

Apparatus
In vitro dissolution medium
Volume of dissolution medium
Medium temperature
Stirring speed
Acceptance criterion



2.6 Analytical Section

2.6.1 What is the property of analytical method?

High turbulence liquid chromatography (HTLC) extraction and liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods were used to analyze sitagliptin concentrations in human biological fluids (plasma, urine and dialysate). The lower limit of quantitation (LLOQ) for the plasma assay is 0.500 ng/mL (1.23 nM) and the linear calibration range is 0.500 to 1000 ng/mL (1.23 to 2455 nM). The LLOQ for the urine assay is 0.100 µg/mL (0.246 µM) and the linear calibration range is 0.100 to 50.0 µg/mL (0.246 to 123 µM). The LLOQ for the dialysate assay is 0.010 ng/mL (0.025 nM) and the linear calibration range is 0.010 to 5.00 ng/mL (0.025 to 12.3 nM). The assays are selective and specific for sitagliptin in human biological fluids. There was no significant interference observed from endogenous components in the control human biological fluids. The accuracy of the intra-day analysis (n=5) of quality control (QC) samples did not deviate by more than 10% of the nominal concentrations. The precision (coefficient of variation, CV%) of the intra-day analysis (n=5) of QC samples was less than 10% at each concentration.

3 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 ✓ § 552(b)(5) Draft Labeling

4. Appendices:

4.1 OCPB Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
<i>General Information About the Submission</i>				
NDA Number	21-995	Brand Name	Januvia™	
OCPB Division (I, II, III)	DPE II	Generic Name	Sitagliptin phosphate	
Medical Division	HFD-510	Drug Class	DPP4 inhibitor	
OCPB Reviewer	Xiaoxiong (Jim) Wei	Indication(s)	Type 2 Diabetes	
OCPB Team Leader	Hae-Young Ahn	Dosage Form	tablets	
		Dosing Regimen	100 mg QD	
Date of Submission	01-26-2006	Route of Administration	oral	
Estimated Due Date of OCPB Review	August 15, 2006	Sponsor	Merck	
PDUFA Due Date	October 16, 2006	Priority Classification	S1	
Division Due Date	August 31, 2006			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"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.	1.1.1.1.1.1.1.1.			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	1		
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
1.2 Healthy Volunteers-				
single dose:	X	2		
multiple dose:	X	2		
1.2.1 Patients-				
single dose:	X	1		
multiple dose:	X	1		
Dose proportionality -				

fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	8		
In-vitro:	X	5		
Subpopulation studies -				
ethnicity:	X	1		
gender:	X	1		
pediatrics:				
geriatrics:	X	1		
renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X		1	
Data sparse:	X			
Thorough QT Study				
	X	1		
II. Biopharmaceutics				
Absolute bioavailability:				
	X	1		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:				
	X	1		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		33		
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	YES	
Comments sent to firm?	No	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Briefing In Content:

JANUVIA belongs to a new class of oral anti-hyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by the intestine throughout the day. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells.

Pharmacokinetics

The pharmacokinetics of sitagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post-dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100-mg dose to healthy volunteers, apparent terminal half-life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady state compared to the first dose. The absolute bioavailability of sitagliptin is approximately 87%. JANUVIA may be administered with or without food.

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Patients with mild renal insufficiency did not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to normal healthy control subjects. An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, and an approximately 4-fold increase was observed in patients with severe renal insufficiency and in patients with ESRD on hemodialysis, as compared to normal healthy control subjects.

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and Cmax of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls

following administration of a single 100-mg dose of JANUVIA. There is no clinical experience in patients with severe hepatic insufficiency.

In Vitro Assessment of Drug Interactions showed that Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin.

A population analysis for MK-0431 pharmacokinetics (PK) was conducted using PK and demographic data from two MK-0431 Phase IIb studies (PN 010 and 014) and fourteen pre-specified Phase I studies (PN 001-008, 012, 013, 017, 027, 029, 033). A 2-compartment linear PK model was developed to describe the plasma concentration data following oral doses ranging from 20-200-mg. A total of 858 subjects/patients that received valid doses and had measured plasma concentrations were included in this analysis.

The to-be-marketed formulation of Januvia was used in pivotal clinical trials. Januvia tablets were tested in three different media and it dissolved in all three media more than 85% in 15 minutes. The sponsor has proposed disintegration for in vitro release specifications.

JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. JANUVIA is also indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a PPAR γ agonist (e.g., thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control.

The recommended dose of JANUVIA is 100 mg once daily as monotherapy or as combination therapy with metformin or a PPAR γ agonist (e.g., thiazolidinedione). In renally impaired patients, the dose may reduce to 50 mg or 25 mg a day. Both low strengths of tablets 25 mg and 50 mg are also planned to market.

- 4.2 Proposed Package Insert (separate file)**
- 4.3 Individual Study Review (see Addendum as a separate file)**
- 4.4 Pharmacotrics review (attached)**

Office of Clinical Pharmacology

Pharmacometrics

NDA	21995
Drug	Sitagliptan (MK-0431)
Pharmacometrics Reviewer	Venkatesh Atul Bhattaram
Pharmacometrics Team Leader	Joga Gobburu

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OCP Proposed Labeling Statements	59

2 Summary

MK-0431 belongs to a novel class of antihyperglycemic agents. Sponsor conducted adequate Phase II and Phase III studies to characterize the dose-response relationship. The primary endpoint in the Phase III studies was change from baseline in HbA1c. There is an evidence of dose-response (% change in HbA1c) relationship and the choice of 100 mg q.d dose is well supported. Several issues with nonlinear mixed effects analysis were identified and communicated to the sponsor. Dose adjustments based on renal function were evaluated in clinical studies and proposed in the label.

3 Recommendations

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4 Introduction

MK-0431 (also known as L-000224715) is in a novel class of antihyperglycemic agents, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and offers the potential for clinically meaningful glucose-lowering efficacy and an improved safety and tolerability profile compared to existing agents. Although several actions potentially contribute to the glucose-lowering effect of DPP-IV inhibitors, the most likely mechanism is through elevated incretin concentrations that lead to enhancement of glucose-dependent insulin secretion and a reduction in glucagon release. Increases in incretin concentrations occur because DPP-IV inhibition reduces the cleavage and inactivation of the active (intact) form of the incretin hormones, including glucagon-like peptide 1 (GLP-1) and glucosdependent inhibitory peptide (GIP). Thus, MK-0431 targets an important component of the pathogenesis of type 2 diabetes, but with the potential for a lower risk of hypoglycemia and no increase in body weight compared to insulin secretagogues.

Key Questions

The review will focus on four key questions:

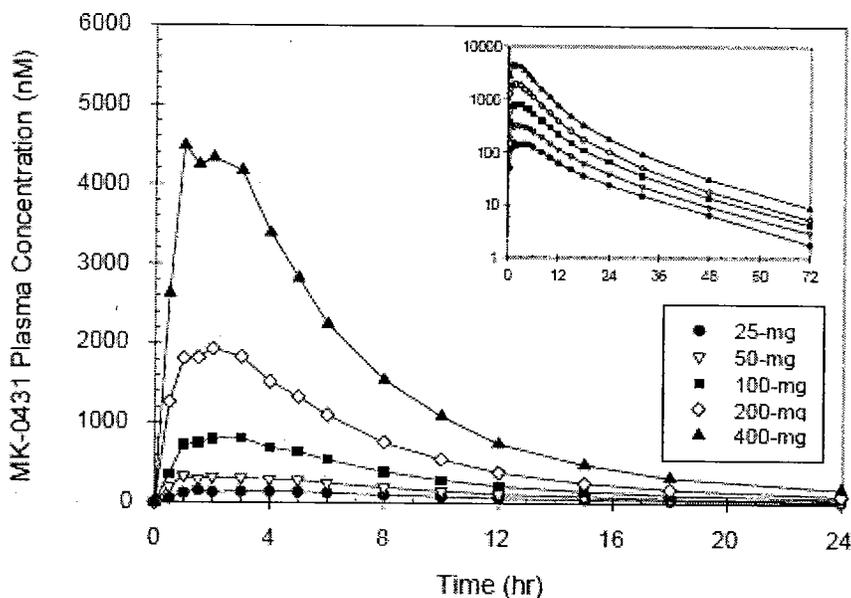
1. Is there is an evidence of dose/concentration-response relationship?
2. Is there a need for dose adjustments for special populations?
3. Is there a need for dose adjustments based on drug-drug interactions?

Note that replies to Questions 2 and 3 will be addressed in this review only if they are based on population pharmacokinetic analysis. If any dose adjustments are based on clinical pharmacology studies, please refer to the review by Dr Jim Wei (Primary Reviewer).

4.1 Basic Clinical Pharmacology

Several clinical pharmacology studies were conducted by the sponsor. Please refer to the review by clinical pharmacology reviewer (Dr Jim Wei) on these studies. Brief information on the pharmacokinetics is being provided here.

The absolute bioavailability of sitagliptin is approximately 87%. The time course of mean MK-0431 plasma concentrations in healthy subjects is shown in figure below.



The summary of the derived pharmacokinetic parameters in healthy male and female subjects is shown in table below:

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Mean MK-0431 Pharmacokinetic Parameters Following Single
Oral Doses of Final Market Image MK-0431 Tablets to
Healthy Male and Female Subjects (N=10) (P033)

MK-0431 Parameter	LS Mean [†]					Slope (90% CI) [‡]	GMR (90% CI) [§] 400 mg/100 mg
	25 mg	50 mg	100 mg	200 mg	400 mg		
AUC _{0-∞} μM·hr	2.20	4.17	8.52	16.7	34.9	1.00 (0.98, 1.01)	1.02 (0.99, 1.06)
C _{max} nM	177	378	950	2184	4949	1.21 (1.17, 1.26)	1.30 (1.13, 1.50)
C _{24 hr} nM	23.8	38.3	63.5	95.7	170	0.70 (0.67, 0.72)	0.67 (0.62, 0.72)
T _{max} hr	3.5	2.5	1.3	2.0	2.5		
t _{1/2} hr	13.1	13.0	12.4	11.7	11.3		
Cl _R mL/min	325	357	350	342	347		
f _{a, 0-∞} [§]	0.707	0.733	0.738	0.703	0.744		

[†] Geometric least-squares mean, back-transformed from log scale.
[‡] Median.
[§] Arithmetic least-squares mean.
^{||} Harmonic least-squares mean.
[¶] Slope of log[PK parameter] versus log[dose] from power-law model.
[§] Ratio of dose adjusted (to 100 mg) geometric least-squares means (400 mg/100 mg).

4.2 Exposure-Response Relationship

1. Is there an evidence of dose/concentration response relationship?

Yes, there is an evidence of dose-response relationship. Sponsor evaluated the effects of various doses and once-a-day/twice-a-day dosing regimen in Phase II studies (P010, P014). In study P010, patients were randomized in a balanced fashion to one of 6 treatment groups: 4 doses of MK-0431 (5, 12.5, 25 or 50 mg b.i.d), or twice-daily dose of MK-0431 (50 mg b.i.d), or to placebo. In study P014, patients were randomized in a balanced fashion to 1 of 5 treatment groups: 3 once-daily doses of MK-0431 (25, 50 or 100 mg) or to a twice-daily dose of MK-0431 (50 mg b.i.d), or to placebo. The studies had 12-week double blind treatment periods. Figure 1 below shows the dose-response relationship from both P010 and P014 studies for the primary endpoint (% change in HbA1c relative to placebo). There was no difference in the primary endpoint when MK-0431 was administered as 50 mg b.i.d or 100 mg q.d. Based on these findings sponsor evaluated the effects of 100 and 200 mg q.d in Phase III studies. The Phase III monotherapy studies (P021V1 and P023V1) were placebo-controlled, double-blind, randomized, parallel group studies. Study P021V1 had a 24-week double-blind treatment period and Study P023V1 had a 18-week double-blind treatment period. Figure 2 shows the time course of changes in HbA1c in the Phase III studies. Overall, the sponsor well identified the intended dose of 100 mg q.d for approval.

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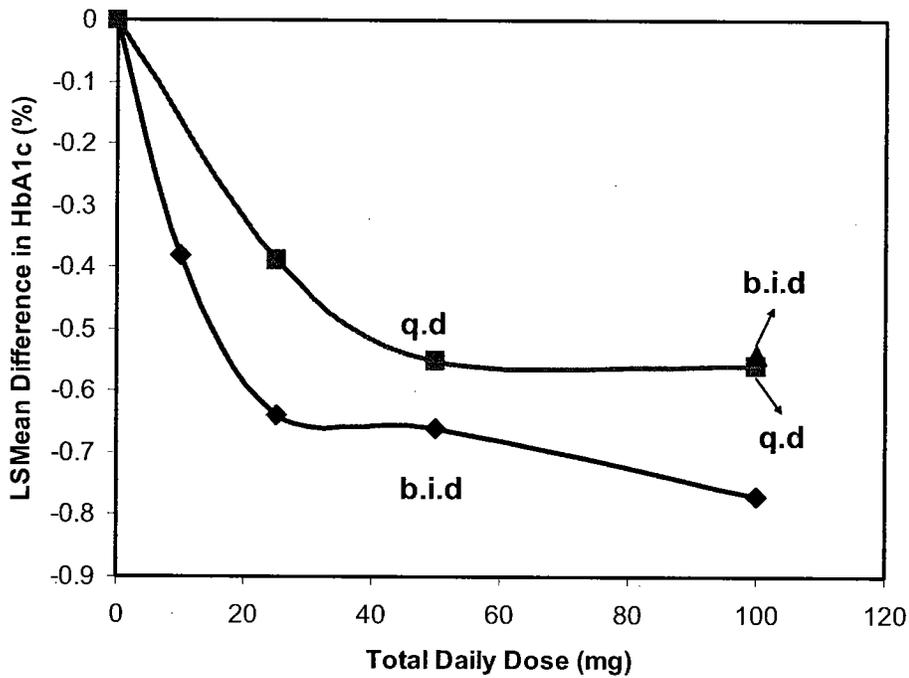


Figure 1. Dose-response (Placebo subtracted LS Mean Difference in %HbA1c) relationship after various dose(s)/dosing regimens of MK-0431.

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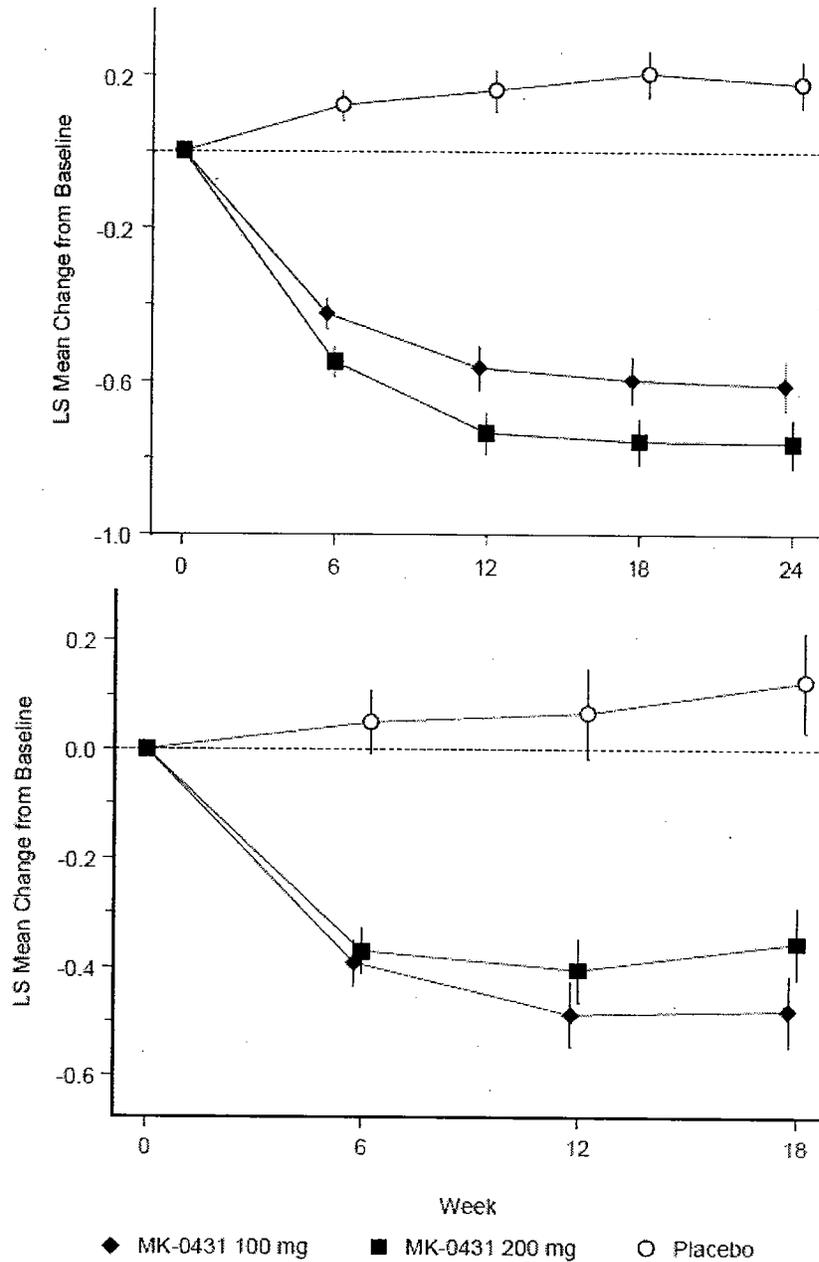


Figure 2. LS Mean Change From Baseline in HbA1c (%) Over Time (LS Mean \pm SE) by Treatment Group All-Patients-Treated Population with Data Carried Forward P021V1, P023V1 Phase III Monotherapy Studies

4.3 Labeling Issues

2. Is there a need for dose adjustments for special populations?
3. Is there a need for dose adjustments based on drug-drug interactions?

For the above two questions, the sponsor used population pharmacokinetic analysis methodology to propose statements in the label. The following section will describe the methodology and findings of the sponsor.

Population analysis for MK-0431 pharmacokinetics (PK) was conducted using PK and demographic data from two MK-0431 Phase IIb studies (PN 010 and 014) and fourteen prespecified Phase I studies (PN 001-008, 012, 013, 017, 027, 029, 033). A 2-compartment linear PK model was developed to describe the plasma concentration data following oral doses ranging from 20-200mg. A total of 858 subjects/patients that received valid doses and had measured plasma concentrations was included in this analysis. The information on various studies included in the analysis is provided in tables below:

Prot No.	Description/Primary Endpoints	Study Population	Design/ Dosing	PK Sampling
001	Single dose tolerability in young males Primary endpoints: safety and tolerability, pharmacokinetics	Healthy young males, ages 18 to 45 years N=16	Panel A (n=8): 1.5, 12.5, 50 and 200 mg doses (fasted) Panel B (n=8): 5, 25, 100 mg doses (fasted) and 25 mg (fed). 2 subjects received placebo in each period All doses were single oral doses	Predose and 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose (36 and 48 hours for doses of 50-mg and above)
002	Single dose tolerability in young males Primary endpoints: safety and tolerability, pharmacokinetics	Healthy young males, ages 18 to 45 years N=18	Panel A (n=9): 200, 600 mg Panel B (n=9): 400, 600 mg 3 subjects received placebo in each period All doses were single oral doses	Predose and 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose

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Prot No.	Description/Primary Endpoints	Study Population	Design/ Dosing	PK Sampling
003	Single dose tolerability in healthy elderly males/females, young females, and obese young males Primary endpoints: safety and tolerability, pharmacokinetics	Healthy elderly male and females, 65 to 80 years, healthy young (non-childbearing) females, 18 to 45 years, young obese males, 18 to 45 years N=38 *	All subjects received a single oral 50 mg dose: elderly males (n=10); elderly females (n=10); young females (n=8); young, obese males (n=10); In each group, 2 subjects received placebo	Predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours postdose
004	Multiple dose tolerability in young males Primary endpoints: safety and tolerability, pharmacokinetics	Healthy young males, ages 18 to 45 years N=70 *	7 panels with 10 subjects in each panel (in each panel, 2 subjects received placebo). Panel A: 25 mg q.d.; Panel B: 50 mg q.d.; Panel C: 100 mg q.d.; Panel D: 200 mg q.d.; Panel E: 400 mg q.d.; Panel F: 800 mg/Day 1, 600 mg q.d./Days 3 to 10; Panel G: 300 mg b.i.d.	<u>q.d. Panels:</u> Predose and 0.5, 1, 2, 4, 6, 8, 10, 12, and 16 hours postdose on Day 1, predose on Days 2 to 9 and predose and 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 32, 48, 72, and 96 hours postdose on Day 10 <u>bid Panel:</u> Predose and 0.5, 1, 2, 4, 6, 8, 10 and 12 hours postdose on Day 1, predose AM on Days 2 to 9 and predose and 0.5, 1, 2, 4, 6, 8, 10 and 12 hours post-AM dose on Day 10
005	Glucose-lowering activity study in type 2 diabetes patients Primary endpoints: safety and tolerability in type 2 diabetes patients, effects of MK-0431 on post-challenge glucose	Patients with mild to moderate type 2 diabetes N=60 *	Subjects received single doses of 25 mg, 200 mg, and placebo, followed by an OGTT at 2 hrs postdose and standard meal challenges at 6 & 24 hrs postdose (n=~40). A subset (n=~20) of patients was administered a second OGTT in lieu of meal at 24 hrs.	Predose and 1, 2, 4, 8, 12 and 24 hours postdose, with additional samples at 36 and 48 hours postdose for a sub-set of patients.

Prot No.	Description/Primary Endpoints	Study Population	Design/ Dosing	PK Sample
006	Formulation study Primary endpoint: comparison of Ph I formulation (capsule) to Ph II formulation (tablet)	Healthy male and female subjects, ages 18 to 65 years N=12 ¹	Subjects received 50 mg (1 x 50-mg) of MK-0431 (either Phase I capsule capsule formulation or Phase II tablet formulation), separated by a 7 day washout interval.	Predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48 and 72 hours postdose
007	28-day multiple-dose tolerability study in middle-aged, obese males and females Primary endpoint: safety and tolerability	Obese male and female volunteers, ages 45 to 65 years N=32 ¹	Subjects received 200 mg b.i.d. (n=32) for 28 days. baseline OGTT administered Day -1, trough OGTT on Day 14 (predose) and peak OGTT on Day 28 (2 hours postdose).	Predose and 0.5, 1, 2, 4, 6, 8, 10 and 12 hours postdose on day 1, at predose on days 2, 3, 4, 5, 7, 10, 14, 17, 21 and 24, and at predose and 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 48 and 72 hours post dose on day 28
008	Renal insufficiency Study Primary endpoint: evaluate the effects of varying degrees of renal insufficiency on MK-0431 pharmacokinetics	Patients with varying degrees of renal insufficiency: 6 mild (CL _{cr} =50-80 mL/min), 6 moderate (CL _{cr} =30-50 mL/min), 6 severe (CL _{cr} <30 mL/min), and 6 end-stage renal disease (ESRD) on hemodialysis, and 6 healthy concurrent controls N=24 ¹	A single 50-mg dose was administered to 24 patients with renal insufficiency, and 6 healthy concurrent controls	Predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72 and 96 hours postdose.

Prot No.	Description/Primary Endpoints	Study Population	Design/ Dosing	PK Sampling
010	Dose-Range Finding Study Primary endpoints: HbA1c	Patients with Type 2 Diabetes, ages 18 to 60 years N=600 †	Placebo, 5, 12.5, 25 and 50 mg of MK0431 B.I.D. and 20 mg glipizide B.I.D. were administered in about 600 Type II diabetic patients (1:1:1:1:1)	Predose, 1 and 2 hours post dose administration fasted or at predose (fasting), and 1 and 3 hours following a standard meal administered approximately 30 minutes after dosing.
012	Metformin interaction study Primary endpoints: pharmacokinetics of MK-0431 with and without metformin, safety and tolerability	Patients with type 2 diabetes, ages 18 to 60 years N=13 †	Following a 1-week run-in period with metformin 1000 mg b.i.d., 12 patients 18 to 60 years of age on stable monotherapy with metformin, were randomized to 3 treatment periods with 7 days of dosing: 50 mg MK-0431 b.i.d. and 1000 mg metformin b.i.d.; 50 mg MK-0431 b.i.d. and placebo to metformin b.i.d.; and 1000 mg metformin b.i.d. and placebo to MK-0431 b.i.d.	Predose on day 4, 5, 6 and 7 and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours postdose on day 7
013	Single dose tolerability study in Japanese male subjects Primary endpoints: safety and tolerability, pharmacokinetics	Healthy young Japanese male subjects, ages 18 to 45 years N=16 †	Panel A (n=8): 5, 25 and 100 mg doses (fasted), and 25 mg (fed) Panel B (n=8): 12.5, 50, 200 and 400 mg doses (fasted) 2 subjects received placebo in each period.	Predose and 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose.
014	Dose-Range Finding Study Primary endpoints: HbA1c	Patients with Type 2 Diabetes, ages 18 to 60 years N=550 †	Placebo, 25, 50 and 100 mg of MK-0431 Q.D. and 50 mg B.I.D. were administered in approximately 550 Type II diabetic patients (1:1:1:1)	predose, 1 and 2 hours post dose (fasting).

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Prot No.	Description/Primary Endpoints	Study Population	Design/ Dosing	PK Sampling
017	Hepatic Insufficiency Study/Open Label Study Primary endpoints: to compare the pharmacokinetic profile of hepatic insufficiency patients to healthy control subjects, safety and tolerability	Patients with moderate hepatic insufficiency, ages 18 to 75 years; healthy matched control subjects N=20*	Open label single dose administration of 100 mg MK-0431	Pradose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72, and 96 hours postdose.
027	Bioequivalence (Ph II/Ph III Formulation) Study Primary endpoint: comparison of Ph. II [redacted] formulation (capsule) to Ph. III/final market image formulation (tablet)	Healthy male or female subjects, ages 18 to 55 years N=12*	Subjects are randomized to a sequence of 2 treatments: (1). A single dose of MK-0431 100 mg [redacted] phosphate form of MK-0431 (Phase IIb formulation) (2). A single dose of MK-0431 100 mg monohydrate (FMI) form of MK-0431 (Phase III) program in the development of final market image (FMI) tablets.	Pradose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, and 72 hours postdose
029	Definitive Bioavailability/Food Effect Study Primary endpoints: Part I: to evaluate the safety and tolerability of rising single dose infusions of intravenous (IV) formulation of MK-0431, to examine MK-0431 pharmacokinetic parameters following single IV doses of MK-0431, to assess the dose proportionality of plasma $AUC_{(0-\infty)}$ following IV doses of MK-0431. Part II: to estimate the absolute bioavailability (fasted) of the 100-mg oral MK-0431 tablet in healthy adult subjects, to examine summary statistics and to assess the influence of food on $AUC_{(0-\infty)}$, C_{max} , T_{max} and apparent terminal $t_{1/2}$ on the 100-mg tablet of MK-0431 in healthy adult subjects.	Healthy male or female subjects, ages 18 to 60 years. N=10* in Part I N=12* in Part II	<u>Part I:</u> In a double-blind, fixed-sequence fashion, 10 subjects received rising sequential IV infusions of 25-, 50-, and 100-mg MK-0431 or placebo (8 subjects received active drug and 2 subjects received placebo (saline). The same 2 subjects in each period received placebo). <u>Part II:</u> In an open-label, randomized fashion, 12 subjects received a single dose of MK-0431 in a balanced, crossover design: 100-mg oral tablet in the fasted state, 100-mg oral tablet in the fed state, and a 100-mg infusion of MK-0431 in the fasted state.	Part I: pradose, 0.25, 0.5, 1, 1.5, 2 (end of infusion), 2.25, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72 hours. All time points are relative to the start of the 2-hr infusion (T=0). Part II: pradose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72 hours. All time points are relative to the start of administration of study drug (T=0).

Prot No.	Description/Primary Endpoints	Study Population	Design/ Dosing	PK Sampling
033	Dose Proportionality Study Primary endpoint: to assess the dose proportionality of MK-0431 final market image tablets within the 25- to 400-mg dose range in healthy adult subjects.	Healthy male or female subjects, ages 18 to 55 years N=10 ^a	Subjects will be randomized to the sequence of 5 treatment periods; in each period, subjects will receive a single open-label 25-, 50-, 100-, 200-, or 400-mg dose of MK-0431.	Predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, and 72 hours postdose.
^a N (total number of subjects) includes MK-0431, active comparatives and placebo.				

Structural model development and selection of covariates (demographic and 96 concomitantly administered drugs) was performed using standard techniques based on log-likelihood ratio tests. For more details, the reader is directed to the submitted report on population pharmacokinetic analysis.

4.3.1 Sponsor's Conclusions

The final model can be expressed as:

$$CL = \{36.7 * \{1 - 0.0927 * [(AGE/52)^{0.75} - 1] - 0.154 * [\min(3.04, SCR) - 1] - 0.267 * D195 - 0.257 * D158 - 0.182 * D300 - 0.370 * RACO + 0.340 * D410 - 0.0864 * DBTS - 0.919 * [\min(32, BMI)/29 - 1] + 0.206 * D336 - 0.263 * D173 - 0.164 * RNF0 + 0.117 * D134 - 0.0779 * RACC + 0.485 * [\min(100, CLCR)/100 - 1] + 0.234 * (AGE/52 - 1) * RACC - 1.65 * (SCR - 1) * RACO + 0.197 * D191\} + 26.1 * [(WTKG/85)^{0.75} - 1] * [1 + N(0, 0.102)]$$

$$V2 = 242 * \{1 + 0.228 * DBTS + 0.616 * (WTKG/85 - 1) - 0.205 * SEXF + 0.0784 * RACH\} * [1 + N(0, 0.143)]$$

$$V3 = 111 * \{1 - 0.232 * RACA + 0.591 * DBTS + 1.13 * (HTCM/170 - 1)\} * [1 + N(0, 0.150)]$$

$$Ka = 1.68 * \{1 - 0.290 * DBTS - 0.630 * FED4\} * [1 + N(0, 1.00)]$$

$$Q = 6.94$$

$$Cpm = Cpp * [1 + N(0, 0.0465)]$$

$$\text{Covariance of IV (CL-V2)} = 0.0182$$

$$\text{Covariance of IV (V2-V3)} = 0.0771$$

$$\text{Covariance of IV (V3-Ka)} = 0.111$$

- The population pharmacokinetics of MK-0431 in the dose range of 20-200 mg can be well described with a three-compartment model (two-compartment disposition model) – one for drug depot, one is central compartment for circulating system and one is peripheral compartment for tissues/organs.
- Out of 30 factors accounting for demographic factors-diabetic status, renal insufficiency, formulations and fed status, age, weight, gender, height, renal function, presence of diabetes,

standard Japanese breakfast, race were identified to be significantly correlated to at least one of MK-0431 PK parameters. However, their effects are not clinically significant (AUC 90% CI: 0.5-2.0) except for moderate/severe renal insufficiency.

- Out of 90 comedications (83 coadministered in N_{>=}5 patients with an MK-0321 dose within the range of 20-200 mg) which were evaluated, eight were identified to be significantly correlated to the apparent terminal clearance, although their effects are not considered clinically significant.

4.3.2 Reviewer Comments

Based on the review of the sponsor's analysis, the following are the comments of the reviewer:

1. The model developed by the sponsor needs to be revised. It is not clear why the sponsor chose to include both serum creatinine and creatinine clearance in the model. Also, age and creatinine clearance are included in the model. Since the drug is renally cleared, one would expect only creatinine clearance to be an important covariate in the model.
2. The model also includes weight and BMI. One would expect these to be correlated with each other and with CLCr.
3. The sponsor evaluated the effects of concomitant medications using a step-wise forward and backward selection process. During the analysis, the effects of each drug would be evaluated individually on pharmacokinetic parameters using log-likelihood ratio test. Analyzing retrospective extrinsic factor covariates such as drug-drug interactions is challenging. This challenge arises from uncertainty in dose and timing of interacting drugs; more importantly if multiple interacting drugs are co-administered.

For example, consider a patient was taking sitagliptan, drug A and drug B. Using step-wise forward and backward selection methodology, the model would include drugs A and B individually and not simultaneously. If effects of drug A is not significant, it would be excluded from analysis. It is possible that there is an unknown interaction between drug A and B which could result in no effects of drug A pharmacokinetics of sitagliptan. If a study were to be conducted with drug A alone, there could be a significant interaction. Ideally a full model should be developed which would include drugs A and B simultaneously for their effects on sitagliptan. This would make it very complicated if one wishes to analyze huge number of drug interactions as the sponsor has conducted. The current analysis by the sponsor does not address this issue which is very important for understanding drug-drug interactions. In

The following comments were sent to the sponsor for additional clarifications:

1. What were the dosage strengths for concomitant drugs that were included in the analysis? For example, Was everybody on same dose of ibuprofen or enalapril etc?
2. What is the range of duration of treatment with concomitant medications? In your report you mention that "If the patient was on coadministered drug before and the day of sampling, the patient's concentration data was considered to have been obtained under conditions of coadministration of that concomitant medication.". So for example, when evaluating the effects of ibuprofen on sitagplitan were the patients in the Sitagplitan+Ibuprofen group taking ibuprofen for similar duration? We would like to know that for all concomitant drugs that you included in the analysis.
3. Were the groups adequately balanced? i.e, did you check if there are any imbalances between for example Sitaglipatan group alone vs Sitagplitan+Ibuprofen alone? We would like to know how you ensured that the groups are similar (Concomitant diseases, demographics, concomitant treatments etc).
4. If you evaluated the effects of covariates using stepwise forward and backward approach, probably you tested the effects of each concomitant drug individually and if it was not significant, it was excluded from the analysis. For example., let us consider two drugs ibuprofen and enalapril. Were there any patients who

were taking these two drugs simultaneously? In that case, stepwise forward approach will evaluate effects of ibuprofen and enalapril individually. What if the effects were a combination and not individual effects? How did you handle such cases?

5. In your model, you included effects of age, serum creatinine and creatinine clearance in the model which we think are not necessary. We would like you to simplify your model and exclude all confounding covariates and repeat the analysis. Any subsequent calculations for drug-drug interactions should include such a model. Although, it might not make a big impact, we would like to rely on a reasonable model before we agree to any conclusions derived using population pk analysis approach.

5 Sponsor Proposed Labeling Statements

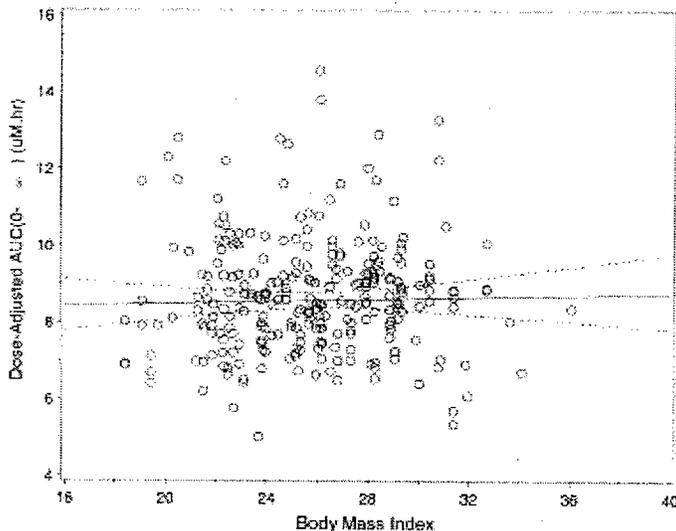
The following are the statements proposed by the sponsor in the label which are based on population pharmacokinetic analysis.

Body Mass Index (BMI)

No dosage adjustment is necessary based on BMI. Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Reviewer's Comments

The following figure which shows the dose adjusted AUC vs body mass index justifies the statement proposed by the sponsor (Ref: Composite Analysis Report: r0006.pdf):



Note: The solid curve is back-transferred from the fitted regression line in $(AUC_{0-\infty}) = 2.1068 + 0.0015 \cdot BMI$. The dotted curves are the 95% confidence bands.

Gender

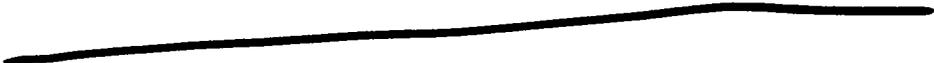
No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Reviewer’s Comments

The following table which shows the dose adjusted AUC vs gender justifies the statement proposed by the sponsor (Ref: Composite Analysis Report: r0006.pdf):

Gender Effects on Plasma MK-0431 AUC_{0-∞} (μM·hr) and C_{max} (nM) Following Administration of Single Oral Doses of 1.5 to 600 mg MK-0431 to Healthy Subjects

Gender	N	N obs	Geometric LS mean ¹	Median	Min	Max	SD ^{2,3}	GMR ⁴	90% CI	p-Value ⁵
AUC_{0-∞} (μM·hr)										
Female	47	79	4.14	6.64	2.06	40.3	3.65	1.11	(1.07, 1.15)	<0.001
Male	104	193	3.74	6.62	0.124	59.5	22.7			
C_{max} (nM)										
Female	47	79	403	718	121	9030	560	1.34	(1.26, 1.42)	<0.001
Male	104	193	301	523	5.75	11300	4972			
Coefficient of Variation ⁶ (%) = 13.61 for AUC _{0-∞} and 24.13 for C _{max} .										
¹ Back-transformed from log scale.										
² Between-Subject Standard Deviation.										
³ GMR = Ratio of geometric least squares means (Female/Male).										
⁴ p-values for comparison between female and male.										
⁵ Root mean square error on the log scale from ANCOVA model x 100.										
Nobs = Number of observations; Min = Minimum; Max = Maximum; LS Mean = Least Squares Mean; CI = Confidence Interval.										



Pediatric

No studies with JANUVIA have been performed in pediatric patients.

Race

No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data, including subjects of white, black, Asian, and other racial groups.

Reviewer’s Comments

The following table which shows the dose adjusted AUC vs race justifies the statement proposed by the sponsor (Ref: Composite Analysis Report: r0006.pdf):

Race Effects on Plasma MK-0431 AUC_{0-∞} (μM·hr) and C_{max} (nM) Following Administration of Single Oral Doses of 1.5 to 600 mg MK-0431 to Healthy Subjects

Race	N	N obs	Geometric LS mean [†]	Median	Min	Max	SD [‡]	GMR [§]	90% CI	p-Value [¶]
AUC_{0-∞} (μM·hr)										
Black	15	15	3.74	7.18	3.35	9.30	1.22	0.92	(0.86, 0.99)	0.064
Hispanic	39	79	3.84	7.45	1.99	40.3	5.54	0.95	(0.91, 0.99)	0.029
Asian	17	42	4.12	3.58	0.393	39.9	29.3	1.02	(0.97, 1.06)	0.539
Caucasian	80	136	4.05	6.22	0.124	59.5	23.1			
C_{max} (nM)										
Black	15	15	317	703	265	1140	169	0.91	(0.80, 1.03)	0.215
Hispanic	39	79	362	822	121	9030	872	1.04	(0.97, 1.12)	0.381
Asian	17	42	370	296	21.4	4280	7170	1.06	(0.98, 1.15)	0.199
Caucasian	80	136	348	562	5.75	11300	5520			
Coefficient of Variation [¶] (%) = 13.61 for AUC _{0-∞} and 24.13 for C _{max} .										
† Back-transformed from log scale.										
‡ Between-Subject Standard Deviation										
§ GMR = Ratio of geometric least squares means relative to Caucasian.										
¶ p-values for comparison between Caucasian and other races.										
¶ Root mean square error on the log scale from ANCOVA model x 100.										
Nobs = Number of observations; Min = Minimum; Max = Maximum; LS Mean = Least Squares Mean; CI = Confidence Interval.										

6 OCP Proposed Labeling Statements

The following are the statements proposed by OCP.

Body Mass Index (BMI)

No dosage adjustment is necessary based on BMI. Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Gender

No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Geriatric

No dosage adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis after accounting for renal function. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Pediatric

No studies with JANUVIA have been performed in pediatric patients.

Race

No dosage adjustment is necessary based on race. Race had no clinically meaningful

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

1 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

Xiao-xiong Wei
8/31/2006 12:39:25 PM
BIOPHARMACEUTICS

Hae-Young Ahn
8/31/2006 05:35:05 PM
BIOPHARMACEUTICS

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

General Information About the Submission

NDA Number	21-995	Brand Name	Januvia™
OCPB Division (I, II, III)	DPE II	Generic Name	Sitagliptin phosphate
Medical Division	HFD-510	Drug Class	DPP4 inhibitor
OCPB Reviewer	Xiaoxiong (Jim) Wei	Indication(s)	Type 2 Diabetes
OCPB Team Leader	Hae-Young Ahn	Dosage Form	tablets
		Dosing Regimen	100 mg QD
Date of Submission	01-26-2006	Route of Administration	oral
Estimated Due Date of OCPB Review	August 15, 2006	Sponsor	Merck
PDUFA Due Date	October 16, 2006	Priority Classification	S1
Division Due Date	August 31, 2006		

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:	X	1		
Isozyme characterization:	X	1		
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	2		
multiple dose:	X	2		
<i>Patients-</i>				
single dose:	X	1		
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	8		
In-vitro:	X	5		
Subpopulation studies -				
ethnicity:	X	1		
gender:	X	1		
pediatrics:				
geriatrics:	X	1		
renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				

Phase 2:				
Phase 3:				
PK/PD:	X			
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:				
Population Analyses -	X	1		
Data rich:	X			
Data sparse:	X			
Thorough QT Study *	X	1		
II. Biopharmaceutics				
Absolute bioavailability:	X	1		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		33		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	YES			
Comments sent to firm?	No			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Briefing In Content:

JANUVIA belongs to a new class of oral anti-hyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by the intestine throughout the day. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells.

Pharmacokinetics

The pharmacokinetics of sitagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100-mg dose to healthy volunteers, apparent terminal half-life (t_{1/2}) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady state compared to the first dose. The absolute bioavailability of sitagliptin is approximately 87%. JANUVIA may be administered with or without food.

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Patients with mild renal insufficiency did not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to normal healthy control subjects. An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, and an approximately 4-fold increase was observed in patients with severe renal insufficiency and in patients with ESRD on hemodialysis, as compared to normal healthy control subjects.

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of JANUVIA. There is no clinical experience in patients with severe hepatic insufficiency.

In Vitro Assessment of Drug Interactions showed that Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin.

A population analysis for MK-0431 pharmacokinetics (PK) was conducted using PK and demographic data from two MK-0431 Phase IIb studies (PN 010 and 014) and fourteen pre-specified Phase I studies (PN 001-008, 012, 013, 017, 027, 029, 033). A 2-compartment linear PK model was developed to describe the plasma concentration data following oral doses ranging from 20-200-mg. A total of 858 subjects/patients that received valid doses and had measured plasma concentrations were included in this analysis.

The to-be-marketed formulation of Januvia was used in pivotal clinical trials. Januvia tablets were tested in three different media and it dissolved in all three media more than 85% in 15 minutes. The sponsor has proposed disintegration for in vitro release specifications.

JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. JANUVIA is also indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a PPAR γ agonist (e.g., thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control.

The recommended dose of JANUVIA is 100 mg once daily as monotherapy or as combination therapy with metformin or a PPAR γ agonist (e.g., thiazolidinedione). In renally impaired patients, the dose may reduce to 50 mg or 25 mg a day. Both low strengths of tablets 25 mg and 50 mg are also planned to market.

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