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*APPLICATION NUMBER:*

**22-044**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA  
Submission Number 22-044  
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Reviewer Name Ilan Irony  
Through: Mary Parks  
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Established Name: Sitagliptin / metformin fixed-dose combination  
(Proposed) Trade Name Janumet  
Therapeutic Class: Dipeptidyl peptidase IV inhibitor / biguanide  
Applicant Merck and Company, Inc.

Priority Designation S

Formulation Oral Tablet  
Dosing Regimen 50 mg / 500 mg and 50 mg /1000 mg twice daily  
Indication Improve glycemic control  
Intended Population Adult patients with Type 2 diabetes mellitus

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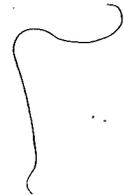
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## 1 EXECUTIVE SUMMARY

This document is the Medical Officer's Clinical Review of sitagliptin phosphate in a fixed-dose combination with metformin hydrochloride. Sitagliptin is a member of a new class of anti-diabetic agents, known as dipeptidyl peptidase inhibitors type IV. The indication sought is the treatment of patients with type 2 diabetes mellitus who do not achieve adequate glycemic control with either agent alone or for patients already being treated with the combination of sitagliptin and metformin.

Type 2 diabetes mellitus (T2DM) is a very prevalent condition characterized by abnormal metabolism and disposal of glucose. T2DM carries significant morbidity and mortality associated with both acute and chronic complications. Although several classes of drugs are available in the treatment of T2DM, many patients remain persistently hyperglycemic.

Sitagliptin phosphate is a new molecular entity and part of a new class of drug products, called dipeptidyl peptidase IV (DPP4) inhibitors. Metformin hydrochloride has been widely prescribed for T2DM, with effects primarily on glucose production in liver and on insulin resistance. The New Drug Application reviewed in this document describes the clinical findings of the coadministration of sitagliptin and metformin during the development of sitagliptin (reviewed under NDA 21995) and the demonstration of bioequivalence between the sitagliptin / metformin fixed-dose combination (FDC) and the coadministration of sitagliptin and metformin.

Coadministration of sitagliptin and metformin was studied in 1569 subjects with an average exposure of 255 days, across 3 different studies. Studies P015 (a Phase 2, 4-week, parallel group, randomized study) and P020 (a 24-week, randomized, placebo-controlled study, followed by an 80-week active-controlled study) have been reviewed in the sitagliptin NDA submission 21995. Data from the Open Label Cohort in Study P036 were submitted to this NDA. Additional data from Study P024 and the Randomized Cohorts of Study P036 were submitted with the 4-Month Safety Update Report for this application.

### 1.1 Recommendation on Regulatory Action

The clinical studies investigating the safety and efficacy of the coadministration of sitagliptin and metformin were reviewed under NDA 21995 and were deemed adequate to support approval of sitagliptin in the treatment of type 2 diabetics with inadequate glycemic control despite treatment with metformin. The approval of the sitagliptin / metformin FDC for second-line treatment (i.e., for patients already on metformin or on sitagliptin who need additional glucose lowering, or for patients already treated with sitagliptin and metformin coadministered) is mainly contingent on the demonstration of bioequivalence between the coadministered and the combined components of the combination.

Study P048 has provided the necessary evidence of the bioequivalence, and therefore this reviewer recommends approval of sitagliptin / metformin FDC for the second-line indications proposed.

## **1.2 Recommendation on Postmarketing Actions**

### **1.2.1 Risk Management Activity**

Although the studies supporting this application have enrolled subjects in a wide range of demographic characteristics (age and race), subjects younger than 18 years of age and pregnant or lactating women have been excluded. The studies enrolled subjects that, in addition to their T2DM, had a variety of co-morbid conditions; however, subjects with congestive heart failure requiring medications, liver cirrhosis, and renal dysfunction have been appropriately excluded, as these constitute contraindications to the use of metformin.

There are no new identified risks for the sitagliptin / metformin FDC that have not been identified for each of its components.

The applicant has proposed standard operating procedures for pharmacovigilance. In ongoing and future clinical studies, the applicant will continue to include routine surveillance for laboratory findings that were more frequently observed among sitagliptin-treated subjects, such as decreased alkaline phosphatase, increased uric acid, creatinine and neutrophil counts.

Exposure to sitagliptin / metformin FDC during pregnancy will be monitored by routine pharmacovigilance and by establishment of a pregnancy registry, similar as described in the sitagliptin NDA. There is no or little potential for abuse or unintended use of this product. Unlike exenatide, a recently approved glucagon-like peptide-1 analogue which has produced significant amount of weight loss in patients with T2DM, sitagliptin was not found to exert a meaningful weight loss in clinical studies, and is unlikely to be abused for this end.

No risk minimization plan is being proposed in this application.

### **1.2.2 Required Phase 4 Commitments**

The applicant has a Phase 4 commitment to study the effects of sitagliptin in the pediatric population. Since this study will not be completed by the time the review of the current application of sitagliptin / metformin FDC is due, the commitment to comply with the Pediatric Research Equity Act is deferred at this time.

### **1.2.3 Other Phase 4 Requests**

Not applicable

### **1.2.4 Recommended Trade Name**

Janumet is the proposed Trade Name. DMETS/OSE/CDER was consulted regarding the trade name, and the consultation report is pending at this time.

## **1.3 Summary of Clinical Findings**

The data supporting the efficacy of coadministration of sitagliptin and metformin were described in detail in the sitagliptin NDA. The doses of sitagliptin and metformin in those clinical studies were similar to the doses proposed for the FDC. Briefly, the applicant initially conducted a placebo-controlled crossover Phase 2 study where subjects taking metformin were randomized to a sequence of sitagliptin-placebo or placebo-sitagliptin for treatment periods of 4 weeks duration (Study P015). The applicant subsequently conducted a randomized, placebo- and active-controlled Phase 3 study of the safety and efficacy of sitagliptin when added to metformin (Study P020).

In addition to these studies reported under NDA 21995, the applicant submitted in the current application additional data to further support the safety of the sitagliptin in combination with metformin. These data comprise 117 subjects who had poor glycemic control at the time of screening and these subjects were assigned to the Open Label Cohort of Study P036, a factorial study currently ongoing. The 4-Month Safety Update Report included new data from 1172 subjects participating in the Phase 3 glipizide-controlled non-inferiority Study P024, safety data from the randomized cohorts in Study P036 as well as updated reports received by the applicant through its established Worldwide Adverse Event System (WAES).

### 1.3.1 Brief Overview of Clinical Program

The clinical program described in this application was conducted in order to support the use of sitagliptin and metformin in fixed-dose combinations in the treatment of patients with T2DM. Sitagliptin is a newly approved dipeptidyl peptidase 4 inhibitor (the first member in this class) and metformin is a biguanide with long established safety and efficacy. The doses proposed for treatment are sitagliptin 50 mg / metformin 500 mg and sitagliptin 50 mg / metformin 1000 mg to be used orally twice daily.

Both components of this fixed-dose combination product have been approved for the treatment of T2DM. For this application, FDA had requested the applicant to:

- Provide demonstration of the bioequivalence between the coadministration of sitagliptin and metformin and the fixed-dose combination and
- Provide additional safety data on the coadministration of sitagliptin and metformin, beyond the experience obtained in the sitagliptin NDA.

A total of 2930 subjects participated in Phase 2 and Phase 3 studies in which sitagliptin 100 mg daily (either as 100 mg qd or 50 mg bid) and metformin at daily doses  $\geq$  1500 mg were coadministered. In these studies 1569 subjects have been exposed to coadministered sitagliptin and metformin for periods of 1 to 404 days, with a mean duration of 255 days.

### 1.3.2 Efficacy

The effect of sitagliptin when administered to subjects with inadequate glycemic control while treated with metformin has been studied in the Phase 3, randomized, multicenter, parallel-group, placebo-controlled and active-controlled Study P020 and its extension. That study was reviewed under NDA 21995 as supportive of the indication of sitagliptin as an add-on medication to metformin.

The main characteristics of the study were:

- Subjects needed to be on stable metformin doses of at least 1500 mg daily and have

HbA1c between 7 and 10 % at randomization.

- 701 subjects were randomized 2:1 favoring sitagliptin 100 mg qd versus placebo.
- After assessment of the primary endpoint at week 24 (Phase A), subjects randomized to placebo were switched to glipizide, and both groups continued in the extension study for 80 weeks currently ongoing (Phase B).

Table 1 summarizes the data on the primary endpoint: change in HbA1c from baseline to week 24 in the ITT population.

**Table 1. Change of HbA1c from baseline to week 24 in Study P020 (ITT population)**

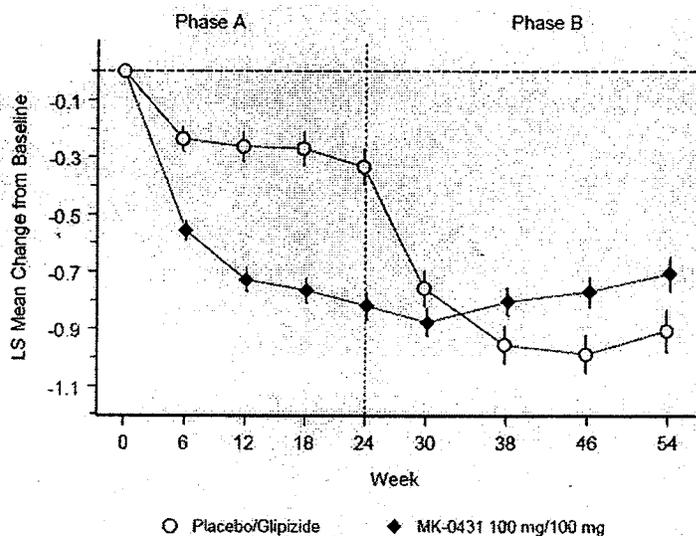
Treatment	N	Mean (SD)		Change from baseline			p-Value
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	
Sitagliptin 100 mg	453	8.0 (0.8)	7.3 (1.0)	-0.7 (0.0)	-0.7 (0.1)	(-0.8, -0.6)	< 0.001
Placebo	224	8.0 (0.8)	7.9 (1.1)	-0.1 (0.1)	0 (0.1)	(-0.1, 0.1)	-
<b>Between Treatment Difference</b>		<b>Difference in LS means (95 % CI)</b>				<b>p-Value</b>	
Sitagliptin 100 mg vs. Placebo		-0.65 (-0.8, -0.5)				< 0.001	

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.

Adapted from the applicant's Table 11-1, reference P020v1

After the initial 24 weeks of study, subjects on placebo were switched to treatment with glipizide. Data from the first 30 weeks of the extension study were reported in the 4-month safety update report that was part of NDA 21995. Figure 1 shows the changes in HbA1c in the 24 weeks of placebo-controlled study and the additional 30 weeks where subjects who had been randomized to placebo in Phase A were treated with glipizide during the ensuing 30 weeks of the extension study (Phase B).

**Figure 1. LS Mean change from baseline in HbA1c (%) over time by treatment group (LS Mean ± SE) in Study P020**



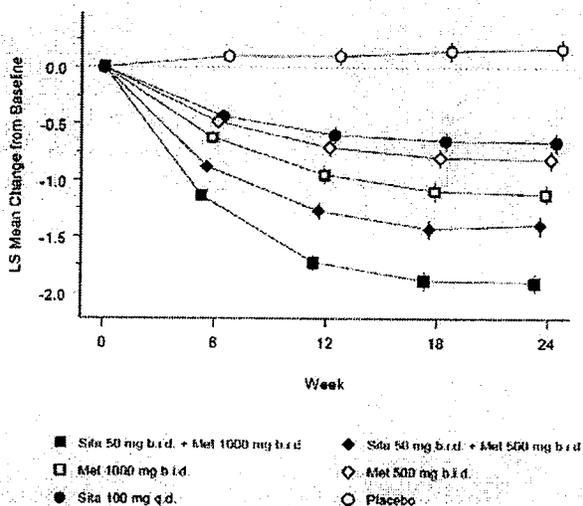
Copied from the applicant's Figure 2.7.3:2 in Reference 2.7.3 Summary of Clinical Efficacy

The significant reduction in HbA1c, with favorable effects on fasting plasma glucose and on the 2-hour post-meal glucose (data not shown) served as the basis for approval of sitagliptin for the treatment of patients with T2DM whose glycemic control is inadequate on metformin therapy alone.

Two other studies investigating effects of sitagliptin in combination with metformin are currently ongoing.

- Study P036 is a randomized, placebo-controlled, factorial study investigating effects on glycemic control of the coadministration of sitagliptin and either low or high metformin doses against the effect of each component (sitagliptin, low or high dose metformin) separately. The primary endpoint is the change in LS mean HbA1c from baseline to week 24. The effect of the coadministration of sitagliptin and each dose of metformin on HbA1c was greater than the effect of each component alone, compared at the same doses of metformin (Figure 2). The mean effect on HbA1c in the Open Label Cohort (not shown in the figure) was similar in magnitude as the effect shown for the coadministration of sitagliptin 50 mg bid and metformin 1000 mg bid.

Figure 2. Changes in Least Square Mean HbA1c (%) among the Randomized Cohorts in Study P036



Copied from the applicant's Figure 11-1, reference p036v1

- Study P024 is an active-controlled, non-inferiority study comparing the glycemic effects of the addition of either sitagliptin or glipizide in subjects with inadequate glycemic control on metformin monotherapy. Only summary efficacy data related to the primary endpoint are being submitted in this NDA.

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**Table 2. Changes from baseline to week 52 in HbA1c in Study P024, in the per protocol population**

Treatment	N	Mean (SD)		Change from baseline		
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sitagliptin 100 mg	382	7.5 (0.8)	6.8 (0.7)	-0.6 (0.0)	-0.7 (0.0)	(-0.7, -0.6)
Glipizide	411	7.5 (0.8)	6.9 (0.7)	-0.7 (0.0)	-0.7 (0.0)	(-0.7, -0.6)
Between Treatment Difference		Difference in LS means (95 % CI)				
Sitagliptin 100 mg vs. Glipizide		<b>-0.01</b> (-0.09, 0.08)				

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.  
 Adapted from the applicant's Table 11-1, reference p024v1, in the 4-Month Safety Update Report

The same analysis in the ITT population (including 576 subjects on sitagliptin and 559 on glipizide, in addition to metformin) yielded similar results, with a difference in LS means for the change in HbA1c from baseline to week 52 of 0.04.

### 1.3.3 Safety

Sources of safety data on the coadministration of sitagliptin and metformin in the NDA 22044 that were submitted with the original application are listed below:

- The Phase 2 Study P015
- The Phase 3 Study P020, including results of the placebo-controlled, 24-week period and the first 30 weeks of the ongoing 80-week Phase B
- The Phase 3 Study P036 Open-label Cohort Interim Safety Assessment.
- In addition, the 4-Month Safety Update Report added safety information on the randomized cohorts of Study P036 and 52 weeks of data from Study P024.
- In these 4 combined studies, 1569 subjects received metformin at daily doses  $\geq$  1500 mg and sitagliptin at daily doses of 100 mg (either as 100 mg qd or 50 mg bid) for a mean period of 36.4 weeks. The clinical safety assessments were based on review of AEs (including SAEs), laboratory abnormalities, electrocardiographic changes, and vital signs.

There are no new concerns regarding the safety of the coadministration of sitagliptin and metformin than those already noted in the review of the sitagliptin NDA and the known safety profile of metformin (for example, the rare risk of lactic acidosis under specified circumstances).

### 1.3.4 Dosing Regimen and Administration

The applicant proposes the use of sitagliptin / metformin FDC as a treatment of patients with T2DM who are not adequately controlled on either metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

The dose of sitagliptin / metformin FDC is mostly driven by the patient's current antidiabetic treatment regimen, and is titrated based on the effectiveness in reaching glycemic goals and the tolerability of the metformin component. The sitagliptin dose that has been selected for marketing, as monotherapy or in combination with metformin or a PPAR  $\gamma$  agonist, is 100 mg qd. The safety, pharmacokinetic and pharmacodynamic profiles of a regimen of 100 mg qd are very similar to those seen with 50 mg bid, as reported under NDA 21995. For patients who are

naïve to treatment with metformin, the dose is usually titrated weekly from 500 mg qd or bid up to 1000 mg bid, in order to decrease gastrointestinal events that may lead to discontinuation due to poor tolerability.

The proposed label proposes the following dosing recommendations:

The starting dose of sitagliptin / metformin FDC should be based on the patient's current regimen. Sitagliptin / metformin FDC should be given twice daily with meals. The following doses are available: sitagliptin 50 mg / metformin hydrochloride 500 mg and sitagliptin 50 mg / metformin hydrochloride 1000 mg.

For patients inadequately controlled on metformin monotherapy

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

For patients inadequately controlled on sitagliptin monotherapy

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

For patients switching from sitagliptin coadministered with metformin

For patients switching from sitagliptin coadministered with metformin, sitagliptin / metformin FDC may be initiated at the dose of sitagliptin and metformin already being taken.

The dose strengths of sitagliptin / metformin FDC do not include a combination of sitagliptin 50 mg with metformin 850 mg. The applicant argued that more than 1% of prescriptions written for metformin in the United States are for either 500 mg or 1000 mg (source cited: IMS Health, NPA Plus™ from 9/2005 to 3/2006). The applicant states that no increased issues of safety or tolerability would be expected if a patient whose glycemic control is not adequate with metformin 850 mg bid were to switch to the sitagliptin 50 mg / metformin 1000 mg bid FDC, with the possibility that the small metformin dose increase will further help improve glycemia. This reviewer agrees with the applicant's assessment.

### 1.3.5 Drug-Drug Interactions

Coadministration of multiple doses of sitagliptin (50 mg) and metformin (1000 mg) given twice daily did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with sitagliptin / metformin FDC have not been performed; however, such studies have been conducted with the individual components of (sitagliptin phosphate and metformin hydrochloride).

Sitagliptin is well absorbed with an absolute bioavailability of 87 %, which does not change substantially when dosing follows a high fat meal. Sitagliptin is eliminated by the kidneys as unchanged drug, with minor metabolism mediated by CYP3A4. Sitagliptin is not an inducer of CYP3A4. The renal clearance is approximately 350 mL/min, suggesting that active tubular

secretion is involved in the renal elimination of sitagliptin, possibly by the organic anionic transporter-3. Sitagliptin is a substrate for p-glycoprotein, but cyclosporin A, a potent p-glycoprotein inhibitor did not affect absorption and excretion of sitagliptin. In clinical studies sitagliptin did not meaningfully alter the pharmacokinetics of metformin, simvastatin, warfarin, oral contraceptives, rosiglitazone or glyburide, therefore suggesting low probability of drug-drug interactions with organic anion transporter, CYP3A4, CYP2C8 and CYP2C9.

GLP1 secretion from the L-cells in the distal portions of the small bowel is likely mediated by vagal stimulation, as it occurs at the onset of a meal, rather than at a time of direct passage of food through the distal intestine. Therefore, one could expect that chronic blockade vagal antagonism, in the form of anti-cholinergic drugs, would blunt the response to sitagliptin. This does not appear to be the case. An analysis of sitagliptin effect on HbA1c in 5 subjects in one of the Phase 3 studies of sitagliptin used in monotherapy (Study P021) who were using anti-cholinergic drugs for urinary or gastrointestinal conditions for at least 3 months shows reductions of HbA1c in par with the groups they were randomized to: 100 mg or 200 mg.

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of sitagliptin / metformin FDC and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

### 1.3.6 Special Populations

Since metformin is contraindicated in patients with renal disease or dysfunction, congestive heart failure requiring pharmacologic therapy and in patients with acute or chronic metabolic acidosis (due to the higher risk of lactic acidosis), sitagliptin / metformin FDC is also contraindicated in these patient populations. Mean sitagliptin AUC and  $C_{max}$  increases in subjects with mild or moderate hepatic insufficiency are not clinically significant, compared to healthy matched controls. On the other hand, no pharmacokinetic studies have been conducted with metformin in patients with any degree of hepatic insufficiency; thus the use of sitagliptin / metformin FDC should be avoided in patients with clinical or laboratory evidence of hepatic disease. The use of metformin in geriatric patients, particularly those older than 80 years, should only be initiated and maintained only after ascertainment of normal renal function.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

#### 2.1.1 Product description

Sitagliptin phosphate is a new molecular entity that belongs to a new class of therapeutic agents recognized as dipeptidyl peptidase IV (DPP4) inhibitors. The chemical name is (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  $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$  and the molecular weight is 523.32. The structural formula is shown in Figure 3:

Figure 3. Structural formula of sitagliptin phosphate

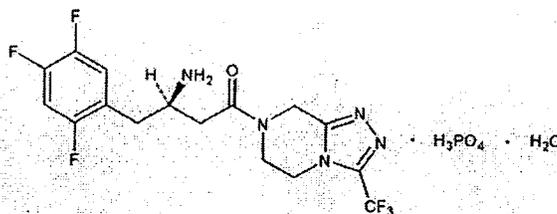


Figure copied from the applicant's structure. PDF under Quality – Drug Substance information in the application

Metformin hydrochloride is a white crystalline powder that is stable and non-hygroscopic. It is freely soluble in water. There are no known hydrates, solvates or polymorphs which are formed at room temperature.

The product composition is shown in Table 3, copied from the applicant's Table 2.3.P-0431A-tablet: 1

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**Table 3. Tablet composition of sitagliptin phosphate and metformin hydrochloride at the different dose strengths proposed for FDC marketing**

Sitagliptin Phosphate (+) Metformin Hydrochloride tablet -  
 Market Composition

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

† — mg of the — s equivalent to — mg of the free base  
 ‡ Removed during processing

2.1.2 Established name and proposed trade name

The established name used in the application is sitagliptin phosphate in fixed-dose combination (FDC) with metformin hydrochloride. The applicant has designated this product during development under the codes MK-0431A.

The proposed trade name is Janumet.

2.1.3 Chemical class

Sitagliptin is a new molecular entity, formulated as a monohydrate phosphate salt. Metformin is a drug in the biguanide class.

2.1.4 Pharmacologic class

Sitagliptin is a potent and selective inhibitor of DPP4. Inhibitors of DPP4 are a new class of incretin enhancers, developed to improve glycemic control in patients with T2DM. Metformin is thought to act by decreasing hepatic glucose output and improving insulin sensitivity.

### 2.1.5 Proposed indications, dosing regimens and age groups

“Janumet is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.”

This proposed indication is for second-line treatment. Because of the variable dose strength of metformin, the dosage is individualized on the basis of the patient’s current regimen, effectiveness and tolerability. Janumet should be taken twice daily with meals, generally with gradual dose titration.

The starting dose of sitagliptin/metformin FDC should be based on the patient’s current regimen. The following doses are available: sitagliptin 50 mg / metformin hydrochloride 500 mg and sitagliptin 50 mg / metformin hydrochloride 1000 mg.

For patients inadequately controlled on metformin monotherapy, the usual starting dose of sitagliptin / metformin FDC should be equal to 100 mg total daily dose (50 mg twice daily) of sitagliptin plus the dose of metformin already being taken.

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

For patients switching from sitagliptin coadministered with metformin, sitagliptin / metformin FDC may be initiated at the dose of sitagliptin and metformin already being taken.

For the < 7 % of patients currently on metformin 850 mg twice daily and not well controlled, the applicant recommends switching to sitagliptin 50 mg / metformin 1000 mg twice daily, resulting in a small increase in the daily metformin dose, which may improve glycemic control and is likely to be well tolerated.

Sitagliptin / metformin FDC is not recommended for patients younger than 18 years of age, during pregnancy or lactation, and in subjects for whom use of metformin is contraindicated.

## 2.2 Currently Available Treatment for Indications

T2DM can be treated with a combination of proper diet, exercise, and the following classes of drugs, alone or in combination:

- Insulin and insulin analogues;
- Sulfonylureas
- Metformin
- Meglitinides
- Thiazolidinediones
- Inhibitors of alpha-glucosidase
- Analogs of Glucagon-like Peptide 1 (GLP1)
- Synthetic analogs of human amylin
- DPP4 inhibitors (sitagliptin was approved on 10/16/06 in the US)

Despite the number of drugs available for the treatment of T2DM, a substantial proportion of patients remain under poor glycemic control.

### **2.3 Availability of Proposed Active Ingredient in the United States**

The product contains 2 active ingredients that are currently marketed in the United States: metformin has been available since 1995 and sitagliptin was approved on October 16, 2006. The major safety concern with the use of metformin has been the rare occurrence of lactic acidosis in certain populations, such as in patients with acute or chronic renal insufficiency and in patients prone to metabolic or respiratory acidosis (congestive heart failure, alcoholism, etc). At the time of this review, there is no sufficient post-marketing safety experience with sitagliptin.

### **2.4 Important Issues With Pharmacologically Related Products**

FDA has notified manufacturers of DPP4 inhibitors that they have “received data indicating that the administration of DPP4 inhibitors to monkeys results in dose-dependent and duration-dependent increases in necrotic skin lesions of the tail, digits, ears, nose and scrotum. The mechanism for this toxicity is not understood. To our knowledge, drug-related skin lesions have not been observed in rats, dogs or humans. This toxicity appears to be a class-related effect...”. Since receiving this notification, Merck has conducted an oral toxicity study in monkeys, and concluded that sitagliptin does not pose the same risks of skin toxicities. The lack of edema or necrotic skin lesions was attributed to the relatively high specificity to DPP4, since a non-specific dipeptidyl peptidase inhibitor and a DPP 8/9-specific inhibitor cause substantial skin and blood toxicity and mortality.

### **2.5 Presubmission Regulatory Activity**

Sitagliptin / metformin FDC has been developed under IND 65,495 (sitagliptin in monotherapy or in combination with either metformin or a PPAR  $\gamma$  agonist) and under IND 70934 (the fixed-dose combination of sitagliptin and metformin).

IND 65,495 was originally submitted on August 9, 2002. The development program was discussed in an End of Phase 2 meeting with FDA on June 9, 2004 and at the Pre-NDA meeting on July 26, 2005. During the End of Phase 2 meeting, Merck had reached agreement on the design of Phase 3 studies, the proposed doses for development in the general population of T2DM and the proposed dose adjustment for subjects with chronic renal insufficiency. FDA had requested an additional PK study exploring the interaction between sitagliptin and cyclosporin, and a thorough QT study. FDA requested analysis of hypoglycemic events and made specific comments in reference to LOCF as a method for imputing missing data in the analysis of efficacy. FDA granted deferral of pediatric studies until the safety of sitagliptin treatment in adults is reviewed and established. Merck had also entered into discussions and agreements with the European and Canadian regulatory Agencies.

IND 70,934 was originally submitted on March 22, 2005. The development program was discussed in an End of Phase 2 meeting with FDA on December 15, 2004.

FDA generally concurred with the proposed indications as an adjunct to diet and exercise to improve glycemic control in patients with T2DM and to improve glycemic control in patients with T2DM when diet and exercise plus treatment with either metformin or sitagliptin alone do not provide adequate control. The proposed \_\_\_\_\_ indications were to be supported by the Phase 3 sitagliptin and metformin coadministration studies P020 (a placebo-

controlled sitagliptin add-on study), P024 (an active-controlled add-on study) and P036 (a factorial study). FDA generally concurred that demonstration of bioequivalence, bridging coadministration in the clinical studies to administration of the FDC tablet, was acceptable. FDA also agreed that no toxicology studies with the combination were required. For Study P036, specific FDA requests to compare the efficacy of each combination dose to its components as the primary analyses for this factorial study were addressed in the data analysis section of the protocol and in a separate Statistical Analysis Plan (SAP).

Subsequent to the End of Phase 2 meeting, the applicant had a pre-NDA meeting with FDA on March 6, 2006 to propose a second-line indication for sitagliptin / metformin FDC based upon results from the Phase 3 study P020, and supported by safety data from the Open-Label Cohort from the ongoing Phase 3 Study P036. FDA generally concurred with this proposal, providing that the application included 54-week data from Study P020 (both from the placebo-controlled Phase A and the ongoing extension Phase B). FDA requested that the initial NDA filing be supported by 6-month formal stability data for the fixed-dose combination. FDA further clarified that a biowaiver based on BCS classification does not apply and that results from an in vivo bioequivalence study with the FMI would be a filing requirement.

The applicant had also entered into discussions and agreements with the European and Canadian regulatory agencies. European regulatory agencies requested that animal toxicity studies be conducted with the coadministration of sitagliptin and metformin.

## 2.6 Other Relevant Background Information

T2DM affects about 6 % of adults in Western Society, and the worldwide prevalence is expected to grow to a total of 220 million patients by the year 2010. The pathogenesis underlying T2DM include insulin resistance, reduced insulin secretion and overproduction of hepatic glucose. Data from the Diabetes Control and Complications Trial (in type 1 diabetics) and the United Kingdom Prospective Diabetes Study (in T2DM) demonstrated lower incidence of chronic diabetic complications in patients randomized to intensive glycemic control. Since these studies, a number of products in new therapeutic classes have been developed and became part of the armamentarium to treat T2DM. Limitations of current therapies include a range of safety and tolerability issues, limited extent and/or durability of efficacy, and inconvenience in dosing or in route of administration. The most common adverse events associated with current agents are hypoglycemia (with sulfonylureas, meglitinides, insulin), weight gain (with sulfonylureas, meglitinides, insulin, thiazolidinediones [TZDs]), and gastrointestinal intolerance (with metformin, alpha-glucosidase inhibitors).

The “incretin effect” relates to an observed 2 – 3 times greater insulin response to an oral glucose load compared to an intravenous glucose load. The mediators (“incretins”) are mainly the glucose-dependent insulinotropic polypeptide (GIP) and the activated form of the glucagon-like peptide 1 (GLP1), accounting for 90% of the incretin effect.

GLP1 is secreted by enteroendocrine L cells located in the distal intestinal mucosa. Its secretion is increased by 2- or 3-fold following glucose or mixed meal ingestion. In the presence of elevated, but not normal or low, glucose concentrations, GLP1 and GIP increase insulin release from pancreatic  $\beta$ -cells, and GLP1 lowers glucagon secretion from pancreatic  $\alpha$ -cells. The rise in insulin enhances glucose uptake in peripheral tissues. The increase in insulin in combination with the decrease in glucagon also lowers hepatic glucose production. These effects on insulin

and glucagon reduce post-meal rises in glucose concentration and likely reduce fasting glucose concentrations. In addition to effects on insulin and glucagon secretion, GLP1 also reduces appetite, decrease the rate of gastric emptying, and promote beta cell proliferation and survival. T2DM affects both of these incretin hormones: while GLP1 secretion in response to meals is decreased, the GIP insulinotropic effect is decreased. Due to the actions mentioned here, GLP1 receptor agonists became appealing as a new class of anti-hyperglycemic agents in the treatment of T2DM. GLP1 is rapidly degraded by DPP4, a ubiquitous peptidase, with a half-life of less than 2 minutes.

Exenatide is a synthetic form of exendin-4 (a peptide that shares 53 % homology with GLP1). Exenatide is resistant to cleavage by DPP4. Its effects on glucose-dependent insulin secretion, absent hypoglycemic risk and weight gain compared favorably to sulfonylureas. Exenatide was approved in the United States for the treatment of T2DM in combination with metformin or sulfonylureas in December 2005. Other GLP1 analogs that are resistant to DPP4 are in different phases of clinical development. A DPP4 inhibitor is another approach to prolong the effect not only of GLP1, but both incretin hormones. This new class of products may have effects on 2 of the 3 key defects underlying the pathogenesis of T2DM—reduced insulin secretion and, by lowering glucagon levels, excessive hepatic glucose production.

Metformin is an antidiabetic drug in the biguanide class. It is used extensively to treat T2DM. Although approved for use in the U.S. in 1995, it has been available in Europe since the 1950s. Metformin acts to lower glucose concentrations by decreasing hepatic glucose output and increasing insulin sensitivity in liver and muscle.

Since DPP4 inhibition with sitagliptin improves insulin secretion and metformin reduces insulin resistance, while both DPP4 inhibition and metformin reduce hepatic glucose production (DPP4 inhibition by lowering glucagon and metformin by direct actions on the liver), the combination of sitagliptin and metformin has the potential to address aspects of all three key defects that contribute to elevated glucose concentrations in patients with T2DM. Metformin has been reported to increase plasma GLP1 levels by a number of investigators; results reflect varying experimental designs and assay sensitivity for intact versus total GLP1. A clinical study included in this application showed that metformin increases active GLP1 levels through increases in total GLP1 levels, and the combination of metformin and sitagliptin caused at least an additive increase in active GLP1 concentrations. This finding of complementary mechanisms of action provides additional support for use of this combination to effectively lower glucose concentrations in patients with T2DM. Taken together, these observations suggest that the use of a DPP4 inhibitor, such as sitagliptin, in combination with metformin is likely to provide greater glycemic control than that provided by either agent when used as monotherapy.

In addition to the complementary mechanisms by which sitagliptin and metformin lower glucose concentrations, these agents are also complementary in terms of their predominant glucose-lowering effects. Metformin predominantly lowers fasting glucose concentrations (through inhibition of gluconeogenesis and glycogenolysis; sitagliptin has a prominent post-meal glucose-lowering effect while also providing reductions in fasting glucose concentrations. Since both elevated fasting and elevated post-meal glucose contribute to the increased HbA1c observed in patients with T2DM, a combination of agents that lowers glucose in both settings should be particularly beneficial.

### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### 3.1 CMC (and Product Microbiology, if Applicable)

Three formulations of sitagliptin have been used in development, all with highly similar pharmacokinetics, and thus can be considered as interchangeable. Initial Phase 1 studies were conducted with a \_\_\_\_\_ capsule formulation (the Phase 1 formulation) containing the \_\_\_\_\_ phosphate salt form of sitagliptin as \_\_\_\_\_ in \_\_\_\_\_ cellulose capsules. Film-coated tablets containing the \_\_\_\_\_ phosphate \_\_\_\_\_ form of sitagliptin (the Phase 2 formulation) were used in the Phase 2 dose ranging studies (P010 and P014). The pharmacokinetics of the Phase 1 and Phase 2 formulations were demonstrated to be similar. A similar film-coated tablet formulation containing the monohydrate phosphate \_\_\_\_\_ form of sitagliptin was used in the Phase 3 studies (P019, P020, P021, and P023) and is the final market image (FMI) formulation (referred to as the Phase 3/FMI formulation). The Phase 2 formulation was shown to be bioequivalent to the Phase 3/FMI formulation at the 100 mg potency. The sitagliptin phosphate drug substance used in the FDC is the same as that used in the manufacturing of sitagliptin alone (Januvia) and that was reviewed in the sitagliptin NDA 21995. Compendial grade metformin hydrochloride drug substance was provided by \_\_\_\_\_ from \_\_\_\_\_.

Table 4 shows the composition of the film coated tablet, as proposed for marketing.

Table 4. Sitagliptin phosphate and metformin hydrochloride tablet composition

Sitagliptin Phosphate (+) Metformin Hydrochloride tablet -  
 Market Composition

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

† \_\_\_\_\_ mg of the \_\_\_\_\_ equivalent to \_\_\_\_\_ mg of the free base.  
 ‡ Removed during processing

Please refer to Dr. Suong Tran's review for the detailed and complete appraisal of CMC issues related to sitagliptin / metformin FDC.

### 3.2 Animal Pharmacology/Toxicology

Sitagliptin is a potent, highly selective, competitive reversible inhibitor of DPP4 that lowers blood glucose levels in both lean and obese animal models of T2DM. The drug is very water soluble and highly bioavailable in rats, dogs, and humans. It is rapidly absorbed in all species studied with a plasma half-life of about 2 to 4 hours in both rats and dogs and about 13 hours in humans. Sitagliptin is widely distributed in the body of rats with concentrations highest in the tissues involved in elimination, liver, kidney, and urinary bladder. In mice, rats, dogs, and rabbits, metabolism is minimal, and in rats, and dogs, the drug is excreted primarily unchanged into urine and feces. All metabolites observed in humans were detected in mice, rats, rabbits, and/or dogs. Renal clearance in rats exceeds the glomerular filtration rate, indicating active secretion of the parent drug. In vitro studies have demonstrated that the human organic anion transporter hOAT3 may be involved in the active transport of sitagliptin from blood into the kidney. Inhibitors of this transporter include probenecid,  $\beta$ -lactam antibiotics, non-steroidal anti-inflammatory drugs, and furosemide.

In Safety Pharmacology studies sitagliptin showed relatively low inhibition of  $I_{Kr}$  potassium current in the hERG assay with an  $IC_{50}$  of 147  $\mu$ M. In vivo in the dog cardiovascular assay the only effects noted were tachycardia with an associated reduction of the P-R interval at an oral dose of 50 mg/kg. At the NOEL of 10 mg/kg, a 6-fold safety margin was found relative to the maximum therapeutic dose. No QTc or other electrocardiographic changes or changes in blood pressure were found at any dose. There were no effects of the drug in vivo on respiratory, cardiovascular, renal, gastric, or CNS function in dogs, mice, and rats.

Sitagliptin is not genotoxic in vitro or in vivo in a battery of assays designed to detect mutagenicity, direct DNA damage, or clastogenicity. The drug is not acutely toxic in either mice or rats with minimum lethal doses in the range of 2000 to 3000 mg/kg. Repeat-dose toxicity studies have demonstrated a wide margin of safety of the drug. The minimum dose producing target organ toxicity in rats and mice after 3 months of treatment is 500 mg/kg/day. In mice, renal toxicity is evident while in rats, liver toxicity is produced at these relatively high doses. In the chronic rat study the NOEL was 180 mg/kg/day, the maximum dose tested. In dog toxicity studies ranging from 2 weeks to 12 months duration, a consistent finding at the 50 mg/kg/day top dose has been the induction of transient physical signs of toxicity. These signs, suggestive of neurotoxicity, have consisted of ataxia, tremor, decreased activity, open-mouth breathing and abnormal respiratory signs. In addition to the physical signs, the only other finding was very slight to slight skeletal muscle degeneration at the 50 mg/kg/day dose in the 14- and 27-week oral toxicity studies. However, in the 53-week oral toxicity study, only the physical signs noted above were observed, indicating no progression of the incidence or severity of the physical signs or the skeletal muscle toxicity with chronic oral administration. The NOEL in the chronic dog study was 10 mg/kg/day. It is important to note in light of the expression of DPP4 (CD26) on activated T cells that no evidence of effect on the immune system was found in any of the sitagliptin repeat-dose studies in rats, mice, or dogs as determined by clinical evaluation, hematology, or histopathology. These results are consistent with in vitro results demonstrating no effect of sitagliptin on activation of T cells. Therefore, it is concluded that inhibition of DPP4 does not affect immune function and that in vitro studies purportedly demonstrating an effect are related to use of non-selective inhibitors. This conclusion is supported by studies in a sub-strain of \_\_\_\_\_ rats harboring a mutation in the DPP4 gene that results in expression of an enzymatically inactive form of DPP4. These studies show comparable immune responsiveness to

several lymphocyte mitogens and antigens in the rats expressing inactive DPP4 compared to rats expressing active DPP4.

Based on the nonclinical evaluation of sitagliptin, it is concluded that selective inhibition of DPP4 is well-tolerated with no evidence of pharmacologically-mediated toxicity in any species. The toxicity profile of sitagliptin after repeated oral dosing has been characterized in rats, mice, and dogs. Maximum-tolerated doses based on target organ toxicity have been clearly identified in each species. Wide margins of safety have been determined for each of the toxicities identified and/or the toxicity is reversible and readily monitorable in patients. Although sitagliptin increased the incidence of hepatic tumors in rats at the MTD of 500 mg/kg/day, this finding is not considered a risk for patients. This conclusion is based on the association of chronic liver injury in rats leading to an increased incidence of liver tumors in carcinogenicity studies. Since no evidence of hepatotoxicity has been found in clinical studies using doses up to 8-fold the MRD, the increased incidence of hepatic tumors in rats is not considered relevant for humans. Sitagliptin poses no significant hazard to reproduction or to the developing fetus based on studies in rats and rabbits.

Data from toxicity studies conducted in monkeys with other DPP4 inhibitors suggested a dose- and duration-dependent increase in necrotic skin lesions of the tail, digits, ears, nose and scrotum. FDA had requested a repeat-dose toxicity of  $\geq 3$  months duration in monkeys, specifically looking for drug-induced skin lesions as well as histologic examination of the kidneys for potential drug-induced toxicity. The study report was submitted during this review cycle, on August 24, 2006. Doses up to 100 mg / kg / day were given to rhesus monkeys by oral gavage for approximately 14 weeks. All animals survived to study termination. There were no treatment-related physical signs, changes in body weights or food consumption at any of the dose-levels compared to the concurrent controls. Significant inhibition of plasma DPP4 enzyme activity was observed in animals from all the drug-treated levels, as expected. There were no treatment-related gross observations in the skin, changes in renal or brain weights, or histomorphologic findings in the kidneys.

The toxicity of sitagliptin coadministered with metformin was studied in dogs, as required by the European regulatory agency. There were no toxicities observed following oral administration of a single oral dose of 50 mg / kg of each component. To determine the potential toxicity and toxicokinetics following coadministration sitagliptin and metformin were both administered orally to dogs for approximately 14 weeks. A dose of 50 mg/kg/day of metformin was selected based upon the doses used in the chronic toxicity studies reported with this compound in dogs and the lack of any toxicokinetic interaction with sitagliptin based on the single dose toxicokinetic study. The doses of sitagliptin were 2, 10, and 50 mg/kg/day, the same doses used in the repeat dose studies to support registration of the monotherapy indication.

Mortality was observed in all treatment female groups, including the metformin alone control, and considered to be due to the relatively high dosage level of metformin. Four of the 6 found dead /early sacrificed females presented with severe physical signs, or body weight losses due to marked decreases in food consumption / anorexia. Decreased serum bicarbonate and increased plasma lactate levels, considered to be indicative of lactic acidosis, were observed in 1 female from the metformin group prior to its sacrifice. Pre- / post-dosing salivation, emesis, and unformed/liquid stools were noted in all treatment female and male groups. Transient ataxia (both sexes) and tremors (females), considered related to sitagliptin administration at 50 mg/kg/day, as well as slight individual increases in plasma lactate (both sexes) were observed in the high-dose combination group. Based on the mortality in females and the occurrence of

physical signs in males in all treatment groups, a no-effect level for treatment-related changes was not determined in this study.

Due to the mortality induced in the previous combination toxicity study, a study with metformin alone was conducted to confirm that the toxicity observed was unequivocally due to metformin and not due to the combination with sitagliptin. Beagle dogs were randomized into 2 groups of 5 females each. One group received 50 mg/kg/day of metformin. The control group received 0.5% (w/v) methylcellulose (vehicle) in deionized water only. The dosing volume for all animals was 5 mL/kg. One treated dog was found dead following a period of body weight loss due to marked decreases in food consumption, and another treated dog was sacrificed because of marked physical signs. Elevated plasma lactate and low serum bicarbonate values, indicative of lactic acidosis, were observed in the early sacrifice dog. Other treatment-related changes consisted of occasional emesis, frequent pre- / post-dosing salivation, and increases in mean plasma lactate values. Since mortality / morbidity occurred at essentially the same incidence in female dogs treated with 50 mg/kg/day of metformin alone (2/5) as in those coadministered metformin and sitagliptin (5/9), the applicant concluded that the previously observed toxicity was due to metformin alone and not an interaction with sitagliptin. The applicant further conducted another study in dogs, using a lower dose of metformin of 20 mg/kg/day. After an initial 2-week run-in period of metformin alone without any signs of toxicity or lactic acidosis, sitagliptin was then coadministered for 14 weeks at doses of 2, 10 and 50 mg / kg/ day. At that dose of metformin, no treatment-related physical signs, changes in body weight, food consumption, electrocardiography or clinical pathology. Taken together, these results suggest the initial toxicity and deaths findings were related to the high dose of metformin used, with induction of lactic acidosis.

Please refer to Dr. Todd Bourcier's review for the complete and detailed assessment of relevant issues related to animal pharmacology and toxicology.

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

All clinical data in support of this NDA come from the studies conducted by the applicant. Clinical data in this NDA was submitted in the electronic Common Technical Document format, with the following path: \\cdsesub1\evsprod\n022044\022044.enx and under NDA 021995 with the following path: \\cdsesub1\evsprod\n021995\021995.enx.

In addition, clinical data were submitted with the 4-month safety update report during the review cycle of this NDA. Important non-clinical and clinical data relevant to clinical monitoring in the sitagliptin program were also obtained from other drugs in the same class (DPP4 inhibitors) being investigated under other INDs in the Division of Metabolism and Endocrinology Products.

### **4.2 Tables of Clinical Studies**

Table 5 (derived from the Tabular Listing of all Clinical Studies in the application) shows studies to establish the safety, tolerability and pharmacokinetic and pharmacodynamic parameters of sitagliptin alone.

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Janumet™ (Sitagliptin / metformin fixed-dose combination)

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Table 6 (also derived from the Tabular Listing of all Clinical Studies in the application) shows studies to establish the safety and efficacy parameters of sitagliptin alone or in combination with metformin or pioglitazone in the treatment of T2DM.

Table 7 shows the studies conducted and reported under the present NDA, which had not been included in the Table 5 and Table 6.

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**Table 5. Pharmacokinetic and pharmacodynamic studies during sitagliptin development**

Study Number	Study design	Number and type of subjects	Parameters examined	Dose range	Duration of exposure
P001C	DB, R, PC, SAD	34 male healthy	PK, PD, safety	1.5 to 600 mg or PBO	1 day
P003	DB, R, PC, SD	38 M, F, obese	PK, PD, safety	50 mg or PBO	1 day
P004	DB, R, PC, MAD, staggered PG	70 healthy males	PK, PD, safety	25 – 400 mg qd vs. PBO OR 800 mg day 1 followed by 600 mg X 10 days (vs. PBO) OR 300 mg bid vs. PBO	10 days
P005	R, PC, 3-period crossover	58 M, F, with T2DM	PK, PD, safety	25 or 200 mg or PBO in random sequence	1 day each, ≥ 7 days apart
P006	OL, R, 2-period, crossover	12 healthy M, F	PK, safety	50 mg as tablet or <del>capsule</del> capsule, ≥ 7 days apart	1 day each
P007	DB, R, PC, MD	32 obese, middle age M, F	PK, PD, safety	200 mg bid or PBO	28 days
P008	OL, 2-part (SD or 2 dose)	24 M, F ESRD, 6 healthy volunteers	PK, Safety	Part 1: 50 mg single dose in ESRD and healthy; part 2: 50 mg qd X 2, 7 days apart	1 or 2 days
P009	OL	6 M healthy	PK, safety	SD <sup>14</sup> C-sitagliptin 83 mg	1 day
P011	DB, DD, R, PC, 3-period crossover	19 M, F with HTN	Ambulatory BP, safety	50 bid, 100 bid or PBO	5 days
P012	DB, DD, R, PC, 3-period crossover	13 M, F with T2DM on metformin	PK, Safety	50 mg or PBO bid and metformin 500 mg or PBO bid	7 days each period
P013	DB, R, PC, SAD	18 M Japanese	PK, PD, safety	Panel A: 5, 25, 100 mg fasting and 25 mg post meal; Panel B: 12.5, 50, 200, 400 mg fasted, 7 days apart	1 day each
P016	OL, 3-period, fixed sequence	8 M healthy	PK, safety	Enterion™ capsules for stomach, or distal small bowel or colon release	1 day each, 7 days apart
P017	OL, SD	20 M, F with moderate hepatic insufficiency	PK, safety	100 mg	1 day
P018	DB, R, PC, 2-part, 2-period crossover	36 M, F healthy	PK, safety	Part 1: 100 mg or PBO with 0.25 mg digoxin qd. Part 2: 200 mg or PBO qd	10 days each period, 2 weeks apart
P022	R, OL, 2-period, crossover, MD sitagliptin effect on SD warfarin	12 M, F healthy	PK, safety	Either single 30 mg dose warfarin during sitagliptin 200 mg qd X 11 days or just warfarin 30 mg once	1 day warfarin during 11 days sitagliptin
P025	R, OL, 2-period crossover	12 M, F healthy	PK, safety	Simvastatin 20 mg once after 200 mg qd X 5 days or simvastatin alone	5 days
P026	OL	18 F healthy with reproductive potential	PK, safety	Ortho-Novum (EE2/NET) qd X 28 days with sitagliptin 200 mg qd X 21 days or PBO	21 days
P027	OL, R, SD, 2-period, crossover	12 M, F healthy	PK (bioequivalence), Safety	100 mg either in <del>capsule</del> form or monohydrate (FMI)	1 day
P029	Part 1: DB, fixed sequence, 3-period, IV dose escalation Part 2: SD, 3-period crossover	22 M, F healthy	PK, bioavailability with food	Part 1: single IV dose 25, 50 or 100 mg Part 2: 100 mg fasting, after standard meal, or IV fasting	1 day each
P031	R, OL, 2-period, crossover	9 M, F healthy	PK, safety	Treatment A: 200 mg X 6 days with 1.25 mg glyburide on day 5; Treatment B: single dose glyburide on day 1	6 days
P032	DB, DD, R, PC, 4-period crossover	86 M, F healthy	PK, PD (QT interval), safety	100 mg, or 800 mg or 400 mg moxifloxacin or PBO	1 day each
P033	OL, R, 5-period, crossover	10 M, F healthy	PK, safety	25, 50, 100, 200 or 400 mg	1 day
P034	OL, R, 2-period, crossover	12 M, F healthy	PK, safety	200 mg X 5 d with 4 mg rosiglitazone d 5 or rosi alone	5 days
P037	OL, R, 2-period, crossover	8 M, healthy	PK, safety	SD 100 mg with or without SD 600 mg cyclosporin	1 day each

DB= double blind; DD= double dummy; R= randomized; PC= placebo-controlled; SD= single dose; SAD= single ascending dose; PBO= placebo; MAD = multiple ascending dose; PG= parallel group; ESRD = end stage renal disease; OL = open label

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**Table 7. Sitagliptin studies listed under NDA 022044 (sitagliptin / metformin FDC)**

Study Number	Study Design	Number and type of subjects	Endpoints	Dose range	Duration of exposure
P038	OL, R, 3-period crossover	24 M, F healthy	PK (bioequivalence) and safety	Sitagliptin/metformin 50/500 or 50/1000 tabs formulated with or without SLS or sitagliptin and metformin given separately	1 day each, ≥ 7 days apart
P048	OL, R, 2-period crossover	48 M, F healthy	PK (bioequivalence) and safety	Sitagliptin/metformin 50/500 or 50/1000 tabs or sitagliptin and metformin given separately	1 day each
P050	DB, DD, R, PC, 4-period crossover	17 M, F healthy	PK, PD (GLP-1), safety	2-day periods of sitagliptin 100 or metformin 500 or metformin / sitagliptin or PBO	4 days for sitagliptin, each period ≥ 7 days apart
P036	DB, PC, R, Factorial design with an Open Label Cohort (OLC)	1091 T2DM randomized*; 117 in OLC	Safety and efficacy of the coadministration of sita / metformin	Sita 100 qd; Met 500 bid, Met 1000 bid; sita 50/met 500 bid; sita 50/met 1000 bid; PBO; sita 50/met 1000 bid OLC	24 weeks (Phase A) and 30 weeks (Phase B extension)
P024*	DB, MC, R, AC, 2-year study	1172 T2DM	Safety and efficacy of sitagliptin compared to glipizide, as add-on to metformin	Sitagliptin 100 mg and metformin ≥ 1500 mg qd	52 weeks in the study report for this NDA

\* Only included in the 4-month Safety Update Report

### 4.3 Review Strategy

Most of the review effort concentrated on 2 issues:

- The efficacy and safety of sitagliptin in monotherapy or coadministered with metformin or with pioglitazone, under NDA 21-995 reviewed by this Medical Officer;
- New data from 3 studies presented under the current NDA: study reports and datasets for the bridging Study P048 and the Open Label Cohort that is part of Study P036 were submitted with the original application, while safety data reported from Study P024 and from the 6 Randomized Cohorts in Study P036 were submitted in the 4-month Safety Update Report. The bridging study, its results and conclusions are summarized here but are thoroughly reviewed by the Clinical Pharmacology (Biopharmaceutics) reviewer, Dr. Jaya Vaidyanathan.

### 4.4 Data Quality and Integrity

As all of the efficacy data and most of the safety data supporting this sitagliptin / metformin FDC were reviewed under NDA 21995, this Medical Officer did not request an audit of clinical sites for the present NDA. Dr. Jaya Vaidyanathan, the Clinical Pharmacology reviewer from the Division of Clinical Pharmacology II (Office of Clinical Pharmacology) requested an inspection of the study site where the pivotal bioequivalence study took place. The principal investigator for

Study P048 was Dr. Maria J. Gutierrez, at the Comprehensive Phase One center in Fort Lauderdale, Florida. Inspection findings are pending at the time of writing this review document.

#### **4.5 Compliance with Good Clinical Practices**

Each clinical study report for the studies conducted under this NDA states the study was conducted in compliance with Good Clinical Practices standards and applicable country and / or local statutes and regulations. The applicant certifies that studies were conducted according to the International Committee on Harmonisation document E6, and applicable regulations in the US Code of Federal Regulations. All study protocols, informed consent form and investigator's brochure were reviewed by each investigator's Institutional Review Board or Ethics Committee. Because many subjects with T2DM were already being treated with antidiabetic medications at the time of screening, adequate wash-off periods were necessary to reflect the subjects' glycemic control without the influence of those treatments. This was important in order to establish a true baseline in the investigation of sitagliptin effects in combination with metformin.

The studies protected subjects from prolonged exposure to excessive hyperglycemia by:

- Excluding subjects with HbA1c greater than 10 % at screening;
- Requiring frequent glucose monitoring;
- Requiring subjects that remained in poor glycemic control with plasma glucose exceeding pre-specified thresholds at certain expected timepoints to receive glycemic rescue therapy. Subjects had their primary efficacy endpoint (HbA1c level) censored beyond the start of glycemic rescue therapy for the purpose of efficacy analysis (due to the confounding effect of the rescue treatment) but they continued to be followed in the studies. This provision allowed for a stronger and more conservative assessment of sitagliptin efficacy, while allowing for a longer period of exposure to sitagliptin for the analysis of safety. Subjects that received glycemic rescue therapy thus were able to remain in the studies until completion of Phase A (double-blind, placebo-controlled portion) but were ineligible to enter the extension studies.
- Enrolling subjects with HbA1c > 11%, FPG >280 mg/dL, or fingerstick glucose >280 mg/dL to the Open Label Cohort in the Factorial Study P036, as these subjects were considered to have hyperglycemia too severe to participate in the randomized, placebo-controlled portion of the study.

Changes in the conduct of the studies and the originally planned analyses did not introduce bias and did not affect the overall conclusions regarding both safety and efficacy of sitagliptin.

Protocol violations were uncommon and did not affect the studies conclusions regarding the efficacy or safety of sitagliptin.

#### **4.6 Financial Disclosures**

The applicant certified that no financial arrangement with investigators was made that could affect study outcome.

Table 8 below lists studies considered "covered studies" for the purpose of 21 CFR 54.2 that have not been reviewed under NDA 21995. FPI means First Patient In and LPO means Last Patient Out. As emphasized before Study P048 is the pivotal pharmacokinetic study to support the bioequivalence between the proposed FDC formulation and the coadministration of sitagliptin and metformin.

**Table 8. Summary of Covered Clinical Trials as Defined by 21 CFR 54.2(e)**

Merck Product and Protocol Number	Protocol Title	FPI	LPO	"Payment of Other Sorts Range"
MK-0431-043	MK-0431 Phase IIa Double-Blind, Efficacy, Placebo-Controlled Study -Type 2 Diabetes Mellitus	22-Jul-2004	25-Apr-2005	22-Jul-2004 Through 30-Apr-2005
MK-0431-050	A Randomized, Placebo-Controlled, Double-Blind, Double-Dummy, Four-Period Crossover Study to Assess the Effects of Concomitant Administration of MK-0431 and Metformin Alone and in Combination on Post-Meal Incretin Hormone Concentrations in Healthy Adult Subjects	26-Jan-2006	03-Mar-2006	26-Jan-2006 Through 31-Jan-2006
MK-0431A-038	A 2-Part, Open-Label, Randomized, 3-Period Crossover Study to Evaluate the Pharmacokinetic Profiles of MK-0431 and Metformin After Oral Administration of Single Doses of MK-0431/Metformin Fixed-Dose Combination Tablet Probe Formulations or Coadministration of MK-0431 With Metformin as Individual Tablets to Healthy Adult Subjects	27-Apr-2005	11-May -2005	27-Apr-2005 Through 31-Jan-2006
MK-0431A-048	An Open-Label, Two-Part, Randomized, Two-Period Crossover Study to Demonstrate the Definitive Bioequivalence After Administration of the Final Market Image (FMI) of the MK-0431/Metformin 50/500 mg and 50/1000 mg Fixed-Dose Combination (FDC) Tablet and Concomitant Administration of 50 mg Doses of MK-0431 and 500 or 1000 mg Doses of Metformin as Individual Tablets and in Healthy Adult Subjects	05-Dec-2005	15-Dec-2005	05-Dec-2005 Through 31-Jan-2006

Copied from the applicant's Table A-1 Summary of Covered Clinical Trials as Defined by 21 CFR54.2 (e) in the document Financial Disclosure

No investigator in these studies met the disclosure criteria regarding financial interests as defined in 21 CFR 54.2 (a, b, c, and f) ("significant payments of other sorts").

## 5 CLINICAL PHARMACOLOGY

Please see Dr. Jaya Vaidyanathan's Biopharmacology review for in-depth pharmacokinetic and pharmacodynamic review of the coadministration of sitagliptin and metformin. Please refer also to the Medical Officer's review of the Pharmacokinetics and Pharmacodynamics of sitagliptin for NDA 21995.

## 5.1 Pharmacokinetics

Two studies were submitted in NDA 22044 that contain important in-vivo data on the pharmacokinetic parameters of sitagliptin / metformin FDC:

- Study P038 was a probe formulation study, examining the effect of addition of sodium lauryl sulfate to the tablet formulation.
- Study P048 was designed to investigate the bioequivalence between the sitagliptin / metformin FDC and the coadministration of sitagliptin and metformin.

Both studies were conducted in healthy adult volunteers.

### Study P038

Dissolution of the drug substance(s) in the combination tablet was relatively slow when compared to the sitagliptin tablet. Product development studies demonstrated that the addition of a surfactant, sodium lauryl sulfate (SLS) increased the dissolution rate and enhanced stability. As a result, a small amount (0.5%) of SLS was included in the final market composition.

Study P038 was an open-label, randomized, 2-part, 3-period crossover study to evaluate the PK profiles of sitagliptin and metformin after oral administration of single doses of the FDC tablet probe formulation (one with and one without SLS) and coadministration of corresponding doses of sitagliptin and metformin as individual tablets in healthy adult subjects. The only important difference between Part 1 and Part 2 is the dose of metformin tested (500 mg versus 1000 mg). In each of the 3 periods, subjects were given one tablet of the FDC with SLS, one tablet without SLS or the 2 components (sitagliptin and metformin) coadministered in a randomized sequence, with a minimum 7-day washout between doses. Twelve male or female subjects, between 20 and 50 years of age, participated in each part of the study.

### Study P038 Results

Summary results for key pharmacokinetic parameters comparing the bioequivalence between the sitagliptin / metformin FDC with or without SLS, for the sitagliptin 50 mg / metformin 500 mg are shown in Table 9 and Table 10, respectively and the sitagliptin 50 mg / metformin 1000 mg are shown in Table 11 and Table 12, respectively.

The results show bioequivalence between the 2 formulations, for both doses tested.

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**Table 9. Summary Statistics of the PK Parameters of Sitagliptin After Single Doses of Sitagliptin 50 mg / Metformin 500 mg Fixed-Dose Combination Tablet Probe Formulations or Coadministration of Sitagliptin and Metformin as Individual Tablets to Healthy Adult Subjects**

Parameter	FDC Tablet Without SLS	FDC Tablet With SLS	Coadministration of Individual Tablets	GMR (90% CI)    for FDC Tablet Without SLS	GMR (90% CI)    for FDC Tablet With SLS
Geometric LS Mean N=12	Geometric LS Mean N=11	Geometric LS Mean N=12	Geometric LS Mean N=12		
AUC <sub>0-∞</sub> (μM·hr)	4.1	4.1	4.1	1.0 (1.0, 1.1)	1.0 (0.9, 1.0)
C <sub>max</sub> (nM)	445	462	441	1.01 (0.89, 1.14)	1.05 (0.92, 1.19)
T <sub>max</sub> (hr)	2.7†	3.0†	3.0†	0.96§	0.30§
Apparent t <sub>1/2</sub> (hr)	12.8‡	12.2‡	12.8‡	0.97§	0.59§

† Median.  
 ‡ Harmonic Mean.  
 § P-Value.  
 || GMR = Geometric LS mean ratio (reference is sitagliptin 50 mg + metformin 500 mg as individual tablets) based on the least-squares means from the ANOVA model.  
 CI = Confidence Interval.

Adapted from the applicant's Table 2.7.1:4, in reference Summary of Biopharmaceutic Studies

**Table 10. Summary Statistics of the PK Parameters of Metformin After Single Doses of Sitagliptin 50 mg / Metformin 500 mg Fixed-Dose Combination Tablet Probe Formulations or Coadministration of Sitagliptin and Metformin as Individual Tablets to Healthy Adult Subjects**

Parameter	FDC Tablet Without SLS	FDC Tablet With SLS	Coadministration of Individual Tablets	GMR (90% CI)    for FDC Tablet Without SLS	GMR (90% CI)    for FDC Tablet With SLS
Geometric LS Mean N=12	Geometric LS Mean N=11	Geometric LS Mean N=12	Geometric LS Mean N=12		
AUC <sub>0-∞</sub> (μM·hr)	8.5	7.6	8.3	1.0 (0.9, 1.01)	0.9 (0.8, 1.0)
C <sub>max</sub> (nM)	1330	1190	1270	1.1 (0.9, 1.2)	1.05 (0.8, 1.0)
T <sub>max</sub> (hr)	2.50†	2.50†	2.00†	0.35§	0.12§
Apparent t <sub>1/2</sub> (hr)	12.7‡	12.4‡	13.6‡	0.74§	0.64§

† Median.  
 ‡ Harmonic Mean.  
 § P-Value.  
 || GMR = Geometric LS mean ratio (reference is sitagliptin 50 mg + metformin 500 mg as individual tablets) based on the least-squares means from the ANOVA model.  
 CI = Confidence Interval.

Adapted from the applicant's Table 2.7.1:5, in reference Summary of Biopharmaceutic Studies

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**Table 11. Summary Statistics of the PK Parameters of Sitagliptin After Single Doses of Sitagliptin 50 mg / Metformin 1000 mg Fixed-Dose Combination Tablet Probe Formulations or Coadministration of Sitagliptin and Metformin as Individual Tablets to Healthy Adult Subjects**

Parameter	FDC Tablet Without SLS	FDC Tablet With SLS	Coadministration of Individual Tablets	GMR (90% CI)    for FDC Tablet Without SLS	GMR (90% CI)    for FDC Tablet With SLS
Geometric LS Mean N=12	Geometric LS Mean N=12	Geometric LS Mean N=12	Geometric LS Mean N=12		
AUC <sub>0-∞</sub> (μM•hr)	3.7	3.8	3.8	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)
C <sub>max</sub> (nM)	391	411	378	1.0 (1.0, 1.1)	1.1 (1.0, 1.2)
T <sub>max</sub> (hr)	3.00†	2.50†	3.25†	0.21§	0.19§
Apparent t <sub>1/2</sub> (hr)	11.6‡	13.2‡	12.8‡	0.17§	0.69§

† Median.  
 ‡ Harmonic Mean.  
 § P-Value.  
 || GMR = Geometric LS mean ratio (reference is sitagliptin 50 mg + metformin 500 mg as individual tablets) based on the least-squares means from the ANOVA model.  
 CI = Confidence Interval.

Adapted from the applicant's Table 2.7.1:6, in reference Summary of Biopharmaceutical Studies

**Table 12. Summary Statistics of the PK Parameters of Metformin After Single Doses of Sitagliptin 50 mg / Metformin 1000 mg Fixed-Dose Combination Tablet Probe Formulations or Coadministration of Sitagliptin and Metformin as Individual Tablets to Healthy Adult Subjects**

Parameter	FDC Tablet Without SLS	FDC Tablet With SLS	Coadministration of Individual Tablets	GMR (90% CI)    for FDC Tablet Without SLS	GMR (90% CI)    for FDC Tablet With SLS
Geometric LS Mean N=12	Geometric LS Mean N=12	Geometric LS Mean N=12	Geometric LS Mean N=12		
AUC <sub>0-∞</sub> (μM•hr)	11.7	11.8	12.2	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)
C <sub>max</sub> (nM)	1860	1910	1800	1.0 (1.0, 1.1)	1.1 (1.0, 1.1)
T <sub>max</sub> (hr)	2.25†	2.50†	2.25†	0.67§	0.99§
Apparent t <sub>1/2</sub> (hr)	11.1‡	13.0‡	13.2‡	0.24§	0.93§

† Median.  
 ‡ Harmonic Mean.  
 § P-Value.  
 || GMR = Geometric LS mean ratio (reference is sitagliptin 50 mg + metformin 500 mg as individual tablets) based on the least-squares means from the ANOVA model.  
 CI = Confidence Interval.

Adapted from the applicant's Table 2.7.1:7, in reference Summary of Biopharmaceutical Studies

### Study P048

Study P048 was an open-label, randomized, 2-part, 2-period crossover study to demonstrate the definitive bioequivalence after administration of a single dose of the sitagliptin / metformin (50 mg / 500 mg or 50 mg / 1000 mg) FDC tablet and concomitant administration of a single dose of sitagliptin (50 mg) and metformin (500 mg or 1000 mg [2 x 500 mg]) as individual tablets in healthy adult subjects. The study was conducted in two parts (Parts I and II) with each part consisting of a 2-period, crossover design. Each part enrolled 24 subjects, and all subjects completed the study. Eligible subjects were male and female healthy volunteers between the ages of 18 and 45 years. Each subject participated in only one part of the study.

<b>Part I</b>	
Treatment A	A single 50-mg dose of sitagliptin and 500-mg dose of metformin as individual tablets, coadministered
Treatment B	A single dose of sitagliptin/metformin 50/500 mg/mg FDC tablet
<b>Part II</b>	
Treatment C	A single 50-mg dose of sitagliptin and 1000-mg dose of metformin (2 x 500 mg), as individual tablets, coadministered
Treatment D	A single dose of sitagliptin/metformin 50/1000 mg/mg FDC tablet

The order in which subjects receive treatments was randomly allocated within each part of the study. There was a minimum 7-day washout between study drug administrations in each treatment period within each part of the study.

#### Study P048 Results

Study P048 demonstrates that the sitagliptin 50 mg / metformin 500 mg and sitagliptin 50 mg / metformin 1000 mg FDC tablets are bioequivalent to coadministration of corresponding doses of sitagliptin and metformin as individual tablets. The 90% confidence intervals (CI) of the geometric mean ratios (GMR; FDC tablet/ coadministration) for the  $AUC_{0-\infty}$  and  $C_{max}$  of sitagliptin 50 mg and metformin 500 mg all were within the prespecified bounds of (0.80, 1.25), as shown in Table 13 and Table 14 for Part I. The results shown in Table 15 and Table 16 for Part II allow similar conclusions to be reached for the bioequivalence between the sitagliptin 50 mg / metformin 1000 mg FDC and the coadministration of the corresponding doses of sitagliptin and metformin.

**Table 13. Sitagliptin PK after Administration of a Single Dose of Sitagliptin 50 mg / Metformin 500 mg FDC Tablet or Corresponding Doses of Sitagliptin and Metformin Coadministered to Healthy Adult Subjects**

Parameter	FDC Tablet	Coadministration of individual tablets	
	Geometric LS Means N= 24	Geometric LS Means N= 24	GMR <sup>†</sup> (90% CI)
$AUC_{0-\infty}$ ( $\mu M \cdot hr$ )	4.0	4.1	0.98 (0.96, 1.00)
$C_{max}$ (nM)	414	415	1.00 (0.94, 1.06)
$T_{max}$ (hr)	2.75 <sup>‡</sup>	2.50 <sup>‡</sup>	0.520 <sup>§</sup>
Apparent $t_{1/2}$ (hr)	12.6 <sup>  </sup>	12.3 <sup>  </sup>	0.572 <sup>§</sup>
<sup>†</sup> GMR = Geometric LS mean ratio (reference is the coadministration of sitagliptin 50 mg and metformin 500 mg as individual tablets) based on the least square means from the ANOVA model <sup>‡</sup> Median <sup>§</sup> p-value <sup>  </sup> Harmonic Mean			

Adapted from the applicant's Tables 11-2, 11-3 and 11-4 in reference P048

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**Table 14. Metformin PK after Administration of a Single Dose of Sitagliptin 50 mg / Metformin 500 mg FDC Tablet or Corresponding Doses of Sitagliptin and Metformin Coadministered to Healthy Adult Subjects**

Parameter	FDC Tablet	Coadministration of individual tablets	
	Geometric LS Means N= 24	Geometric LS Means N= 24	GMR <sup>†</sup> (90% CI)
AUC <sub>0-∞</sub> (μM•hr)	7.3	7.3	1.00 (0.95, 1.04)
C <sub>max</sub> (nM)	1180	1180	1.00 (0.94, 1.06)
T <sub>max</sub> (hr)	2.75 <sup>‡</sup>	2.50 <sup>‡</sup>	0.781 <sup>§</sup>
Apparent t <sub>1/2</sub> (hr)	11.6 <sup>  </sup>	9.79 <sup>  </sup>	0.154 <sup>§</sup>

<sup>†</sup>GMR = Geometric LS mean ratio (reference is the coadministration of sitagliptin 50 mg and metformin 500 mg as individual tablets) based on the least square means from the ANOVA model  
<sup>‡</sup>Median  
<sup>§</sup>p-value  
<sup>||</sup>Harmonic Mean

Adapted from the applicant's Tables 11-6, 11-7 and 11-8 in reference P048

**Table 15. Sitagliptin PK after Administration of a Single Dose of Sitagliptin 50 mg / Metformin 1000 mg FDC Tablet or Corresponding Doses of Sitagliptin and Metformin Coadministered to Healthy Adult Subjects**

Parameter	FDC Tablet	Coadministration of individual tablets	
	Geometric LS Means N= 24	Geometric LS Means N= 24	GMR <sup>†</sup> (90% CI)
AUC <sub>0-∞</sub> (μM•hr)	3.9	4.0	0.97 (0.95, 0.99)
C <sub>max</sub> (nM)	397	423	0.94 (0.88, 1.01)
T <sub>max</sub> (hr)	2.50 <sup>‡</sup>	2.50 <sup>‡</sup>	0.518 <sup>§</sup>
Apparent t <sub>1/2</sub> (hr)	13.7 <sup>  </sup>	13.1 <sup>  </sup>	0.467 <sup>§</sup>

<sup>†</sup>GMR = Geometric LS mean ratio (reference is the coadministration of sitagliptin 50 mg and metformin 1000 mg as individual tablets) based on the least square means from the ANOVA model  
<sup>‡</sup>Median  
<sup>§</sup>p-value  
<sup>||</sup>Harmonic Mean

Adapted from the applicant's Tables 11-10, 11-11 and 11-12, in reference P048

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**Table 16. Metformin PK after Administration of a Single Dose of Sitagliptin 50 mg / Metformin 1000 mg FDC Tablet or Corresponding Doses of Sitagliptin and Metformin Coadministered to Healthy Adult Subjects**

Parameter	FDC Tablet	Coadministration of individual tablets	
	Geometric LS Means N= 24	Geometric LS Means N= 24	GMR <sup>†</sup> (90% CI)
AUC <sub>0-∞</sub> (μM•hr)	11.9	11.9	1.00 (0.94, 1.07)
C <sub>max</sub> (nM)	1870	1850	1.01 (0.93, 1.10)
T <sub>max</sub> (hr)	2.00 <sup>‡</sup>	2.50 <sup>‡</sup>	0.143 <sup>§</sup>
Apparent t <sub>1/2</sub> (hr)	13.9 <sup>  </sup>	13.6 <sup>  </sup>	0.764 <sup>§</sup>
<sup>†</sup> GMR = Geometric LS mean ratio (reference is the coadministration of sitagliptin 50 mg and metformin 1000 mg as individual tablets) based on the least square means from the ANOVA model <sup>‡</sup> Median <sup>§</sup> p-value <sup>  </sup> Harmonic Mean			

Adapted from the applicant's Tables 11-14, 11-15 and 11-16, in reference P048

## 5.2 Pharmacodynamics

### Study P050

#### Study goals and design

The effect of administration of sitagliptin alone and metformin alone or in combination on post-meal incretin hormone (active and total GLP1 and GIP) and glucose concentrations in healthy adult subjects were determined in Study P050. This was a randomized, placebo-controlled, double-blind, double-dummy, four-period crossover study to assess the effects of concomitant administration of sitagliptin and metformin alone or in combination on post-meal incretin concentrations in 18 healthy subjects. Each subject participated in four 2-day treatment periods (i.e., 2 doses of sitagliptin and 3 doses of metformin) in a crossover manner. There was a minimum of a 7-day washout between the last dose of study drug in one treatment period and the first dose of study drug in the subsequent treatment periods.

The 4 treatments administered are shown in Table 17:

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**Table 17. Treatment Groups in Study P050**

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

Two subjects were discontinued from the study after period 1 due to compliance issues with tests procedures. On day 2, subjects took their assigned medication and, 2 hours later, received a standardized breakfast, consisting of 765 calories (25% fat, 55% carbohydrate and 20 % protein). Blood samples for active and total GLP1 and GIP were collected pre-meal and specified intervals post-meal. The primary endpoint for analyses was the 4-hour post-meal weighted average active GLP1 after concomitant administration of sitagliptin and metformin versus after administration of sitagliptin alone, compared by an ANOVA model. Secondary endpoints of the study were

- The effect on the 4-hour post-meal weighted average active GLP1 after concomitant administration of sitagliptin and metformin and after administration of metformin alone and after active treatments as compared to placebo were compared in the same way as for the primary hypothesis.
- The effect on the 4-hour post-meal weighted average total GLP1, ratio of active to total GLP-1, and active, total GIP, and ratio of active to total GIP after concomitant administration of sitagliptin and metformin and after administration of sitagliptin or metformin alone and after active treatments as compared to placebo were compared in the same way as for the primary hypothesis.

#### Summary of study results

Compared with placebo, both sitagliptin alone and metformin alone increased the 4-hour weighted average active GLP1 concentrations approximately 80% to 95%, whereas the increase for the combination of sitagliptin and metformin was approximately 310%, suggesting an additive effect of the combination with respect to post-meal increase in active GLP1 concentrations. Metformin, but not sitagliptin, also increases circulating concentrations of total GLP1 by approximately 80% compared with placebo (similar to the effect on active GLP1 concentrations), suggesting that the effect of metformin on active GLP1 concentrations is primarily due to an increase in total GLP1 concentrations. In contrast, administration of sitagliptin enhances active GLP1 concentrations by stabilization of active versus total GLP1 concentrations by inhibition of the DPP4 enzyme.

Compared to placebo, sitagliptin increased the 4-hour weighted average active GIP concentrations by approximately 70 %, whereas treatment with metformin did not alter active GIP concentrations. The majority of the effect of active GIP after coadministration of sitagliptin

and metformin (90 % increase compared to placebo for the 4-hour weighted post-meal average) resulted from the sitagliptin, without significant contribution from metformin.

### 5.3 Exposure-Response Relationships

From the Phase 1 data and the effects on proximal markers of DPP4 inhibition (for example, post-prandial levels of active GLP1) and distal (for example, plasma glucose levels and their excursions and HbA1c) observed in Phase 2 studies, it appeared that a dose of either 50 mg given twice daily or 100 mg once daily would achieve both the 80 % maximal inhibition of DPP4 and maximal reductions in HbA1c, glucose and elevations of GLP-1 and GIP. The two Phase 2 studies reported under NDA 21995 for sitagliptin supporting the selection of 100 mg daily were Studies P010 and P014. These studies have not shown a clear distinction in the capacity to lower glucose and HbA1c between the doses of 25 mg bid, 50 mg qd, 50 mg bid or 100 mg qd (Table 18 and Table 19, with the mean glycemic response from these dose cohorts shown in bold font).

**Table 18. Change in mean HbA1c from baseline to week 12 in the dose-ranging Study P010 (ITT population)**

Treatment	N	Mean		Change from baseline			
		Baseline (SD)	Week 12 (SD)	Mean (SD)	LS Mean	95% CI for LS Mean	Within group p-Value
Placebo	121	7.88 (0.96)	8.14 (1.23)	0.27 (0.90)	0.23	(0.10, 0.37)	<0.001
Sita 5 mg bid	122	7.89 (0.94)	7.77 (1.22)	-0.13 (0.82)	-0.15	(-0.29, -0.01)	0.031
Sita 12.5 mg bid	122	7.85 (0.88)	7.48 (0.98)	-0.38 (0.71)	-0.41	(-0.55, -0.27)	<0.001
<b>Sita 25 mg bid</b>	<b>120</b>	<b>7.89 (0.94)</b>	<b>7.50 (1.14)</b>	<b>-0.39 (0.84)</b>	<b>-0.43</b>	<b>(-0.56, -0.29)</b>	<b>&lt;0.001</b>
<b>Sita 50 mg bid</b>	<b>121</b>	<b>7.83 (0.95)</b>	<b>7.34 (1.01)</b>	<b>-0.49 (0.66)</b>	<b>-0.54</b>	<b>(-0.68, -0.40)</b>	<b>&lt;0.001</b>
Glipizide	119	7.82 (0.95)	7.11 (0.91)	-0.72 (0.84)	-0.76	(-0.90, -0.62)	<0.001

**Table 19. Change in mean HbA1c from baseline to week 12 in dose and regimen Study P014 (ITT population)**

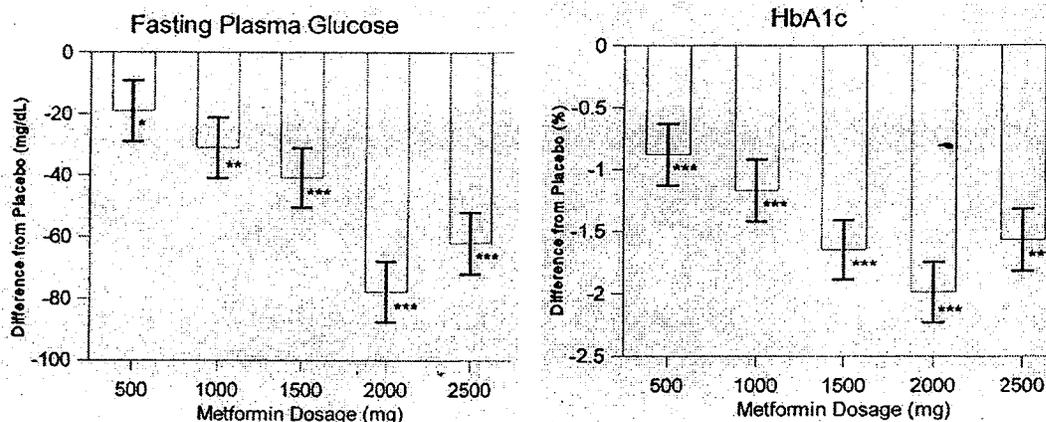
Treatment	N	Mean		Change from baseline			
		Baseline (SD)	Week 12 (SD)	Mean (SD)	LS Mean	95% CI for LS Mean	Within-Group p-Value
Placebo	107	7.59 (0.89)	7.76 (1.11)	0.17 (0.60)	0.12	(-0.02, 0.26)	0.102
Sita 25 mg qd	107	7.71 (0.91)	7.47 (1.30)	-0.23 (0.87)	-0.28	(-0.42, -0.14)	<0.001
<b>Sita 50 mg qd</b>	<b>107</b>	<b>7.60 (0.94)</b>	<b>7.22 (1.02)</b>	<b>-0.38 (0.68)</b>	<b>-0.44</b>	<b>(-0.58, -0.30)</b>	<b>&lt;0.001</b>
<b>Sita 100 mg qd</b>	<b>106</b>	<b>7.78 (0.90)</b>	<b>7.38 (1.11)</b>	<b>-0.40 (0.81)</b>	<b>-0.44</b>	<b>(-0.58, -0.30)</b>	<b>&lt;0.001</b>
<b>Sita 50 mg bid</b>	<b>108</b>	<b>7.79 (0.85)</b>	<b>7.41 (1.10)</b>	<b>-0.38 (0.76)</b>	<b>-0.43</b>	<b>(-0.56, -0.29)</b>	<b>&lt;0.001</b>

The sitagliptin dose approved for marketing is 100 mg qd based on the preponderance of evidence supporting its efficacy from the Phase 3 studies.

Based on a placebo-controlled, randomized study evaluating metformin doses ranging from 500 mg to 2500 mg daily in 441 patients, a dose-response for fasting plasma glucose and HbA1c was observed for these doses administered from qd to t.i.d. The results of that study are summarized in the Figure 4<sup>1</sup>:

<sup>1</sup> Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of Metformin in Type I diabetes. Results of a Double-blind, placebo-controlled, dose-response trial. Am. J. Med. 103 (6): 491-497, 1997.

Figure 4. Metformin effects on fasting plasma glucose and HbA1c in a dose-response trial of type 2 diabetics



Due to problems with gastrointestinal tolerability reactions, the most common approach used in practice when prescribing metformin is titration on a weekly basis to achieve a total daily dose of 1500 to 2000 mg.

Because metformin needs to be dosed more frequently than once daily, the applicant decided to split the sitagliptin dose of 100 mg daily into 50 mg to be used in the FDC tablets.

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

The indication proposed by the applicant in labeling text is as follows:

“JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.” The applicant recommends that the FDC be used as a “second line” treatment in this application, although the applicant’s development plan

#### 6.1.1 Methods

NDA 21995 provided all the necessary data to support the efficacy of sitagliptin administered with metformin to improve glycemic control. The present application adds an important pharmacokinetic study intended to demonstrate the bioequivalence between the sitagliptin / metformin FDC and the coadministration of sitagliptin and metformin necessary to bridge efficacy and safety data from NDA 21995. In addition, the original application reports safety data from Study P036 (only the Open Label Cohort). The 4-Month Safety Update Report provides not only additional safety data from both Studies P024 and P036, but also some efficacy results. As the applicant will be submitting these results in later efficacy supplements to NDA

21995 and are not relying on the efficacy data for approval of this current submission, the efficacy results are only briefly summarized in this section of the review.

### 6.1.2 General Discussion of Endpoints

The primary endpoint for all studies was the mean change in HbA1c from baseline to the end of the placebo-controlled study period (week 24 in Studies P020 and P036, and week 52 in Study P024). This endpoint is adequate to demonstrate long-term changes in glycemic control. HbA1c is generally considered the most reliable surrogate of the glycemic control, and ultimately predicts late chronic complications of T2DM, both microvascular and macrovascular, as demonstrated in the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS).

Important secondary endpoints in all Phase 3 studies were the fasting plasma glucose and the post-prandial plasma glucose, measured as change from baseline to the end of the placebo-controlled study period. Fasting plasma glucose is a measure of hepatic glucose production, which in turn is regulated by the balance of fasting concentrations of insulin and glucagon, among other factors. In the DCCT, improvement in fasting plasma glucose levels correlated with reductions in microvascular complications. Post-prandial glucose measured 2 hours after a standardized meal also correlates with long term glycemic control and with chronic complications of diabetes.

### 6.1.3 Study Design

#### Study P036

This study was conducted to investigate the effect of the coadministration of sitagliptin and metformin in treatment-naïve diabetics, to be submitted as an efficacy supplement to NDA 21995. Safety data from this study has been submitted by the applicant to provide additional support for sitagliptin / metformin FDC.

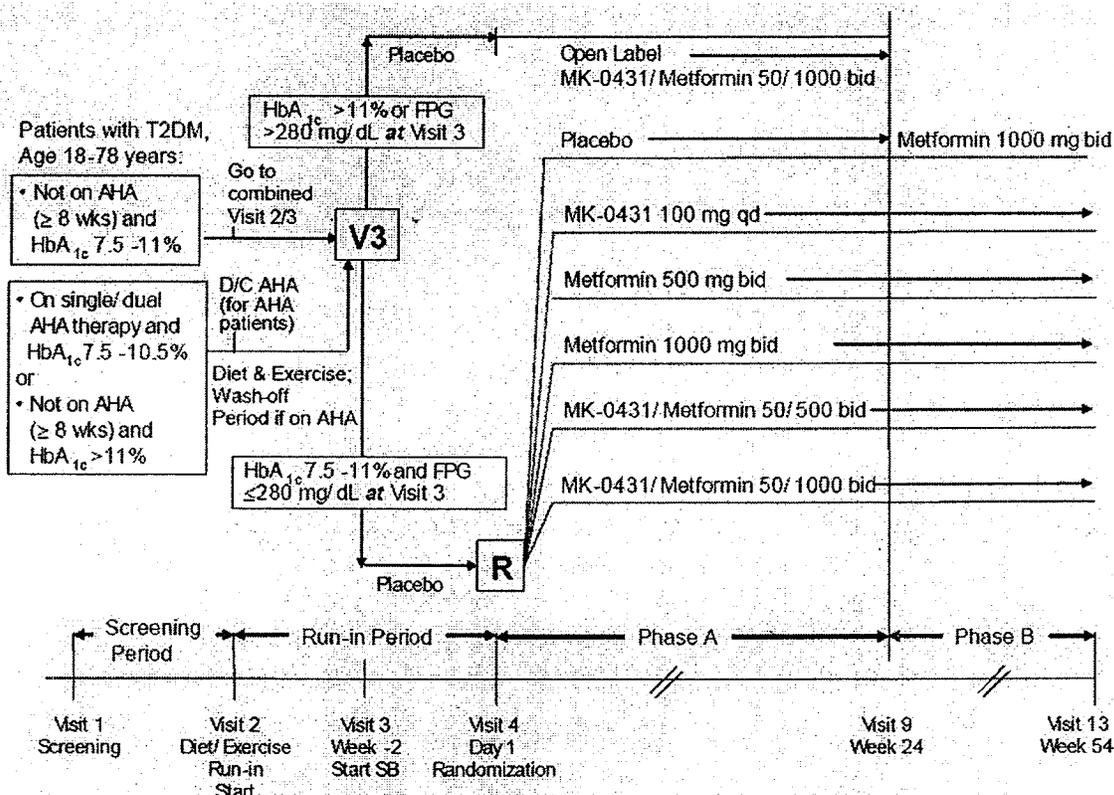
A brief description of the study follows to facilitate the understanding of the goals and findings related to the safety of sitagliptin coadministered with metformin within this study.

Study 036 is a multinational, randomized, double-blind, factorial design, parallel group, Phase 3 study to evaluate the safety and efficacy of the coadministration of sitagliptin and metformin in subjects with T2DM with inadequate glycemic control. The goal of the study is to assess the effect of coadministration of sitagliptin and metformin compared to metformin or sitagliptin alone on HbA1c, FPG and 2-hour post-meal glucose after 24 weeks. The total study duration is 69 weeks for each subject. This study period includes a 1-week screening, an antidiabetic medication wash off run-in period of up to 12 weeks, a 2-week single-blind placebo run-in period, and a 54-week double-blind treatment period. The latter includes a 24-week placebo-controlled period (designated Phase A) and a 30-week active controlled period (Phase B).

Subjects were eligible for randomization if they are  $\geq 18$  and  $\leq 78$  years of age with T2DM and not on antidiabetic agents for  $\geq 8$  weeks at Visit 3 (week -2) when HbA1c should be  $\geq 7.5\%$  and  $\leq 11\%$ . The estimated 1050 eligible subjects were randomized with equal chances to each of 6 treatment arms: placebo, sitagliptin 100 mg qd, metformin 500 mg bid, metformin 1000 mg bid, sitagliptin 50 mg / metformin 500 mg bid or sitagliptin 50 mg / metformin 1000 mg bid. Subjects with HbA1c  $> 11\%$  or fasting plasma glucose  $> 280$  mg/dL were ineligible for randomization

but were assigned to an Open Label Cohort (OLC). Subjects in this cohort were considered to have hyperglycemia too severe to participate in the randomized, placebo-controlled portion of the study. They received open label sitagliptin 50 mg / metformin 1000 mg bid after initial titration lasting 4 weeks. Figure 5 shows the design of Study P036.

Figure 5. Design of Study P036



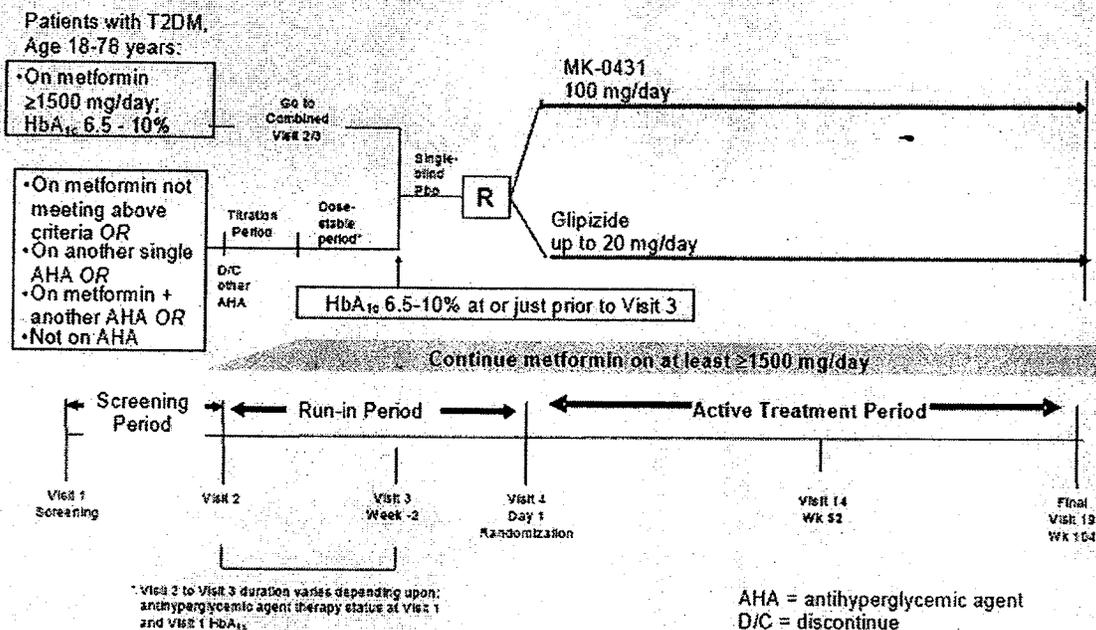
All subjects had a protocol-specified, 4-week, forced titration to achieve a maximal daily dose of sitagliptin 50 mg bid (or correspondent placebo) and metformin at either 500 or 1000 mg bid (or placebo). At Visit 4/Day 1, metformin was started at 500 mg qAM and increased in increments of 500 mg per week to achieve a stable study dose of 1000 mg bid at Week 4. Sitagliptin was started at 50 mg qAM and increased, after one week, to achieve a stable study dose of 50 mg bid at Week 2. Subjects who are randomized and do not meet protocol-specified progressively stricter glycemic cutpoints during either Phase A or Phase B of the double-blind treatment period, can then receive glycemic rescue therapy with glyburide / glybenclamide 5 mg qd, which can be titrated as needed up to 20 mg qd. Subjects in the OLC exceeding these glycemic cutpoints during the 24-week open-label treatment period are not eligible for glycemic rescue therapy in the study and are discontinued from the study. After 24 weeks (end of Phase A), subjects who were randomized to placebo will start metformin 500 mg titrated weekly by 500 mg up to 1000 mg bid, while subjects randomized to the other treatment arms will continue to receive treatment in their original allocations in a double-blind fashion.

The applicant provides interim safety data obtained in the 117 subjects with T2DM who participated in the OLC and completed a Visit 5 (Week 3) as of March 3, 2006. These data reflect incidences of clinical and laboratory adverse experiences. At the 4-Month Safety Update Report, efficacy data reflecting 24 weeks of the Phase A were presented for the randomized cohorts as well as the OLC.

#### Study P024

The clinical study report for this study was included in the 4-month Safety Update Report to support the safety of the combination of sitagliptin and metformin, used in a large group of subjects at doses similar to those proposed for the sitagliptin / metformin FDC. Study P024 was designed as a non-inferiority study comparing the efficacy of sitagliptin to that of glipizide (the active comparator) for a period of 2 years, with the primary endpoint (change in HbA1c from baseline) assessed at week 52. This is a multinational, randomized, parallel-group study with one active-controlled double-blind period. Eleven hundred and seventy-two (1172) patients with T2DM who had inadequate glycemic control on metformin at a dose of at least 1500 mg/day were randomized. The design of the study included a screening diet/exercise run-in period of up to 19 weeks (including a 1-week screening period [Visits 1 to 2], a metformin dose titration/dose stable period of up to 16 weeks [Visits 2 to 3], and a 2-week single-blind placebo run-in period [Visits 3 to 4]) prior to randomization into the active-controlled, double-blind treatment period. After completion of 52 weeks, patients continued to 104 weeks, during which patients continued on the same treatment they received since randomization (please refer to Figure 6). Patients with T2DM on metformin at a stable dose of  $\geq 1500$  mg/day and treated 10 weeks with inadequate glycemic control (i.e., HbA1c  $\geq 6.5\%$  and  $\leq 10.0\%$ ) and who met all other enrollment criteria were to directly enter the 2-week single-blind placebo run-in period at a combined Visit 2/3. The dose of glipizide was titrated from 5 mg q AM (generally every 3 weeks) to a maximum dose of 20 mg / day, considered to be at least maximally effective. The sample size was calculated to provide power to detect an effect on HbA1c, but also to detect a difference in incidence rate of hypoglycemic events and in change in body weight from baseline (with correction of the type 1 error due to multiple comparisons). The primary population for analyses is the "per protocol" (PP) population, but supported by analysis in the intent-to-treat (ITT) population. Missing data was to be imputed by the last observation carried forward method for the ANCOVA. The PP population consisted of all randomized subjects with a baseline measurement, a measurement at the time point of interest, and no major violations (the population was identified before unblinding, according to the SAP). The primary population for all safety analyses was the ITT population.

Figure 6. Diagram showing Study P024 design



### 6.1.4 Efficacy Findings

Findings supporting the approval of sitagliptin treatment in combination with metformin under NDA 21995 are briefly summarized here.

#### Study P015

A 4-week Phase 2 study in subjects with inadequate glycemic control while on metformin also demonstrated improved weighted plasma glucose concentrations in those subjects treated with add-on sitagliptin 50 mg bid compared to placebo.

#### Study P020

The bulk of the substantial evidence of efficacy came from demonstration of mean reduction in HbA<sub>1c</sub> from baseline to week 24 in 701 subjects not adequately controlled with diet, exercise, and metformin at doses  $\geq 1500$  mg qd. Of these, 464 subjects were randomized to sitagliptin 100 mg daily and 237 subjects were randomized to placebo (Table 20).

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**Table 20. Change of HbA1c from baseline to week 24 in Study P020 (ITT population)**

Treatment	N	Mean (SD)		Change from baseline			p-Value
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	
Sitagliptin 100 mg	453	8.0 (0.8)	7.3 (1.0)	-0.7 (0.0)	-0.7 (0.1)	(-0.8, -0.6)	< 0.001
Placebo	224	8.0 (0.8)	7.9 (1.1)	-0.1 (0.1)	0 (0.1)	(-0.1, 0.1)	-
Between Treatment Difference		Difference in LS means (95 % CI)				p-Value	
Sitagliptin 100 mg vs. Placebo		-0.65 (-0.8, -0.5)				< 0.001	

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.

Adapted from the applicant's Table 11-1, reference P020v1

### Study P024

The results of this study (up to week 52) were reported only in the 4-month Safety Update Report, and only for the purpose of expanding the safety database for the combination of sitagliptin and metformin. The efficacy results are only briefly summarized here. Of the 2141 subjects screened, 1172 were randomized. Most exclusions at screening were related to not meeting HbA1c range (34%) or having creatinine > threshold for exclusion (14%).

The disposition of subjects in Study P024 and the composition of the Per Protocol Population are shown in Table 21.

**Table 21. Disposition of subjects and composition of the Per Protocol Population in Study P024**

	Number (%)		
	Sitagliptin 100 mg	Glipizide	Total
TOTAL RANDOMIZED	588	584	1172
INCLUDED IN PP <sup>†</sup> ANALYSIS	382 (65.0)	411 (70.4)	793 (67.7)
INCLUDED IN APT <sup>‡</sup> ANALYSIS	576 (98.0)	559 (95.7)	1135 (96.8)
EXCLUDED FROM PP ANALYSIS	206 (35.0)	173 (29.6)	379 (32.3)
No Baseline Data	2 (0.3)	2 (0.3)	4 (0.3)
No Treatment Data at Week 52	197 (33.5)	167 (28.6)	364 (31.1)
Major Protocol Violators	18 (3.1)	7 (1.2)	25 (2.1)
Drug Compliance <75%	3	1	4
Used of Prohibited AHA <sup>§</sup>	3	1	4
Used of Corticosteroid <sup>  </sup>	1	0	1
Change in Metformin Dose <sup>¶</sup>	10	4	14
Incorrect Doubled-Blind Study Medication <sup>¶</sup>	1	1	2
EXCLUDED FROM APT ANALYSIS	12 (2.0)	25 (4.3)	37 (3.2)
No Baseline Data	2 (0.3)	2 (0.3)	4 (0.3)
No On-Treatment Data	10 (1.7)	23 (3.9)	33 (2.8)

<sup>†</sup> PP: Per Protocol.  
<sup>‡</sup> APT: All-Patients-Treated.  
<sup>§</sup> Patients taking any prohibited antihyperglycemic medications after randomization (Visit 4) for a total of ≥14 days or ≥7 consecutive days.  
<sup>||</sup> Patients taking corticosteroid for ≥14 days during the last 90 days of Week 52.  
<sup>¶</sup> Change in metformin dose or incorrect double-blind study medication for ≥12 consecutive weeks during the study period of interest, or for a total of ≥14 days during the last 90 days of Week 52.

It is important to keep in mind that, in non-inferiority studies, primary analysis based on the per protocol subset of the ITT population is allowed under the ICH, but only when the analysis of the same endpoint in the entire randomized population lends support for the same conclusion. It is also significant that investigators were appropriately instructed to uptitrate glipizide (as a blinded study medication) to reduce glucose but to avoid hypoglycemia; therefore, the average dose of glipizide was 10 mg per day, rather than the maximal recommended dose of 20 mg qd or bid.

**Results**

The primary analysis, conducted in the per-protocol population, consisting of all randomized subjects with HbA1c measured at both baseline and at week 52 and who had no major protocol violations is shown in Table 22.

**Table 22. Changes from baseline to week 52 in HbA1c in Study P024, in the per protocol population**

Treatment	N	Mean (SD)		Change from baseline		
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sitagliptin 100 mg	382	7.5 (0.8)	6.8 (0.7)	-0.6 (0.0)	-0.7 (0.0)	(-0.7, -0.6)
Glipizide	411	7.5 (0.8)	6.9 (0.7)	-0.7 (0.0)	-0.7 (0.0)	(-0.7, -0.6)
<b>Between Treatment Difference</b>		<b>Difference in LS means (95 % CI)</b>				
<b>Sitagliptin 100 mg vs. Glipizide</b>		<b>-0.01 (-0.09, 0.08)</b>				

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.

Adapted from the applicant's Table 11-1, reference p024v1, in the 4-Month Safety Update Report

The supportive analysis of efficacy was conducted in the ITT population (Table 23).

**Table 23. Changes from baseline to week 52 in HbA1c in Study P024, in the ITT population**

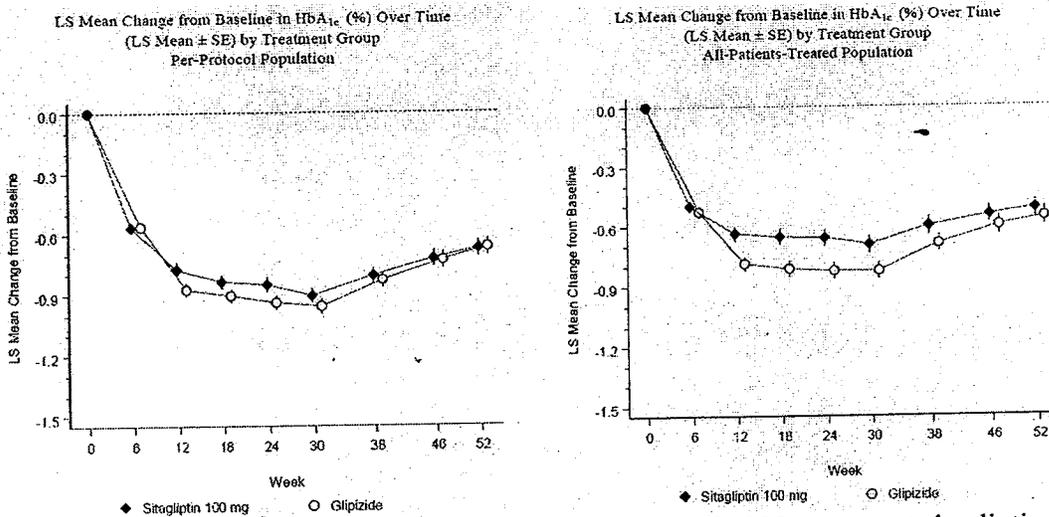
Treatment	N	Mean (SD)		Change from baseline		
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sitagliptin 100 mg	576	7.7 (0.9)	7.1 (1.0)	-0.5 (0.0)	-0.5 (0.0)	(-0.6, -0.4)
Glipizide	411	7.6 (0.9)	7.1 (0.9)	-0.6 (0.0)	-0.6 (0.0)	(-0.6, -0.5)
<b>Between Treatment Difference</b>		<b>Difference in LS means (95 % CI)</b>				
<b>Sitagliptin 100 mg vs. Glipizide</b>		<b>0.04 (-0.04, 0.13)</b>				

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.

Adapted from the applicant's Table 11-2, reference p024v1, in the 4-Month Safety Update Report

Figure 7 shows the effect of sitagliptin in combination with metformin versus glipizide in combination with metformin over the 52 weeks of Study P024 in both the Per Protocol and in the ITT population.

**Figure 7. Effect of sitagliptin versus glipizide, both in combination with metformin, over time, on HbA1c in the Per Protocol and the ITT population in Study P024**



The applicant has submitted an efficacy supplement to NDA 21995 to support sitagliptin treatment in patients with T2DM who have inadequate glycemic control with diet, exercise and a sulfonylurea, and these results are presented to support changes in the Clinical Studies Section of labeling demonstrating non-inferiority of sitagliptin to glipizide on their respective effects on HbA1c. These data have not been critically reviewed in this document, and the summary of the results are presented in this document solely for comprehensiveness of the review.

Study P036

Out of 3544 subjects screened, 2336 were excluded (53 % of them for not meeting HbA1c inclusion criteria at Visit 1), 1091 subjects were randomized to one of 6 treatment groups and 117 subjects were enrolled in the OLC. Reasons for discontinuation of subjects during the study are listed in Table 29. Among the randomized cohorts, 905 subjects completed 24 weeks of treatment, while among the OLC, 79 completed the study period.

The primary analysis was conducted in the ITT population; missing data were imputed by the last observation carried forward method. Table 24 and Panel A in Figure 8 show the summary of the mean changes in HbA1c from baseline to week 24 and the changes from baseline over time, respectively in the randomized cohorts of Study P036. All active treatment groups had significant improvements in glycemic control compared to placebo, with mean differences (95% CI) ranging from -0.8 % (-1.1, -0.6) for sitagliptin 100 mg qd versus placebo to -2.1 % (-2.3, -1.8) for the sitagliptin 50 /metformin 1000 mg bid versus placebo. The coadministration of sitagliptin with each dose of metformin was superior in improving glycemic control compared to the mean effect observed in the monotherapy groups.

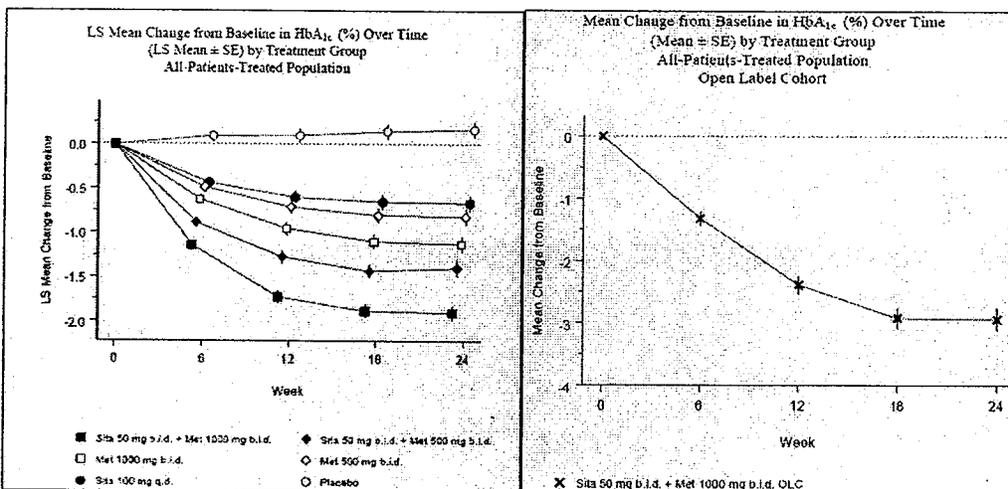
The profiles over time for the within-group mean change from baseline in HbA1c for the ITT population in the OLC are shown in Panel B of Figure 8. The OLC had within-group mean changes from baseline for HbA1c at Week 24 of -2.94% in the ITT population.

**Table 24. Changes in HbA1c from baseline to Week 24 in the randomized cohorts in Study P036**

Treatment Group	N	Mean (SD)		Change from baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sita 100 mg qd	175	8.9 (1.0)	8.2 (1.5)	-0.7 (0.1)	-0.7 (0.1)	(-0.8, -0.5)	<0.001
Met 500 mg bid	178	8.9 (1.0)	8.0 (1.4)	-0.9 (0.1)	-0.8 (0.1)	(-1.0, -0.7)	<0.001
Met 1000 mg bid	177	8.7 (0.9)	7.6 (1.3)	-1.1 (0.1)	-1.1 (0.1)	(-1.3, -1.0)	<0.001
Sita 50 mg bid + Met 500 mg bid	183	8.8 (1.0)	7.4 (1.2)	-1.4 (0.1)	-1.4 (0.1)	(-1.6, -1.2)	<0.001
Sita 50 mg bid + Met 1000 mg bid	178	8.8 (0.95)	6.9 (1.1)	-1.9 (0.1)	-1.9 (0.1)	(-2.1, -1.7)	<0.001
Placebo	165	8.7 (1.0)	8.9 (1.5)	0.2 (0.1)	0.2 (0.1)	(0.0, 0.3)	0.049
<b>Comparing Coadministration with Individual Components</b>		<b>Difference in LS Means (95% CI)</b>				<b>p-Value</b>	
Sita 50 mg bid + Met 500 mg bid vs. Met 500 mg bid		-0.6 (-0.8, -0.4)				<0.001	
Sita 50 mg bid + Met 500 mg bid vs. Sita 100 mg qd		-0.7 (-1.0, -0.5)				<0.001	
Sita 50 mg bid + Met 1000 mg bid vs. Met 1000 mg bid		-0.8 (-1.0, -0.5)				<0.001	
Sita 50 mg bid + Met 1000 mg bid vs. Sita 100 mg qd		-1.2 (-1.5, -1.0)				<0.001	
<b>Comparing Active Treatment Groups with Placebo</b>		<b>Difference in LS Means (95% CI)</b>				<b>p-Value</b>	
Sita 100 mg qd vs. Placebo		-0.8 (-1.1, -0.6)				<0.001	
Met 500 mg bid vs. Placebo		-1.0 (-1.2, -0.7)				<0.001	
Met 1000 mg bid vs. Placebo		-1.3 (-1.5, -1.1)				<0.001	
Sita 50 mg bid + Met 500 mg bid vs. Placebo		-1.6 (-1.8, -1.3)				<0.001	
Sita 50 mg bid + Met 1000 mg bid vs. Placebo		-2.1 (-2.3, -1.8)				<0.001	

Adapted from the Applicant's Table 11-1, reference p036v1

**Figure 8. Changes in HbA1c over time in Study P036. Panel A: randomized cohorts; Panel B: OLC**



Adapted from the applicant's Figures 11-1 and 11-2, reference p036v1

### 6.1.5 Clinical Microbiology

Not applicable.

### 6.1.6 Efficacy Conclusions

As described in this section, the efficacy data have been summarized for completeness of the review; efficacy of sitagliptin coadministered with metformin in treatment-naïve diabetics and a comparison between effects of sitagliptin and a sulfonylurea on glycemic control will be reviewed when future efficacy supplements are submitted under the sitagliptin-NDA 21995.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

Sitagliptin was investigated in 34 clinical studies to support approval of its use in monotherapy and in combination with pioglitazone and with metformin in patients with T2DM, under NDA 21995. That development program involved treatment of 3276 subjects, with a cumulative exposure of 1339 subject-years.

The present NDA contains new safety data (from both the original application and the 4-Month Safety Update Report) on the use of metformin in combination with sitagliptin, as follows:

- 24-week data in Study P036 (both the Open Label Cohort and the Randomized Cohorts)
- 52-week data in Study P024
- Spontaneous SAEs reported to the applicant from all clinical studies conducted until March 3, 2006 (cutoff date for the reports in the original application) and until August 15, 2006 (the cutoff for the 4-Month Safety Update Report).

#### 7.1.1 Deaths

##### Study P036

No deaths occurred in the OLC of Study P036 during the reporting period. From the 4-Month Safety Update Report, one death was reported in the placebo group: Subject AN 48140, a 50 year old male died due to sudden cardiac death on day 70. The subject had significant PMHx of HTN and CAD, and was being treated with enalapril, amlodipine and metoprolol.

##### Study P024

One death in the sitagliptin group and 3 in glipizide group occurred in Study P024. Please refer to narratives of these death events below.

##### Sitagliptin

Subject AN 41249, treated with sitagliptin 100 mg qd, was a 66-year old male who, on study day 180, was found unconscious, the victim of a hit-and-run accident while riding his bicycle. His

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past medical history was significant for T2DM, seasonal allergy, hyperlipidemia, hyperthyroidism, and HTN. He was being treated with metformin, simvastatin, methimazole, lisinopril, and aspirin. Upon admission to the hospital, the subject's glucose value was 162 mg/dL and it was not suspected that the subject experienced a hypoglycemic episode prior to the accident. On Day 180, a left frontal ventriculostomy, nasogastric tube placement, and endotracheal intubation were performed. On Day 187, Chest CT showed "probable left renal cell carcinoma" which was considered by the investigator to be an SAE. No further tests were performed to confirm renal cell carcinoma prior to the patient's death. On Day 191, ventilator support was withdrawn, and the patient died within hours thereafter. The patient's last dose of study therapy was Day 179.

Glipizide

Subject 41187, a 65-year old male, treated with glipizide, had a sudden cardiac death on day 357 into study P024. His past history was significant for T2DM, HTN, and actinic keratosis. He was treated with metformin, lisinopril, felodipine, atorvastatin, hydrochlorothiazide, ASA, calcium ascorbate, fructo-oligosaccharides, and sildenafil. On Day 357, the subject collapsed after an approximately 3.5 hour plane trip. He went into cardiac arrest and was brought to the hospital. A cardiac ultrasound indicated pulseless electrical activity. A Focused Assessment with Sonography for Trauma (FAST) ultrasound was negative for abdominal fluid and negative for pericardial effusion. The subject died on the same day (Day 357). The subject's last dose of study therapy was on Day 356. No autopsy was done. The condition that gave rise to the immediate cause of death, as listed on the death certificate, was atherosclerotic cardiovascular disease. The reporting investigator felt that sudden cardiac death was probably not related to study therapy.

Subject 41893, a 67-year old male, died 5 days after acute myocardial infarction. His past medical history was significant for T2DM, angina pectoris, prostatic hypertrophy, erectile dysfunction, atrial fibrillation, ankle edema, and lipomas. He had been treated with glipizide, metformin, sotalol, aspirin, magnesium oxide and furosemide. On Day 405, the subject experienced an acute myocardial infarction and was hospitalized. Chest x-rays were performed on Day 405 and Day 408 and suggested pneumonia. The investigator considered the pneumonia to be an NSAE and felt that it was probably not related to study therapy. An angiography revealed serious 3-vessel disease with subtotal stenosis in the right coronary artery. Non ST elevation myocardial infarction (inferolateral) was confirmed. On Day 406, acute percutaneous transluminal coronary angioplasty and coronary artery stent placement was performed. A coronary artery bypass graft was planned. On Day 408, due to disorientation, a brain computerized tomography was performed. No new findings were observed. The investigator considered the disorientation to be an NSAE and felt that it was probably not related to study therapy. On Day 409 the subject experienced an NSAE of chest pain which the investigator felt was probably not related to study therapy. On Day 410, the subject was found dead in bed at the hospital. A post-mortem examination revealed recent myocardial infarction (apex of septum), general atherosclerosis and bilateral pleural fluid.

Subject 42185, a 49-year old male, had an acute myocardial infarction on Study Day 45 and died. His past medical history included T2DM, dyslipidemia, angina pectoris, low back pain, gonarthrosis, deafness right ear, headache, increased thirst, tendonitis, toothache, obesity, and

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heat exhaustion. He was treated with metformin, simvastatin, aspirin, and acetaminophen. On Day 35, the subject began experiencing decreased energy. This was considered an NSAE that the reporting investigator felt was possibly related to study therapy. On Day 45, the subject was working in his garden, and experienced chest pain. He went to lie down and was later found gasping. Resuscitation was attempted, but was unsuccessful and the subject died. The cause of death was myocardial infarction. No autopsy was done.

### 7.1.2 Other Serious Adverse Events

The overall incidence of SAEs in Studies P036 and P024 was low, and was similar in the different treatment groups in each of the studies. The SAEs were distributed through different organs and systems, without any clear pattern pointing to specific treatments raising concerns about specific SAEs. The majority of subjects experiencing an SAE continued on the studies.

#### **Study P036**

As shown in Table 25 and Table 26, the frequency of SAEs was low in each of the treatment groups, and similar among them. There were no particular SOC or specific SAEs that raised concerns regarding the coadministration of sitagliptin and metformin (either low or high dose), as compared to these treatments given alone.

**Table 25 . Frequency of SAEs and discontinuation due to SAEs by treatment group in Study P036**

Treatment	SAEs N (%)	Discontinued due to SAE N
Sitagliptin	9 (5)	4
Metformin 500 bid	4 (2.2)	2
Metformin 1000 bid	3 (1.6)	0
Sita 50 / Met 500 bid	6 (3.2)	1
Sita 50 / Met 1000 bid	1 (0.5)	0
Placebo	10 (5.7)	5
OLC	3 (2.6)	0

Table 26 shows SAEs reported in the Randomized cohorts as well as the OLC in Study P036.

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**Table 26. SAEs in Study P036 as reported in the 4-Month Safety Update Report**

SAE by System Organ Class	S N=179	M500 N=182	M1000 N=182	SM500 N=190	SM1000 N=182	Placebo N=176	OLC N=117
	n (%)	n (%)	n (%)				
<b>Cardiac Disorders</b>	<b>2 (1.1)</b>	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	<b>2 (1.1)</b>	0 (0)
Cardiac Failure	0 (0)	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)
Coronary Artery Disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>2 (1.1)</b>	0 (0)
Myocardial Infarction	<b>1 (0.6)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Palpitations	<b>1 (0.6)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Congenital, Familial And Genetic Disorders</b>	0 (0)	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)
Exomphalos	0 (0)	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)
<b>Gastrointestinal Disorders</b>	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	<b>2 (1.1)</b>	0 (0)
Intestinal Obstruction	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)	0 (0)
Pancreatitis Acute	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
Umbilical Hernia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
<b>General Disorders / Administration Site Conditions</b>	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Non-Cardiac Chest Pain	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Hepatobiliary Disorders</b>	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)	<b>2 (1.1)</b>	0 (0)
Cholangitis Acute	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
Cholecystitis	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cholelithiasis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
<b>Infections And Infestations</b>	<b>1 (0.6)</b>	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)	<b>2 (1.1)</b>	<b>1 (0.9)</b>
Arthritis Infective	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
Bronchitis Acute	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cellulitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
Pneumonia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.9)</b>
Scrotal Abscess	<b>1 (0.6)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Injury, Poisoning And Procedural Complications</b>	0 (0)	0 (0)	<b>1 (0.5)</b>	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)
Femur Fracture	0 (0)	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)
Upper Limb Fracture	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)	0 (0)
<b>Metabolism And Nutrition Disorders</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
Ketoacidosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
<b>Musculoskeletal And Connective Tissue Disorders</b>	0 (0)	0 (0)	0 (0)	<b>1 (0.5)</b>	<b>1 (0.5)</b>	0 (0)	0 (0)
Arthritis	0 (0)	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)
Intervertebral Disc Protrusion	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)
<b>Neoplasms Benign, Malignant And Unspecified</b>	<b>4 (2.2)</b>	<b>1 (0.5)</b>	<b>1 (0.5)</b>	<b>1 (0.5)</b>	0 (0)	<b>1 (0.6)</b>	<b>1 (0.9)</b>
Basal Cell Carcinoma	0 (0)	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	<b>1 (0.9)</b>
Bladder Neoplasm	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)	0 (0)
Malignant Melanoma	<b>1 (0.6)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Esophageal Adenocarcinoma	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pancreatic Carcinoma	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
Prostate Cancer	<b>1 (0.6)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pyogenic Granuloma	<b>1 (0.6)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Retroperitoneal Neoplasm	<b>1 (0.6)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Nervous System Disorders</b>	<b>1 (0.6)</b>	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
Syncope	<b>1 (0.6)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thalamic Infarction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<b>1 (0.6)</b>	0 (0)
<b>Renal And Urinary Disorders</b>	<b>1 (0.6)</b>	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)
Hydronephrosis	0 (0)	0 (0)	0 (0)	<b>1 (0.5)</b>	0 (0)	0 (0)	0 (0)
Micturition Urgency	<b>1 (0.6)</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Vascular Disorders</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	<b>1 (0.9)</b>
Peripheral Vascular Disorder	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	<b>1 (0.9)</b>

SAEs include data after initiation of glycemic rescue therapy

S= sitagliptin 100 mg qd; M500 = metformin 500 mg bid; M1000= metformin 1000 mg bid; SM500 = sitagliptin 50 mg / metformin 500 mg bid; SM1000 + sitagliptin 50 mg / metformin 1000 mg bid; OLC = sitagliptin 50 mg / metformin 1000 mg bid in open label cohort

Bold numbers show incidence > 0 (> 0%)

Adapted from Table 14-44, reference p036v1

**Study P024**

SAEs reported from Study P024 in the 4-Month Safety Update Report are shown in Table 27, organized by system organ class (MedDRA Version 9.0).

**Table 27. SAEs reported in Study P024**

	Sitagliptin 100 mg (N = 588)		Glipizide (N = 584)	
	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	42	(7.1)	42	(7.2)
Patients With No Adverse Experience	546	(92.9)	542	(92.8)
<b>Cardiac Disorders</b>	<b>11</b>	<b>(1.9)</b>	<b>9</b>	<b>(1.5)</b>
Angina Pectoris	0	(0.0)	3	(0.5)
Angina Unstable	1	(0.2)	0	(0.0)
Atrial Fibrillation	1	(0.2)	0	(0.0)
Atrial Flutter	0	(0.0)	1	(0.2)
Cardiac Failure Congestive	2	(0.3)	1	(0.2)
Coronary Artery Disease	2	(0.3)	0	(0.0)
Coronary Artery Occlusion	1	(0.2)	0	(0.0)
Coronary Artery Stenosis	1	(0.2)	0	(0.0)
Hypertensive Heart Disease	1	(0.2)	1	(0.2)
Myocardial Infarction	0	(0.0)	1	(0.2)
Pericardial Effusion	0	(0.0)	1	(0.2)
Supraventricular Tachycardia	2	(0.3)	1	(0.2)
<b>Ear And Labyrinth Disorders</b>	<b>1</b>	<b>(0.2)</b>	<b>0</b>	<b>(0.0)</b>
Sudden Hearing Loss	1	(0.2)	0	(0.0)
<b>Eye Disorders</b>	<b>1</b>	<b>(0.2)</b>	<b>0</b>	<b>(0.0)</b>
Cataract	1	(0.2)	0	(0.0)
<b>Gastrointestinal Disorders</b>	<b>5</b>	<b>(0.9)</b>	<b>3</b>	<b>(0.5)</b>
Abdominal Pain	1	(0.2)	0	(0.0)
Abdominal Strangulated Hernia	0	(0.0)	1	(0.2)
Diarrhoea	1	(0.2)	0	(0.0)
Dyspepsia	1	(0.2)	0	(0.0)
Enterocolitis	0	(0.0)	1	(0.2)
Gastrointestinal Haemorrhage	1	(0.2)	0	(0.0)
Inguinal Hernia	1	(0.2)	0	(0.0)
Rectal Polyp	1	(0.2)	0	(0.0)
Umbilical Hernia	1	(0.2)	0	(0.0)
Upper Gastrointestinal Haemorrhage	0	(0.0)	1	(0.2)
<b>General Disorders And Administration Site Conditions</b>	<b>3</b>	<b>(0.5)</b>	<b>4</b>	<b>(0.7)</b>
Chest Pain	0	(0.0)	1	(0.2)
Fatigue	1	(0.2)	0	(0.0)
Non-Cardiac Chest Pain	0	(0.0)	2	(0.3)
Oedema Peripheral	1	(0.2)	0	(0.0)
Polyserositis	0	(0.0)	1	(0.2)
Pyrexia	1	(0.2)	0	(0.0)
<b>Hepatobiliary Disorders</b>	<b>6</b>	<b>(1.0)</b>	<b>0</b>	<b>(0.0)</b>
Bile Duct Stone	1	(0.2)	0	(0.0)
Cholecystitis Acute	1	(0.2)	0	(0.0)
Cholecystitis Chronic	1	(0.2)	0	(0.0)
Cholelithiasis	3	(0.5)	0	(0.0)
Hydrocholecystis	1	(0.2)	0	(0.0)

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	Sitagliptin 100 mg (N = 588)		Glipizide (N = 584)	
	n	(%)	n	(%)
<b>Infections And Infestations</b>	2	(0.3)	7	(1.2)
Arthritis Bacterial	1	(0.2)	0	(0.0)
Cellulitis	1	(0.2)	2	(0.3)
Dengue Fever	0	(0.0)	1	(0.2)
Gastroenteritis Viral	0	(0.0)	1	(0.2)
Helicobacter Infection	0	(0.0)	1	(0.2)
Pneumonia	0	(0.0)	1	(0.2)
Pneumonia Streptococcal	0	(0.0)	1	(0.2)
<b>Injury, Poisoning And Procedural Complications</b>	4	(0.7)	2	(0.3)
Ankle Fracture	0	(0.0)	1	(0.2)
Lower Limb Fracture	1	(0.2)	0	(0.0)
Medical Device Complication	1	(0.2)	0	(0.0)
Polytraumatism	1	(0.2)	0	(0.0)
Postoperative Thrombosis	0	(0.0)	1	(0.2)
Tendon Injury	1	(0.2)	0	(0.0)
<b>Metabolism And Nutrition Disorders</b>	0	(0.0)	2	(0.3)
Diabetic Foot	0	(0.0)	1	(0.2)
Obesity	0	(0.0)	1	(0.2)
<b>Musculoskeletal And Connective Tissue Disorders</b>	3	(0.5)	3	(0.5)
Arthralgia	0	(0.0)	1	(0.2)
Intervertebral Disc Protrusion	0	(0.0)	2	(0.3)
Lumbar Spinal Stenosis	0	(0.0)	1	(0.2)
Musculoskeletal Pain	1	(0.2)	0	(0.0)
Osteoarthritis	2	(0.3)	0	(0.0)
<b>Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Potyps)</b>	5	(0.9)	7	(1.2)
Basal Cell Carcinoma	1	(0.2)	2	(0.3)
Bladder Cancer	1	(0.2)	0	(0.0)
Breast Cancer	0	(0.0)	1	(0.2)
Colon Cancer	1	(0.2)	0	(0.0)
Gastric Cancer	1	(0.2)	0	(0.0)
Malignant Melanoma	0	(0.0)	1	(0.2)
Prostate Cancer	0	(0.0)	1	(0.2)
Rectal Cancer	0	(0.0)	1	(0.2)
Renal Cell Carcinoma Stage Unspecified	0	(0.0)	1	(0.2)
Squamous Cell Carcinoma Of Skin	1	(0.2)	0	(0.0)
<b>Nervous System Disorders</b>	2	(0.3)	5	(0.9)
Carotid Artery Stenosis	0	(0.0)	1	(0.2)
Dizziness	0	(0.0)	1	(0.2)
Guillain-Barre Syndrome	0	(0.0)	1	(0.2)
Loss Of Consciousness	0	(0.0)	1	(0.2)
Lumbar Radiculopathy	2	(0.3)	0	(0.0)
Syncope	0	(0.0)	1	(0.2)
Transient Ischaemic Attack	0	(0.0)	1	(0.2)

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	Sitagliptin 100 mg (N = 588)		Glipizide (N = 584)	
	n	(%)	n	(%)
<b>Pregnancy, Puerperium And Perinatal Conditions</b>	0	(0.0)	1	(0.2)
Abortion Spontaneous	0	(0.0)	1	(0.2)
<b>Psychiatric Disorders</b>	0	(0.0)	1	(0.2)
Hallucination	0	(0.0)	1	(0.2)
<b>Renal And Urinary Disorders</b>	2	(0.3)	2	(0.3)
Nephrolithiasis	1	(0.2)	1	(0.2)
Renal Colic	1	(0.2)	0	(0.0)
Renal Mass	0	(0.0)	1	(0.2)
<b>Respiratory, Thoracic And Mediastinal Disorders</b>	3	(0.5)	2	(0.3)
Acute Pulmonary Oedema	1	(0.2)	0	(0.0)
Asthma	1	(0.2)	0	(0.0)
Epistaxis	1	(0.2)	0	(0.0)
Pickwickian Syndrome	0	(0.0)	1	(0.2)
Pneumothorax	0	(0.0)	1	(0.2)
<b>Skin And Subcutaneous Tissue Disorders</b>	1	(0.2)	1	(0.2)
Angioneurotic Oedema	0	(0.0)	1	(0.2)
Urticaria	1	(0.2)	0	(0.0)
<b>Vascular Disorders</b>	1	(0.2)	1	(0.2)
Deep Vein Thrombosis	0	(0.0)	1	(0.2)
Iliac Artery Stenosis	1	(0.2)	0	(0.0)
Peripheral Artery Aneurysm	1	(0.2)	0	(0.0)

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Copied from the applicant's Table 12-11, reference P024v1

### 7.1.3 Dropouts and Other Significant Adverse Events

#### **Study P024**

In this study, 1172 subjects were randomized and 798 (68.1%) completed the study. A slightly greater proportion of subjects in the glipizide group reached Week 52: 65.6% in the sitagliptin treatment group and 70.5% in the glipizide treatment group. Reasons for discontinuation were similar between treatment groups with slightly more subjects in the sitagliptin group discontinuing for lack of efficacy and lost to follow-up. A similar proportion of subjects discontinued due to an AE (clinical or laboratory) in the 2 treatment groups (Table 28).

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**Table 28: Subjects who discontinued from Study P024, by treatment group**

	<b>Sitagliptin</b> N=588	<b>Glipizide</b> N = 584
<b>Discontinued</b>	<b>202</b>	<b>172</b>
Clinical AE	17	20
Laboratory AE	8	6
Lack of Efficacy	86	58
Lost to Follow-up	19	10
Discontinued for Other	10	11
Subject Moved	6	2
Subject Withdrew Consent	25	28
Protocol-specified discontinuation criteria	19	25
Protocol Deviation	10	10
Site Terminated	2	2

Based on the applicant's Figure 10-1, reference p024v1

### **Study P036**

Table 29 shows the disposition of 1208 subjects in Study P036: 1091 subjects who were randomized to one of six treatment groups and of 117 subjects who were allocated to the OLC. Except for placebo and the OLC, the rates of discontinuation were similar among the randomized cohorts; in these 2 cohorts, there was a higher rate of study discontinuation due to perceived lack of efficacy.

**Table 29. Subject discontinuation in Study P036, by treatment group**

<b>Reason for drop out</b>	<b>Sitagliptin</b> N=179	<b>Metformin</b> <b>500 bid</b> N=182	<b>S50M500</b> N=190	<b>S50M100</b> N=182	<b>Metformin</b> <b>1000</b> N=182	<b>Placebo</b> N=176	<b>OLC</b> N=117
<b>Discontinued</b>	37	29	26	18	26	49	38
Clinical AE	6	4	4	1	5	7	3
Lab AE	2	0	0	0	0	2	0
Lack of Efficacy	3	5	2	2	3	12	19
Lost to F/U	3	2	3	8	4	8	3
Discontinued for Other	2	1	0	1	0	2	1
Withdrew Consent	12	11	9	3	12	12	4
Protocol-specified criteria	3	3	5	3	0	3	5
Protocol Deviation	6	3	3	0	2	3	3

Adapted from the applicant's Figure 10-1, reference p036v1.

#### **7.1.3.1 Overall profile of dropouts**

As seen in Study P020 and other studies supporting the approval of sitagliptin, the majority of dropouts in Studies P024 and P036 were related to perceived lack of efficacy. The proportion of dropouts due to clinical or laboratory AEs was similar between sitagliptin/ metformin groups and their respective controls in Studies P024 and P036.

#### **7.1.3.2 Adverse events associated with dropouts**

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Overall, the proportion of subjects who discontinued from the study due to a clinical AE was low and similar across the 6 treatment groups in the Randomized Cohort. The highest incidence of discontinuation due to clinical AEs occurred in the placebo group; the lowest incidence occurred in the sitagliptin 50/ metformin 1000 mg bid group. The number of subjects discontinued due to clinical AEs per treatment group is provided below:

- Sitagliptin 100 mg qd - 6 (3.4%)
- Metformin 500 mg bid - 4 (2.2%)
- Metformin 1000 mg bid - 5 (2.7%)
- Sitagliptin 50 / metformin 500 mg bid - 5 (2.6%)
- Sitagliptin 50 / metformin 1000 mg bid – 2 (1.1%)
- Placebo – 7 (4.0%)

Table 30 lists the specific AEs resulting in discontinuation of subjects in Study P036.

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 NDA 22044, Submission 000  
 Janumet™ (Sitagliptin / metformin fixed-dose combination)

**Table 30. Subjects discontinued from Study P036 due to AEs**

Subject number	Gender	Race	Age	Therapy (mg / day)	Day of Onset	Adverse Event	Day Dropped	Serious
<b>Sitagliptin 100 mg</b>								
47084	M	white	56 yr	Sitagliptin 100	125	Drug hypersensitivity	167	N
47121	M	white	65 yr	Sitagliptin 100	139	Prostate cancer	148	Y
47219	F	black	49 yr	Sitagliptin 100	10	Palpitations	23	Y
48048	M	white	68 yr	Sitagliptin 100	114	Myocardial infarction	120	Y
47608	M	white	50 yr	Sitagliptin 100	55	Dyslipidemia	66	N
47787	F	multi	65 yr	Sitagliptin 100	122	Retroperitoneal neoplasm	133	Y
<b>Metformin 500 mg bid</b>								
47086	M	white	54 yr	Metformin 1000	6	GERD	15	N
47079	M	white	72 yr	Metformin 1000	6	Esophageal Adenocarcinoma	10	Y
48253	M	Hispa	51 yr	Metformin 1000	2	Urticaria	7	N
47725	F	multi	57 yr	Metformin 1000	56	Cholecystitis	56	Y
<b>Metformin 1000 mg bid</b>								
47529	M	Hispa	57 yr	Metformin 2000	2	Dyspnea	11	N
47264	F	white	57 yr	Metformin 2000	52	Anorexia	73	N
47919	M	Hispa	55 yr	Metformin 2000	3	Rash maculo-papular	17	N
47643	F	white	56 yr	Metformin 2000	85	Abdominal pain	134	N
					Flatulence			
47645	F	white	67 yr	Metformin 2000	4	Diarrhea	23	N
<b>Sitagliptin 50 / Metformin 500 mg bid</b>								
47123	F	white	67 yr	S100M1000	1	Arthralgia	81	N
47340	F	black	69 yr	S100M1000	132	Cardiac failure congestive	169	N
48057	F	Polyn	61 yr	S100M1000	4	Rash	33	N
47753	M	white	52 yr	Off Drug 1 day	80	Cardiac failure	79	Y
47670	M	white	47 yr	S100M1000	2	Abdominal pain upper	37	N
<b>Sitagliptin 50 / Metformin 1000 mg bid</b>								
47116	F	black	62 yr	S100M2000	82	GERD	110	N
47840	M	Hispa	49 yr	S100M2000	135	Pruritus	169	N
<b>Placebo</b>								
47268	M	white	51 yr	Off Drug 2 days	163	Coronary artery disease	161	Y
47309	M	white	55 yr	Off Drug 1 day	148	Coronary artery disease	147	Y
47286	F	white	57 yr	Placebo	31	Pancreatic carcinoma	38	Y
47581	M	white	63 yr	Placebo	17	Neuropathy peripheral	22	N
47987	M	white	70 yr	Placebo	83	Abdominal pain upper	84	N
47690	M	white	57 yr	Placebo	96	Pancreatitis acute	96	Y
48307	F	white	58 yr	Off Drug 1 day	15	Ketoacidosis	14	Y
<b>OLC</b>								
52111	M	white	48 yr	S100M2000	28	Urticaria	43	N
52691	F	black	56 yr	S100M2000	22	Vomiting	22	N
53141	M	white	30 yr	S100M2000	63	DM insulin-dependent	63	N

Adapted from the applicant's Table 12-11, reference p036v1 in the 4-Month Safety Update Report

### **Study P024**

Sixteen subjects in the sitagliptin group and 21 subjects in the glipizide group were discontinued from Study P024 due to AEs. There was no clear pattern of AEs that was predominant as a reason for discontinuation. While there were no cases of hypoglycemia in the sitagliptin group, 3 subjects were discontinued from the glipizide group due to hypoglycemia (perceived as AE). Please refer to Table 31 for a list of subjects and their AEs resulting in study discontinuation.

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**Table 31. Subjects discontinued from Study P024 due to AEs**

Subject number	Gender	Race	Age	Therapy (mg/day)	Day of Onset	Adverse Event	Day Dropped	Serious
<b>Sitagliptin</b>								
42337	M	White	60 yr	Sita 100	67	Congestive Cardiac failure	67	Y
41082	F	Hispanic	39 yr	Sita 100	2	Asthenia	29	N
41249	M	White	65 yr	Off Drug 1 day	180	Polytraumatism	179	Y
42293	F	Asian	61 yr	Sita 100	257	Cough	287	N
41753	M	White	72 yr	Sita 100	102	Alcoholism	193	N
41813	F	White	65 yr	Sita 100	46	Urticaria generalized	46	N
42147	M	White	76 yr	Sita 100	109	Urticaria	190	Y
41669	M	White	59 yr	Sita 100	138	Dyspepsia	171	N
41670	M	White	63 yr	Sita 100	96	Lethargy	133	N
42099	F	Black	53 yr	Sita 100	169	Second degree AV block	322	N
42392	M	White	57 yr	Sita 100	78	Bile duct stone	78	Y
42266	M	Asian	60 yr	Sita 100	155	Herpes zoster	157	N
42112	F	Hispanic	67 yr	Off Drug 10 days	373	Gastric cancer	387	Y
41433	F	White	51 yr	Sita 100	339	Polymyalgia	364	N
41523	M	White	76 yr	Off Drug 1 day	319	Colon cancer	318	Y
41500	F	White	42 yr	Sita 100	33	Benign salivary gland neoplasm	34	N
<b>Glipizide</b>								
42411	F	Black	57 yr	Glipizide 5	278	Herpes zoster	321	N
41090	M	White	62 yr	Glipizide 10	32	Renal cell CA stage unspecified	63	Y
41222	M	White	44 yr	Glipizide 5	68	Diarrhea	91	N
42351	F	Polynesia	51 yr	Off Drug 1 day	137	Renal mass	136	Y
41272	F	White	49 yr	Placebo	103	Eructation	113	N
41301	F	White	60 yr	Glipizide 15	134	Hypoglycemia	135	N
42489	M	White	62 yr	Glipizide 5	274	Diarrhea	334	N
42297	M	White	77 yr	Glipizide 5	223	Guillain-Barre syndrome	223	Y
42132	F	Multi	70 yr	Glipizide 15	213	Polyserositis	222	N
41836	M	White	75 yr	Glipizide 20	162	Rectal cancer	321	Y
42127	F	Hispanic	60 yr	Glipizide 5	8	Drug hypersensitivity	8	N
41621	M	White	57 yr	Glipizide 5	2	Hypoglycemia	21	N
41661	M	White	59 yr	Glipizide 5	141	Malignant melanoma	247	Y
41667	F	White	62 yr	Glipizide 5	2	Constipation	12	N
						Dizziness		N
42234	F	Asian	55 yr	Off Drug 5 days	273	Hypoglycemia	268	N
41595	M	White	57 yr	Off Drug 1 day	40	Angina pectoris	39	Y
41972	F	White	44 yr	Glipizide 5	24	Hypoglycemia	24	N
41725	M	White	69 yr	Placebo	331	Spinal Osteoarthritis	352	N
41491	M	White	65 yr	Glipizide 10	43	Diarrhea	65	N
41495	M	White	60 yr	Glipizide 5	28	Congestive Cardiac Failure	28	Y
41481	M	White	53 yr	Glipizide 5	7	Urticaria	18	N

Adapted from the applicant's Table 12-13, Reference p024v1

### 7.1.3.3 Other significant adverse events

#### 7.1.3.3.1 Hypoglycemic events

Hypoglycemia is a common AE with many of the products currently used to treat T2DM. GLP1-induced insulin secretion is glucose-dependent; therefore, at normal or low glucose levels, one should not expect that an increase in endogenous GLP1 (such as that expected with DPP4 inhibition) will induce insulin secretion in quantities that could result in hypoglycemia. However, the safety review of a GLP1 analog (Exenatide) demonstrated that treatment emergent hypoglycemic events were observed more frequently in those subjects treated compared to placebo and the proportion of these hypoglycemic events was dose-dependent. The applicant defined hypoglycemia as “symptomatic events assessed by the investigator as likely to be hypoglycemia regardless of whether a fingerstick blood glucose was performed at the time the subject had symptoms.

#### **Study P036**

In the 4-Month Safety Update Report, the overall incidence of hypoglycemia observed among the randomized cohorts in Study P036 with the combination of sitagliptin and metformin was similar to that observed with metformin alone as assessed by comparing the pooled (higher- and lower-dose) coadministration groups (1.6%) with the pooled (higher- and lower-dose) metformin monotherapy groups (0.8%).

Among the randomized cohorts, 11 subjects reported AE of hypoglycemia, all considered mild to moderate in intensity. Seven of these AEs had concomitant fingerstick blood glucose levels ranging from 50 to 112 mg/dL (Table 32).

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**Table 32. Summary of Clinical Assessment of Hypoglycemia in the randomized cohorts of Study P036**

Treatment Group	N	Subjects with ≥ 1 episode <sup>†</sup> n (%)		
		Overall	Requiring Non-Medical Assistance and Not Exhibiting Marked Severity <sup>‡</sup>	Requiring Medical Assistance or Exhibiting Marked Severity <sup>‡</sup>
Sita 100 mg qd	179	1 (0.6)	0 (0.0)	0 (0.0)
Met 500 mg bid	182	1 (0.5)	1 (0.5)	0 (0.0)
Met 1000 mg bid	182	2 (1.1)	0 (0.0)	0 (0.0)
Sita 50 mg bid + Met 500 mg bid	190	2 (1.1)	0 (0.0)	0 (0.0)
Sita 50 mg bid + Met 1000 mg bid	182	4 (2.2)	0 (0.0)	0 (0.0)
Placebo	176	1 (0.6)	0 (0.0)	0 (0.0)
			<b>Total Number of Episodes<sup>†</sup></b>	
			Requiring Non-Medical Assistance and Not Exhibiting Marked Severity <sup>‡</sup>	Requiring Medical Assistance or Exhibiting Marked Severity <sup>‡</sup>
Treatment Group	Overall			
Sita 100 mg qd	1		0	0
Met 500 mg bid	2		1	0
Met 1000 mg bid	2		0	0
Sita 50 mg bid + Met 500 mg bid	2		0	0
Sita 50 mg bid + Met 1000 mg bid	4		0	0
Placebo	1		0	0

<sup>†</sup> Any given episode may belong to multiple categories.

<sup>‡</sup> Markedly depressed level of consciousness, loss of consciousness, or seizure.

Adapted from the applicant's Table 12-13, in reference p036v1

In the OLC, 2 subjects had a clinical AE of hypoglycemia: one subject (AN 52952) had a concurrent fingerstick measurement of 115 mg/dL, while the other (subject AN 52501) reported the event at approximately 11:30 pm after having eaten a light supper, with a concurrent fingerstick measurement of 26 mg/dL.

In addition to the AE of "hypoglycemia", the investigator's review of glucose logs have revealed asymptomatic events of decreased glucose, termed "blood glucose decreased" as the defining AE term. These occurred for 1 (0.5%), 1 (0.5%), 1 (0.5%) and 1 (0.6%) subject in the metformin 1000 mg bid monotherapy, the sitagliptin 50 mg /metformin 500 mg bid coadministration, the sitagliptin 50 mg / metformin 50 mg /1000 mg bid coadministration, and the placebo groups, respectively.

### **Study P024**

Table 33 shows summary data on the rates of hypoglycemia (subject-described) in the sitagliptin and glipizide groups in Study P024.

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**Table 33. Summary of Clinical Assessment of Hypoglycemia in Study P024**

Treatment	N	Subjects with $\geq 1$ episode <sup>†</sup> n (%)		
		Overall	Requiring Non-Medical Assistance and Not Exhibiting Marked Severity <sup>‡</sup>	Requiring Non-Medical Assistance and Not Exhibiting Marked Severity <sup>‡</sup>
Sitagliptin	588	29 (4.9)	1 (0.2)	1 (0.2) (fingerstick glucose 42 mg/dL)
Glipizide	584	187 (32.0)	8 <sup>§</sup> (1.4)	7 <sup>  </sup> (1.2)
Treatment		Total Number of Episodes <sup>†</sup>		
		Overall	Requiring Non-Medical Assistance and Not Exhibiting Marked Severity <sup>‡</sup>	Requiring Non-Medical Assistance and Not Exhibiting Marked Severity <sup>‡</sup>
Sitagliptin		50 <sup>§</sup>	1	1
Glipizide		657	15	7

<sup>†</sup>Any given episode may belong to multiple categories.  
<sup>‡</sup>Markedly depressed level of consciousness, loss of consciousness, or seizure.  
<sup>§</sup>The following subjects in the sitagliptin treatment group had 2 to 4 episodes of hypoglycemia (AN 41123, 41139, 41367, 41484, 41584, 41593, 41746, 41829, 41914, 42099, 42169, and 42194). AN42183 had 5 episodes; all were considered mild in intensity.  
<sup>||</sup>AN 41057 is counted in both categories due to having two episodes.

Adapted from Table 12-15 under Reference p024 v1

The applicant conducted analyses in the difference in proportion of hypoglycemia between treatments (CMH test stratified by prior anti-diabetic treatment status) and concluded these were statistically significant for the overall number of episodes ( $p < 0.001$ ), as well as for episodes not requiring medical assistance or not exhibiting marked severity ( $p = 0.02$ ) or for episodes requiring medical assistance or exhibiting marked severity ( $p = 0.037$ ). These analyses were prospectively defined and the study was adequately powered to test them.

Although the study has no placebo control group, the rates of hypoglycemic AEs and reports of “blood glucose decreased” are consistent with the reports from the placebo-controlled studies, including Study P020, which investigated effects of sitagliptin in combination with metformin. We can conclude from these results that the rate of hypoglycemia with sitagliptin treatment is low (although not absent) and the episodes are, in general, mild.

#### 7.1.3.3.2 Gastrointestinal events

GLP1 has known effects on slowing gastric emptying. In addition, a higher incidence of nausea and, to a lesser extent, diarrhea and vomiting, were seen in subjects treated with exenatide, a GLP1 analog. These facts serve as a basis for the applicant to consider these gastrointestinal events as of special interest, and subject to statistical analysis. Metformin also has a profile of increased nausea, abdominal pain and diarrhea, which is only partially attenuated with the gradual weekly dose increase.

From the 4-Month Safety Update Report, in Study P036 the overall gastrointestinal safety profile of the combination of sitagliptin and metformin was comparable to that of metformin alone as assessed by the overall incidence of Gastrointestinal Disorders SOC adverse experiences comparing the pooled (higher- and lower-dose) coadministration groups (21.2%) with the pooled (higher- and lower-dose) metformin monotherapy groups (20.6%). Between-group differences in the incidence of adverse experiences within the Gastrointestinal Disorders SOC were observed, including those which were prespecified (diarrhea, nausea, abdominal pain, and vomiting).

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**Table 34. Selected Clinical AEs in the Gastrointestinal Disorders SOC excluding data after initiation of glycemic rescue therapy in Study P036**

	Sita 100 qd		Met 500 bid		Met 1000 bid		Sita 50 bid + Met 500 bid		Sita 500 bid + Met 1000 bid		Placebo		Sita 50 bid + Met 1000 bid OLC	
	N=179		N=182		N=182		N=190		N=182		N=176		N=117	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
<b>Gastrointestinal Disorders</b>	11	(6.1)	17	(9.3)	37	(20.3)	22	(11.6)	27	(14.8)	12	(6.8)	19	(16.2)
Abdominal Pain*	6	(3.4)	5	(2.7)	9	(4.9)	5	(2.6)	6	(3.3)	4	(2.3)	6	(5.1)
Diarrhea	5	(2.8)	9	(4.9)	19	(10.4)	12	(6.3)	16	(8.8)	7	(4.0)	10	(8.5)
Nausea	2	(1.1)	5	(2.7)	15	(8.2)	8	(4.2)	10	(5.5)	2	(1.1)	7	(6.0)
Vomiting	0	(0)	0	(0)	2	(1.1)	2	(1.1)	6	(3.3)	1	(0.6)	4	(3.4)
<b>Gastrointestinal Disorders</b>	27	(15.1)	29	(15.9)	46	(25.3)	34	(17.9)	45	(24.7)	19	(10.8)	32	(27.4)
Constipation	9	(5.0)	5	(2.7)	5	(2.7)	5	(2.6)	2	(1.1)	2	(1.1)	5	(4.3)

\* Including abdominal pain, abdominal discomfort, upper abdominal pain, and stomach discomfort.

Adapted from the applicant's Table 12-14 and 12-15, in Reference p036v1 from the 4-Month Safety Update Report

From Table 34, there is a metformin dose-proportional increase in nausea and diarrhea. Sitagliptin alone, on the other hand, tends to increase constipation. There were no clinically meaningful differences in the incidences of diarrhea, nausea and vomiting in the group receiving coadministered sitagliptin and metformin compared to the group receiving metformin alone, when properly comparing the groups according to the metformin dose (500 mg bid versus 1000 mg bid) received. The rates of pre-specified AEs seen in Table 34 is similar to the rates of these events in the analysis of all data included (all AEs counted, regardless of initiation of glycemic rescue therapy).

The relative date of onset of diarrhea was approximately 2 months for both the metformin groups and the sitagliptin / metformin coadministration groups, and the diarrhea was self-limiting, not causing any discontinuation from therapy or from the study.

The applicant analyzed the proportions of these pre-specified AEs among the treatment groups in Study P036 and found the following statistically significant comparisons, in pre-specified and adequately powered analyses between active treatment groups versus placebo or between the monotherapies (sita 100 versus either metformin 500 bid or metformin 1000 bid) (Table 35).

**Table 35. Analyses of Incidence of Specific GI AEs in Study P036, excluding data after initiation of glycemic rescue therapy**

	Difference in Proportions (%) (95 % CI <sup>^</sup> )	p-value*
<b>Diarrhea</b>		
Met 1000 bid vs. Placebo	6.5 (1.0, 12.1)	0.024
Sita 100 vs. Met 1000 bid	-7.6 (-13.2, -2.5)	0.005
<b>Nausea</b>		
Met 1000 bid vs. placebo	7.1 (2.8, 12.1)	0.002
Sita 50 bid + Met 1000 bid vs. Placebo	4.4 (0.5, 8.8)	0.036
Sita 100 qd vs. Met 1000 bid	-7.1 (-12.1, -2.8)	0.002

<sup>^</sup> Confidence Interval computed using the Wilson score method

\* Based on Fisher's exact test

Adapted from the applicant's Tables 12-16 and 12-17, reference p036v1

There were no statistically significant differences in rates of vomiting or abdominal pain among the groups, neither as compared to placebo nor by comparing the monotherapies.

#### Study P024

Pre-specified gastrointestinal AEs occurred with similar rates among the sitagliptin-treated and the glipizide-treated subjects (Table 36).

**Table 36. Incidence of pre-specified gastrointestinal events in Study P024**

AE	Sitagliptin (N=588)		Glipizide (N=237)	
	n	(%)	n	(%)
Abdominal Pain*	10	2.7	12	2.1
Diarrhea	34	5.8	32	5.5
Nausea	15	2.6	16	2.7
Vomiting	5	0.9	9	1.5

\* Including upper and lower abdominal pain

Adapted from Table 12-19, reference p024v1

#### 7.1.4 Other Search Strategies

In view of the deaths of dogs receiving metformin doses of 50 mg / kg (resulting probably from lactic acidosis) alone or with concomitant administration of variable doses of sitagliptin, this reviewer analyzed lactic acid and bicarbonate levels in subjects receiving metformin doses > 1500 mg qd and sitagliptin in Study P020, and in the OLC of Study P036. No changes in mean serum lactic acid or bicarbonate were observed in those studies. No cases of lactic acidosis were reported from Studies P036 and P024 in the 4-Month Safety Update Report.

The prolonged use of metformin is associated with a subclinical impairment in the absorption of vitamin B12, with the theoretical possibility of megaloblastic anemia as a consequence of chronic B12 deficiency. Mean levels of serum Hb were slightly decreased during the studies supporting the approval of sitagliptin. Therefore a specific search was used to detect the presence of anemia, particularly related to B12 deficiency in the studies with enhanced data submitted with the 4-Month Safety Update Report. In Study P036, no subject in the placebo, or any sitagliptin group alone had B12 deficiency reported. One subject (0.5%) in the metformin 1000 bid and 2 subjects (1.1%) in the metformin 500 mg bid developed Vitamin B12 deficiency. No subject in any sitagliptin / metformin combination developed Vitamin B12 deficiency. No subject in Study P024 had Vitamin B12-related anemia reported, and only one subject had a substantial decrease in serum Hb related to gastric cancer (AN 42112).

#### 7.1.5 Common Adverse Events

##### 7.1.5.1 Eliciting adverse events data in the development program

The overall safety of coadministration of sitagliptin and metformin was assessed during the development by review of clinical and laboratory adverse events, laboratory abnormalities

meeting predefined limits of change (PDLC) criteria and by review of mean changes in safety laboratory analytes, ECG intervals and vital signs.

Hypoglycemia, nausea, vomiting, abdominal pain and diarrhea were designated tier 1 AEs (based on the effects of GLP1 on insulin secretion and gastrointestinal motility) and were subject to statistical analysis (Please refer to Section 7.1.3.3, in this review document).

Hypoglycemia was assessed both at the clinical sites through collection of blood chemistry as well as by the subjects outside of the clinical site, through a sponsor-supplied glucometer, with frequency of the assessments determined by each investigator.

Subjects had their AEs reviewed continuously through the study periods and by telephone 2 weeks after the study period. Visits to the clinical site were scheduled every 6 weeks during the controlled phase of Study P020 (Phase A), Studies P036 and P024, and every 8 weeks during the extension of Study P020 (Phase B), where assessments of vital signs, review of AEs and use of concomitant medications, review of glycemia logs, diet and exercise took place. Complete blood counts, hemoglobin A1C, and chemistry panel were assessed at every visit, while fasting insulin and pro-insulin, lipid panel, urinalysis and ECG were performed at the baseline (randomization) visit and at the end of study.

This reviewer concurs with the applicant's frequency and nature of assessments during the development to provide a comprehensive compilation of safety information on the coadministration of sitagliptin and metformin.

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant has used MedDRA dictionary Version 9.0 for preferred terms and for classification of AEs into system organ classes. This reviewer compared the terms used by the investigator in describing an AE (verbatim) to the preferred term, particularly in cases of SAEs or AEs leading to dropouts, and these events seem to have been appropriately classified.

#### 7.1.5.3 Incidence of common adverse events

##### **Study P024**

Specific AEs that were reported more commonly among sitagliptin-treated subjects, compared to glipizide-treated subjects were:

##### **Fatigue**

Fatigue was reported more commonly among sitagliptin-treated subjects (18 subjects or 3.1%) compared to glipizide-treated subjects (5 subjects or 0.9% for glipizide). Fatigue had the same time of onset as among glipizide-treated, with variable duration from < 7 days to continuing at the time of the report (up to 218 days), and the same mild to moderate severity. Fatigue was not a reason for study discontinuation in any subject. These cases of fatigue did not correlate to changes in serum bicarbonate concentrations suggestive of a trend towards lactic acidosis.

##### **Urinary Tract Infection**

More subjects in the sitagliptin group had UTI compared to the glipizide group (38 subjects or 6.5 % against 23 or 4 %). The time of onset ranged from day 1 to day 379 in the sitagliptin and

from day 23 to day 361 in the glipizide group. There were 2 subjects in each group who had repeat UTI. No episode of UTI resulted in study discontinuation.

Arthralgia, pain in extremity and osteoarthritis were more frequently reported in the sitagliptin group. The joints affected were predominantly knee (7 subjects), shoulder (2), finger (2) and hip (1), while other subjects did not report the joint location. Two of these were considered severe.

Hypoglycemia, as an AE, was reported significantly more frequently in the glipizide group as compared to the sitagliptin group.

### **Study P036**

The overall gastrointestinal safety profile of the combination of sitagliptin and metformin was comparable to that of metformin alone as assessed by the overall incidence of AEs in the Gastrointestinal Disorders system organ class (SOC) comparing the pooled (sitagliptin 50 mg / metformin 500 mg bid and sitagliptin 50 mg / metformin 1000 mg bid) coadministration groups (21.2%) with the pooled metformin monotherapy (500 mg bid and 1000 mg bid) groups (20.6%). In the Infections and Infestations SOC, a higher incidence of specific clinical AEs was observed for bronchitis (including acute bronchitis) in the sitagliptin 50 mg / metformin 1000 mg bid group (9 subjects, 4.9%) compared with the placebo group (5 subjects, 2.8%) and with the 4 other treatment groups (incidence ranged from 1.1% to 2.2%). All events of bronchitis in the sitagliptin 50 mg / metformin 1000 mg bid group were considered mild or moderate in intensity, none resulted in study discontinuation, and all resolved while subjects continued on study drug. Generally, the onset of bronchitis was not temporally associated with the initiation of study drug, with the mean relative day of onset being between 80 and 100 days for all groups.

The incidences of AEs by SOC for subjects in the OLC were generally similar to those in the Randomized Cohorts. Diarrhea was the most frequently reported AE (10 patients, 8.5%; compared with 10.4% in the higher-dose metformin monotherapy group). Four subjects (3.5%) were reported to have the AEs of gastroenteritis or viral gastroenteritis; all were considered mild to moderate in intensity and all resolved within 5 days while patients continued on study medication. Three subjects (2.6%) were reported to have the AE of bronchitis; all were considered mild to moderate in intensity, and all resolved while subjects continued on study medication. In the OLC, few subjects were reported to have an AE of arthralgia (3 subjects, 2.6%); all events of arthralgia were considered mild or moderate, no action was taken regarding the study drug, no events resulted in discontinuation, and no events were considered related to the open-label study drug by the investigator. Subject in the OLC had a low incidence (3 subjects, 2.6%) of the AE of headache; all events were mild or moderate, no action was taken regarding the study drug, and no events resulted in discontinuation. One event of headache (for subject AN 52571) was considered possibly related to the study drug by the investigator; this event resolved while the subject continued study therapy.

#### 7.1.5.4 Common adverse event tables

The most common AE reported, associated with either metformin alone or with sitagliptin combined with metformin was diarrhea.

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**Study P024**

**Table 37. Common Adverse Events in Study P024 by treatment group, with incidence greater than 2 % in the sitagliptin treatment group, in decreasing frequency**

Adverse Event Preferred Term	Sitagliptin 100 mg N = 588		Glipizide 5 - 20 mg N = 584	
	n	%	n	%
Nasopharyngitis	73	12.41	56	9.59
Upper respiratory tract infection	70	11.9	74	12.67
Diarrhea	59	10.03	44	7.53
Urinary tract infection	38	6.46	23	3.94
Headache	37	6.29	34	5.82
Arthralgia	31	5.27	26	4.45
Hypoglycemia	31	5.27	188	32.19
Dizziness	29	4.93	18	3.08
Bronchitis	28	4.76	25	4.28
Back pain	27	4.59	27	4.62
Fatigue	27	4.59	9	1.54
Influenza	25	4.25	34	5.82
Pain in extremity	24	4.08	11	1.88
Hypertension	23	3.91	24	4.11
Nausea	23	3.91	26	4.45
Cough	22	3.74	26	4.45
Sinusitis	22	3.74	14	2.4
Blood glucose increased	17	2.89	16	2.74
Constipation	17	2.89	14	2.4
Osteoarthritis	15	2.55	5	0.86
Gastroenteritis	13	2.21	16	2.74
Edema peripheral	13	2.21	20	3.42
Alanine aminotransferase increased	12	2.04	16	2.74
Dyspepsia	12	2.04	14	2.4

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**Study P036**

**Table 38. Common Adverse Events reported in Study P036 by treatment groups, with incidence greater than 2% in the sitagliptin 50 mg / metformin 1000 mg bid group and with decreasing rate of frequency in that group**

Adverse Event Preferred Term	Sita 100		Sita 50 / Met 500 bid		Sita 50 + Met 1000 bid		OLC		Met 1000 bid		Met 500 bid		Placebo	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Diarrhea	9	5.1	15	8.2	18	10.1	11	9.4	21	17.9	11	6.2	9	5.4
URI	12	6.9	16	8.7	13	7.3	6	5.1	11	6.2	12	6.7	12	7.3
Headache	8	4.6	16	8.7	10	5.6	6	5.1	12	6.8	13	7.3	11	6.7
Nausea	3	1.7	9	4.9	10	5.6	7	6.0	15	8.5	7	3.9	4	2.4
Arthralgia	9	5.1	6	3.3	9	5.1	3	2.6	2	1.1	5	2.8	7	4.2
Back pain	11	6.3	6	3.3	8	4.5	1	0.9	7	3.9	9	5.1	6	3.6
Bronchitis	4	2.3	5	2.7	8	4.5	3	2.6	2	1.1	0	0.0	1	0.6
Nasopharyngitis	8	4.6	8	4.4	7	3.9	6	5.1	5	2.8	10	5.6	13	7.9
Vomiting	1	0.6	2	1.1	7	3.9	4	3.4	3	1.7	2	1.1	1	0.6
Influenza	10	5.7	9	4.9	6	3.4	8	6.8	11	6.2	9	5.1	4	2.4
Blood glucose increased	11	6.3	3	1.6	5	2.8	7	6.0	3	1.7	3	1.7	13	7.9
Dyspepsia	1	0.6	4	2.2	5	2.8	5	4.3	2	1.1	3	1.7	0	0.0
UTI	1	0.6	7	3.8	5	2.8	6	5.1	7	3.9	4	2.3	4	2.4
Abdominal pain	1	0.6	1	0.5	4	2.3	2	1.7	5	2.8	1	0.6	0	0.0
Hypoglycemia	5	2.9	2	1.1	4	2.3	2	1.7	6	3.4	1	0.6	6	3.6
Muscle spasms	1	0.6	1	0.5	4	2.3	4	3.4	3	1.7	7	3.9	0	0.0
Pruritus	2	1.1	1	0.5	4	2.3	1	0.9	0	0.0	1	0.6	0	0.0
Sinusitis	3	1.7	4	2.2	4	2.3	4	3.4	3	1.7	4	2.3	4	2.4

7.1.5.5 Identifying common and drug-related adverse events

**Study P024**

The incidence of drug-related clinical AEs was notably lower in the sitagliptin treatment group than in the glipizide treatment group due to the higher incidence of drug-related hypoglycemia in the glipizide treatment group. The most commonly reported drug-related clinical AEs were hypoglycemia, diarrhea, nausea, and headache. These drug-related AEs occurred commonly in 1 or 2 subjects only for each SOC classification, and occurred in multiple organ systems, not allowing us to distinguish a pattern of safety concerns. Table 39 shows the drug-related AEs that occurred more frequently in the sitagliptin-metformin group by  $\geq 1$  subject and with frequency  $\geq 2$  subjects.

**Table 39. Drug-related AEs in Study P024 more frequently reported in the sitagliptin /metformin group that occurred in more than one subject with a difference between groups of more than one subject**

	Sitagliptin N=588		Glipizide N=584	
	N	%	n	%
Constipation	7	(1.2)	4	(0.7)
Dry Mouth	2	(0.3)	0	(0.0)
Fatigue	5	(0.9)	3	(0.5)
Lung Infection and URI (combined)	2	(0.3)	0	(0.0)
Weight Decreased	4	(0.7)	0	(0.0)
Syncope Vasovagal	2	(0.3)	0	(0.0)
Hypertension	3	(0.5)	1	(0.2)

**Study P036**

Overall, incidences of drug-related AEs in the active treatment groups ranged from 6.7% (in the sitagliptin monotherapy group) to 16.5% (in the metformin 1000 mg bid group); incidence in the placebo group was 9.7%. The most commonly reported (11.0% in the metformin 1000 mg bid

and 11.5% in the sitagliptin 50 mg / metformin 1000 mg bid group) drug-related clinical AEs occurred in the Gastrointestinal Disorders SOC and included abdominal pain (including abdominal pain, abdominal discomfort, upper abdominal pain, and stomach discomfort), constipation, diarrhea, dyspepsia, and nausea.

The incidence of specific clinical AEs considered related to study drug in the OLC was similar to those in the Randomized Cohort. Specifically, the incidence of gastrointestinal-related AEs was most similar to the metformin 1000 mg bid and sitagliptin 50 mg / metformin 1000 mg bid groups.

#### 7.1.5.6 Additional analyses and explorations

Additional analyses and explorations are unnecessary given the similar rates of AEs that occurred in the groups of subjects treated with sitagliptin / metformin compared to the control groups (placebo in Study P036 and glipizide in Study P024).

#### 7.1.6 Less Common Adverse Events

This reviewer looked at the presence of specific serious events that compose the Proposed Rule for Safety Reporting Requirements for Human Drug and Biological Products, published in the Federal Register on March 14, 2003 (Volume 68, Number 50) as well as those listed in the FDA Guidance for Industry – Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics, May 2000. These are:

Congenital anomalies, acute renal failure, acute respiratory failure, sclerosing syndromes, ventricular fibrillation, pulmonary hypertension, Torsades de Pointe, pulmonary fibrosis, malignant hypertension, confirmed or suspected transmission of infectious agent by marketed product, seizure, agranulocytosis, confirmed or suspected endotoxin shock, aplastic anemia, significant hemolytic anemia, toxic epidermal necrolysis, thrombocytopenia, liver necrosis, rhabdomyolysis, acute liver failure, idiopathic thrombocytopenic purpura, anaphylaxis, and intussusception.

No subject exposed to sitagliptin in monotherapy or in combination with metformin had any of the above SAEs.

#### 7.1.7 Laboratory Findings

##### 7.1.7.1 Overview of laboratory testing in the development program

The safety laboratory testing included chemistry panel and complete blood count with differential, urinalysis, lipid panel and, when appropriate, pregnancy tests. Chemistry and CBC panels were assessed at the screening and randomization visits, as well as every 6 weeks for the first 52 weeks and generally every 8 – 10 weeks during the second year of Study P024. A similar schedule of assessments of safety laboratory parameters was enforced in Study P036. In addition, urinalyses and urine protein were assessed at regular pre-specified intervals during the studies. The frequency of assessments is appropriate to capture laboratory abnormalities and AEs in order to provide adequate safety data for the review of sitagliptin / metformin FDC.

#### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory findings from the placebo-controlled Study P020 have been reviewed under NDA 21995. New clinical laboratory data in this application comes from studies P024 and P036. These 2 studies have different designs and different control groups, so a review of the summary laboratory data from the separate studies is adequate.

The strategy proposed by the applicant in the analyses of safety laboratory data was to review the summary statistics for mean changes from baseline over time and to review the incidence of safety analyte measurements meeting specific predefined limits of change (PDLC). For each analyte the applicant selected several PDLC thresholds for analyses, from minor variations from the normal to clinically significant changes. This reviewer agrees with the proposed strategy.

#### 7.1.7.3 Standard analyses and explorations of laboratory data

##### 7.1.7.3.1 Analyses focused on measures of central tendency

##### **Study P024**

There were no significant between-group differences noted in most of the laboratory parameters assessed in Study P024. Changes from baseline to week 52 in specific analytes are reported and discussed below, as small differences were observed between the sitagliptin and the glipizide groups. These small differences are unlikely to represent clinically relevant changes, and they were noted in some of the liver enzymes (ALT, AST and alkaline phosphatase), as well as the serum hemoglobin level and absolute neutrophil count. In addition, this reviewer included summary data on serum creatinine, a parameter that has demonstrated a small mean increase in the studies reviewed under NDA 21995.

##### **Liver Function Tests**

##### *Serum transaminases*

In the sitagliptin group, a small mean decline in both AST and ALT were noted from baseline until approximately Week 18 of 1 IU/L and 2.2 IU/L, respectively. The initial small mean decline was followed by a gradual rise, which did not return to baseline concentrations by week 52. In the glipizide group, a smaller mean decline in both AST and ALT was noted until week 12, followed by a small increase in the serum concentrations of both enzymes until week 52, to levels of less than 1 IU/L above baseline. A between-group difference of approximately 2.2 IU/L was observed in ALT (from baseline values of approximately 20 IU/L in both treatment groups). A between-group difference at Week 52 of approximately 1 IU/L (from baseline values of approximately 16 IU/L).

##### *Alkaline Phosphatase*

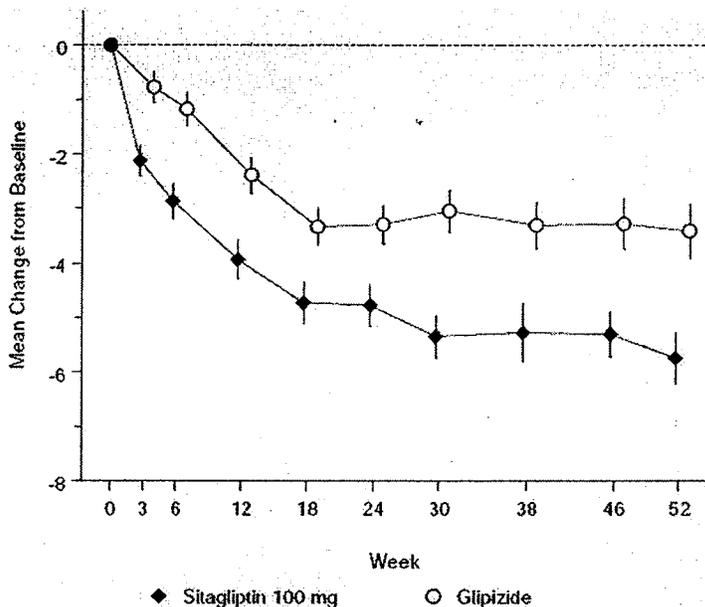
Alkaline phosphatase levels showed small declines in both treatment groups over the 52 weeks of Study P024, although the decline was more pronounced in the sitagliptin group (Table 40 and Figure 9).

**Table 40. Change from Baseline in Mean Serum Alkaline Phosphatase (IU/L) in Study P024, by treatment groups**

Treatment	N	Baseline	Week 52	Change	
		Mean (SD)	Mean (SD)	Mean (SE)	Range
Sitagliptin 100 mg	391	53.7 (16.2)	47.9 (14.8)	-5.7 (0.5)	-68.0 to 39.0
Glipizide	417	52.6 (15.1)	49.2 (15.5)	-3.4 (0.5)	-38.0 to 98.0

Adapted from the applicant's Table 2.7.4: 54 in Reference Summary of Clinical Safety

**Figure 9. Mean Change (± SE) from Baseline in Serum Alkaline Phosphatase (IU/L) in Study P024, by treatment group**



The small reduction in alkaline phosphatase was also observed in the studies of sitagliptin in monotherapy or of sitagliptin used in combination with pioglitazone, which were reviewed under NDA 21995.

A subset of subjects in both the glipizide and sitagliptin groups had bone specific alkaline phosphatase measured at baseline and at week 52. Bone specific alkaline phosphatase declined in both groups, although slightly more in the sitagliptin group, compared to the glipizide group. The small reduction in alkaline phosphatase associated with sitagliptin and glipizide is comprised of reductions in both liver and bone components. The reduction in liver alkaline phosphatase is associated with other improvements in liver-associated enzymes (e.g., ALT), perhaps related to a reduction in hepatic steatosis due to improved glycemic control. The reduction in bone specific alkaline phosphatase is likely to reflect a reduction in bone turnover that has been reported to occur with improved glycemic control.

#### Serum creatinine

This parameter is analyzed in this review document in view of the subtle but consistent changes in serum creatinine found in the studies of sitagliptin reviewed under NDA 21995, and in view of the more pronounced increase in serum creatinine in subjects with moderate degrees of renal impairment in Study P028, also reviewed under NDA 21995. The latter findings are not

applicable in the review of this NDA, since metformin is contraindicated in patients with chronic renal insufficiency, and no subjects with impaired renal function were enrolled in Study P024. Nonetheless, there were no between-group differences in serum creatinine, as shown in Table 41.

**Table 41. Change from baseline in serum creatinine (mg/dL) in Study P024**

Treatment	N	Baseline	Week 52	Change from baseline	
		Mean (SD)	Mean (SD)	Mean (SE)	Range
Sitagliptin	392	0.96 (0.15)	0.92 (0.18)	-0.04 (0.00)	-0.30 to 0.30
Glipizide	417	0.96 (0.15)	0.93 (0.18)	-0.03 (0.00)	-0.40 to 0.30

Adapted from the applicant's Table 14-41, in reference p024v1

### Complete Blood Counts

#### *Absolute Neutrophil Counts (ANC)*

Small mean increases in ANC were observed in both treatment groups in Study P024 over the 52 weeks of the study, starting at week 6, reaching a peak at week 12 and remaining relatively stable until the end of the study. The increase in mean ANC from baseline to week 52 was slightly greater in the sitagliptin group (266 cells /  $\mu$ L) compared to the glipizide group (101 cells/  $\mu$ L). This finding is also consistent with the changes in ANC observed in the sitagliptin studies reviewed under NDA 21995. These findings are unlikely to represent clinically meaningful changes and are not associated with infections.

#### *Hemoglobin*

Very small reductions in mean Hb were observed in both treatment groups over the 52 weeks of Study P024, with slightly greater reduction in the sitagliptin group (between-group difference of 0.07 g/dL) (Table 42).

**Table 42. Mean changes in serum Hb (g/dL) from baseline to week 52 in Study P024, by treatment group**

Treatment	N	Baseline	Week 52	Change from baseline	
		Mean (SD)	Mean (SD)	Mean (SE)	Range
Sitagliptin 100 mg	386	14.4 (1.2)	14.2 (1.4)	-0.2 (0.0)	-4.5 to 2.2
Glipizide	414	14.4 (1.3)	14.2 (1.4)	-0.2 (0.0)	-3.3 to 3.6

Prolonged treatment with metformin has been infrequently associated with decreased availability of Vitamin B12 and with megaloblastic anemia. Vitamin B12 serum levels were not measured during the study. However, the mean corpuscular volume, a Vitamin B12-dependent parameter of erythrocyte maturation, did not increase during the study (Table 43).

**Table 43. Change from baseline to week 52 in Mean Corpuscular Volume (fL) in Study P024**

Treatment	N	Baseline	Week 52	Change from baseline	
		Mean (SD)	Mean (SD)	Mean (SE)	Range
Sitagliptin 100 mg	386	89.5 (4.8)	88.9 (5.1)	-0.6 (0.1)	-18.3 to 5.0
Glipizide	414	89.80 (5.88)	89.63 (6.01)	-0.17 (0.11)	-13.1 to 20.4

Adapted from the applicant's Table 14-54 in reference p024v1

### Study P036

Similar to Study P024, most clinical laboratory parameters have demonstrated no between-group differences and are not reported in this document. The few analytes that have shown differences between the sitagliptin and the glipizide groups are being discussed below.

*Alkaline Phosphatase*

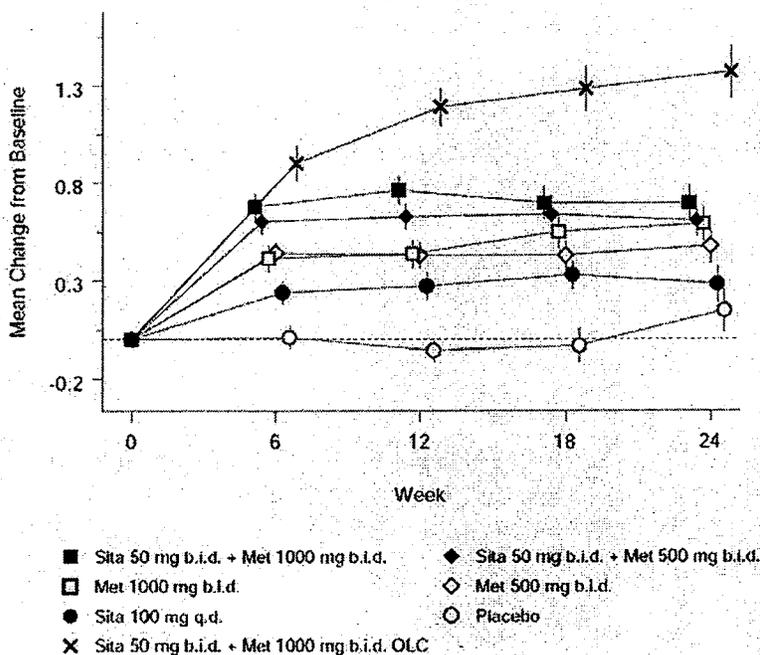
Consistent with the findings in Study P024 and with other studies of sitagliptin alone or in combination with other anti-diabetic treatments, mean serum levels of alkaline phosphatase were reported to decrease slightly over time in Study P036 in all active treatment groups (randomized cohorts and the OLC) compared to placebo, starting at week 6. The decline in alkaline phosphatase appeared to be proportional to the degree of glycemic improvement in that Study.

*Uric acid*

There was a small increase in the mean change over time in the serum uric acid levels (from baseline values of approximately 5 mg/dL) for all of the active treatment groups compared with the placebo group. Mean increases, compared with placebo, were apparent by Week 6 and remained relatively stable, within each treatment group, over time, except for the OLC, where a gradual increase in mean serum uric acid continued until Week 24 (Figure 10).

Figure 10. Mean change from baseline in serum uric acid (mg/dL) over time in Study P036

Mean Change From Baseline in Serum Uric Acid (mg/dL) Over Time (P036)  
 Mean ±SE by Treatment Group  
 Excluding Data After Initiation of Glycemic Rescue Therapy



Copied from the applicant's Figure 2.7.4.7, in reference Summary of Clinical Safety (4-Months Safety Update Report).

Four subjects (one each in the sitagliptin monotherapy, the 1000 mg bid metformin monotherapy, the sitagliptin 50 mg / metformin 1000 mg bid coadministration, and the placebo groups) had AEs of gout or gouty arthritis. All episodes were considered mild or moderate in intensity, none resulted in discontinuation, and all resolved while the subjects continued treatment with study drug. Of these 4 subjects, 2 (one each in the metformin monotherapy and one in the coadministration groups) had a medical history of gout; the latter had an AE of increased serum uric acid (prior to randomization on Day 1).

In a similar manner to the active treatment groups in the Randomized Cohort, subjects in the OLC demonstrated a small mean increase in uric acid by Week 6 of 0.9 mg/dL (from a baseline value of approximately 4.3 mg/dL) rising to a mean increase of 1.37 mg/dL at Week 24. No subject in the OLC were reported to have had an AE of gout.

It is relevant to note that the Pooled Phase 3 Studies that supported the approval of sitagliptin in monotherapy or in combination with metformin and with PPAR agonists, the mean uric acid concentrations increased slightly and early into the studies in the sitagliptin groups compared to placebo, and did not increase further until week 18 or week 24. The mean increase in both sitagliptin groups was about 0.2 mg /dL, from a baseline of approximately 5.3, compared to a mean increase of 0.02 in the placebo group. There was no observed increased incidence of AEs related to the early increase in serum uric acid levels (such as gout, hyperuricemia or laboratory AE of increased uric acid) compared to controls.

### Complete Blood Count

#### *White Blood cell count and ANC*

All active treatment groups and the OLC had increases in the number of leukocytes compared to placebo, which remained unchanged over the 24 weeks of the study. The increases were noted from week 6 with a peak at week 12, and then remained stable. Mean changes in ANC paralleled the increases observed in total leukocyte counts.

#### *Hemoglobin*

Subjects in the Randomized Cohorts demonstrated small mean decreases (up to 0.51 g/dL) from baseline in hemoglobin over 24 weeks. The sitagliptin monotherapy group was most similar to the placebo group. The greatest mean reduction compared with placebo occurred in the sitagliptin 50 mg / metformin 1000 mg bid group, with a difference from placebo of -0.39 g/dL at Week 24. At Week 24, the difference from placebo for the OLC was -0.82 g/dL. These small mean reductions in hemoglobin tended to correlate, by treatment group, with increasing improvement of glycemic parameters. Similarly to the findings in Study P024, there were no changes in the mean corpuscular volume of erythrocytes that would suggest a relative deficiency of Vitamin B12 as a consequence of treatment with metformin causing anemia.

#### *7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal*

##### **Study P024**

There were no between-group differences in the proportion of subjects who had change in specific laboratory parameters beyond those limits pre-specified in the Study P024 protocol. In particular, the pre-defined limits of change for the laboratory parameters highlighted in the section of the review above (7.1.7.3.1. Analyses focused on measures of central tendency) are listed in Table 44 below:

**Table 44. Subjects meeting pre-defined limits of change from baseline for selected laboratory parameters in Study P024**

Lab parameter	Pre-defined limit of change	Treatment	n / N (%)	% Difference with Placebo (95% CI)
Hb (g/dL)	One value with a decrease $\geq$ 1.5 g/dL	Sitagliptin	49/577 (8.5)	-0.1 (-3.4, 3.2)
		Glipizide	48/561 (8.6)	
WBC ( $10^3/\mu\text{L}$ )	One value with increase $\geq$ 20% and value > ULN	Sitagliptin	39/577 (6.8)	0.5 (-2.4, 3.4)
		Glipizide	35/561 (6.2)	
ANC ( $10^3/\mu\text{L}$ )	One value with increase $\geq$ 50% and value > ULN	Sitagliptin	14/576 (2.4)	1.4 (-0.2, 3.1)
		Glipizide	6/556 (1.1)	
Creatinine (mg/dL)	One value with increase $\geq$ 0.3 mg/dL	Sitagliptin	30/585 (5.1)	-0.8 (-3.5, 1.9)
		Glipizide	34/573 (5.9)	
AST (IU/L)	One value with increase > 300% and value > ULN	Sitagliptin	2/585 (0.3)	-0.7 (-1.9, 0.4)
		Glipizide	6/573 (1.0)	
ALT (IU/L)	One value with increase > 300% and value > ULN	Sitagliptin	4/586 (0.7)	-0.5 (-1.9, 0.7)
		Glipizide	7/573 (1.2)	

Adapted from the applicant's Table 14-59, in reference P024v1

**Study P036**

Small differences in the frequency of values meeting pre-defined limits of change criteria for WBC count, ANC, and hemoglobin in the treatment groups of the Randomized Cohort that received active study drug compared with placebo are described below. Analyses of other blood chemistry and hematology analytes revealed no clinically meaningful difference in the proportion of subjects whose values met pre-defined criteria. The same analytes for which changes meeting protocol pre-defined criteria are shown in Table 44 in Study P024 are also shown in Table 45 for study P036.

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**Table 45. Subjects meeting pre-defined limits of change from baseline for selected laboratory parameters in Study P036**

Lab parameter	Pre-defined limit of change	Treatment	n/N (%)	% Difference with Placebo (95% CI)
Hb (g/dL)	Last value with a decrease $\geq 1.5$ g/dL	Sita 100	8/171 (4.7)	1.6 (-3, 6.2)
		Met 500 bid	4/174 (2.3)	-0.8 (-5, 3.1)
		Met 1000 bid	13/173 (7.5)	4.4 (-0.6, 9.6)
		Sita 50/ Met 500 bid	7/178 (3.9)	0.8 (-3.7, 5.2)
		Sita 50 / Met 1000 bid	14/170 (8.2)	5.1 (0, 10.5)
		Placebo	5/160 (3.1)	
		OLC	23/111 (20.7)	
WBC ( $10^3/\mu\text{L}$ )	One value with increase $\geq 20\%$ and value $>$ ULN	Sita 100	16/171 (9.4)	5.6 (0.1, 11.3)
		Met 500 bid	4/174 (2.3)	-1.5 (-5.9, 2.6)
		Met 1000 bid	9/173 (5.2)	1.5 (-3.4, 6.3)
		Sita 50/ Met 500 bid	12/178 (6.7)	3.0 (-2.1, 8.1)
		Sita 50 / Met 1000 bid	14/170 (8.2)	4.5 (-0.8, 10.0)
		Placebo	6/160 (3.8)	
		OLC	11/111 (9.9)	
ANC ( $10^3/\mu\text{L}$ )	Last value with increase $\geq 20\%$ and value $>$ ULN	Sita 100	2/170 (1.2)	1.2 (-1.3, 4.2)
		Met 500 bid	0/170 (0)	0.0 (-2.4, 2.2)
		Met 1000 bid	1/172 (0.6)	0.6 (-1.8, 3.2)
		Sita 50/ Met 500 bid	2/176 (1.1)	1.1 (-1.4, 4.0)
		Sita 50 / Met 1000 bid	6/168 (3.6)	3.6 (0.5, 7.6)
		Placebo	0/158 (0)	
		OLC	2/107 (1.9)	
Creatinine (mg/dL)	One value with increase $\geq 0.3$ mg/dL	Sita 100	0/174 (0)	-0.6 (-3.3, 1.6)
		Met 500 bid	0/178 (0)	-0.6 (-3.3, 1.6)
		Met 1000 bid	0/176 (0)	-0.6 (-3.3, 1.6)
		Sita 50/ Met 500 bid	1/184 (0.5)	-0.1 (-2.8, 2.5)
		Sita 50 / Met 1000 bid	5/177 (2.8)	2.2 (-0.9, 5.9)
		Placebo	1/168 (0.6)	
		OLC	1/112 (0.9)	
AST (IU/L)	One value with increase $> 400\%$ and value $>$ ULN	Sita 100	1/174 (0.6)	0.6
		Met 500 bid	0/177 (0)	0
		Met 1000 bid	0/176 (0)	0
		Sita 50/ Met 500 bid	0/184 (0)	0
		Sita 50 / Met 1000 bid	0/177 (0)	0
		Placebo	0/168 (0)	
		OLC	0/112 (0)	
ALT (IU/L)	One value with increase $> 400\%$ and value $>$ ULN	Sita 100	1/174 (0.6)	0.6
		Met 500 bid	0/177 (0)	0
		Met 1000 bid	0/176 (0)	0
		Sita 50/ Met 500 bid	0/184 (0)	0
		Sita 50 / Met 1000 bid	0/177 (0)	0
		Placebo	0/168 (0)	
		OLC	0/112 (0)	

Adapted from the applicant's Table 14-85, reference P036v1

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

**Study P024**

**Table 46. Laboratory AEs that led to drop outs in Study P024**

Laboratory AE	Sita 100 (N=588)		Glipizide (N=584)	
	n	(%)	n	(%)
ALT increased	2/587	(0.3)	3/577	(0.5)
Alkaline Phosphatase increased	1/587	(0.2)	0/577	(0)
Blood creatinine increased	1/587	(0.2)	0/577	(0)
Blood potassium increased	1/587	(0.2)	0/577	(0)
Creatinine clearance decreased	1/585	(0.2)	1/575	(0.2)
Hemoglobin A1c increased	1/585	(0.2)	1/575	(0.2)

Adapted from the applicant's Table 14-24, in Reference p024v1

**Study P036**

**Table 47. Laboratory AEs that led to drop outs in Study P036**

Laboratory AE	Sita 100 (N=179)		Met 500 bid (N=182)		Met 1000 bid (N=182)		Sita 50 + Met 500 bid (N=190)		Sita 50 + Met 1000 bid (N=182)		Placebo (N=176)		Sita 50+ Met 1000 bid OLC (N=117)	
	N	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
AST increased	1/176	(0.6)	0/179	(0)	0/180	(0)	0/188	(0)	0/178	(0)	0/170	(0)	0/114	(0)
Blood creatinine increased	1/176	(0.6)	0/180	(0)	0/180	(0)	0/188	(0)	0/178	(0)	0/170	(0)	0/114	(0)
Blood sodium decreased	0/176	(0)	1/179	(0.6)	0/180	(0)	0/188	(0)	0/178	(0)	0/169	(0)	0/114	(0)
Creatinine clearance decreased	0/176	(0)	0/180	(0)	0/180	(0)	0/188	(0)	0/178	(0)	1/170	(0.6)	0/114	(0)

Adapted from Table 14-101 in Reference p036v1

The rates of dropouts due to laboratory AEs was very low in all groups treated in Studies P024 and P036. There is no clear indication of laboratory AEs being associated with sitagliptin and metformin coadministration, either at the higher doses or lower doses of metformin.

**7.1.7.4 Additional analyses and explorations**

No dose-dependency or time dependency are apparent in any of the laboratory findings and laboratory AE-dependent dropouts, as the rates of these AEs are low in all groups, and are not predominantly a manifestation of abnormalities in one organ or system.

**7.1.7.5 Special assessments**

There were no laboratory parameters in the review of this application that indicated a risk of toxicity associated with treatment of diabetics with the combination of sitagliptin and metformin. As this reviewer indicated previously, the development program excluded subjects with any degree of renal impairment, as this constitutes a contraindication for metformin use. Subjects with other conditions that represent a higher risk for biguanide-related lactic acidosis were also appropriately excluded from the trials.

## 7.1.8 Vital Signs

### 7.1.8.1 Overview of vital signs testing in the development program

The approach used by the applicant in monitoring vital signs was similar among the different studies and was adequate to capture variations in vital signs that could indicate safety concerns.

### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs from the placebo-controlled Study P020 have been reviewed under NDA 21995. New data on vital signs in this application comes from Studies P024 and P036. These 2 studies have different designs and different control groups, so a review of the summary vital signs data from the separate studies is adequate.

The strategy proposed by the applicant in the analyses of vital signs data was to review the summary statistics for mean changes in each vital sign from baseline during the study period and to review the incidence of vital signs assessments meeting specific predefined limits of change (PDLIC). This reviewer agrees with the proposed strategy.

### 7.1.8.3 Standard analyses and explorations of vital signs data

#### 7.1.8.3.1 *Analyses focused on measures of central tendencies*

#### **Study P036**

There were no changes in mean body temperature, respiratory rate, blood pressure or pulse rate among the treatment groups participating in Study P036 (Table 48). Small variations among treatment groups were noted in the changes in body weight from baseline to week 24: it is interesting to note that the mean placebo group lost 1 kg, while the OLC gain 1 kg, on average (Table 49). These changes were not discussed by the applicant, and cannot be explained by the review of data.

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**Table 48. Mean changes from baseline to week 24 in Vital Signs in Study P036**

Treatment Group	N	Baseline	Week 24	Change from baseline	
		Mean (SD)	Mean (SD)	Mean (SE)	Range
<b>Body Temperature (Degrees Centigrade)</b>					
Sita 100 mg qd	110	36.5 (0.4)	36.4 (0.4)	-0.1 (0)	-1.3 to 1.7
Met 500 mg bid	127	36.5 (0.5)	36.5 (0.4)	-0.0 (0)	-1.6 to 2.4
Met 1000 mg bid	135	36.5 (0.4)	36.5 (0.4)	-0.0 (0)	-1.6 to 1.4
Sita 50 mg bid + Met 500 mg bid	147	36.5 (0.4)	36.5 (0.4)	-0.0 (0)	-1.1 to 1.4
Sita 50 mg bid + Met 1000 mg bid	155	36.6 (0.4)	36.5 (0.4)	-0.1 (0)	-1.6 to 1.2
Placebo	87	36.5 (0.4)	36.5 (0.4)	-0.0 (0)	-1.1 to 0.8
Sita 50 mg bid + Met 1000 mg bid OLC	85	36.5 (0.4)	36.5 (0.4)	-0.1 (0)	-1.1 to 0.8
<b>Respiratory rate (breaths / min)</b>					
Sita 100 mg qd	111	16.6 (2.7)	16.5 (2.7)	-0.1 (0.2)	-8.0 to 6.0
Met 500 mg bid	127	16.9 (2.9)	16.8 (2.6)	-0.1 (0.3)	-10.0 to 6.0
Met 1000 mg bid	136	16.7 (3.0)	16.6 (2.7)	-0.1 (0.3)	-18.0 to 12.0
Sita 50 mg bid + Met 500 mg bid	152	16.1 (2.7)	16.3 (2.5)	0.2 (0.2)	-6.0 to 10.0
Sita 50 mg bid + Met 1000 mg bid	156	16.4 (2.9)	16.8 (2.6)	0.3 (0.2)	-12.0 to 8.0
Placebo	90	17.3 (2.7)	17.3 (2.9)	-0.0 (0.3)	-6.0 to 12.0
Sita 50 mg bid + Met 1000 mg bid OLC	86	17.3 (3.0)	17.2 (2.4)	-0.1 (0.3)	-12.0 to 6.0
<b>Diastolic BP (mm Hg)</b>					
Sita 100 mg qd	113	76.7 (9.0)	76.8 (9.6)	0.0 (0.8)	-26.0 to 19.0
Met 500 mg bid	129	77.8 (7.9)	78.6 (9.0)	0.8 (0.8)	-24.0 to 18.0
Met 1000 mg bid	138	78.0 (9.8)	77.7 (10.1)	-0.3 (0.7)	-30.0 to 18.5
Sita 50 mg bid + Met 500 mg bid	153	78.5 (8.3)	77.9 (8.5)	-0.6 (0.7)	-18.5 to 29.0
Sita 50 mg bid + Met 1000 mg bid	159	78.5 (8.6)	78.4 (8.2)	-0.1 (0.6)	-31.0 to 25.0
Placebo	91	77.6 (8.0)	78.8 (8.2)	1.1 (0.8)	-16.0 to 20.0
Sita 50 mg bid + Met 1000 mg bid OLC	88	76.1 (8.0)	76.8 (8.4)	0.8 (0.8)	-21.0 to 17.0
<b>Systolic BP (mm Hg)</b>					
Sita 100 mg qd	113	126.6 (14.2)	127.8 (13.4)	1.2 (1.2)	-36.0 to 35.0
Met 500 mg bid	129	127.1 (12.8)	128.1 (14.7)	1.0 (1.2)	-32.0 to 40.0
Met 1000 mg bid	138	129.3 (14.9)	127.8 (14.9)	-1.5 (1.2)	-58.0 to 33.0
Sita 50 mg bid + Met 500 mg bid	153	127.5 (15.6)	125.3 (13.8)	-2.2 (1.0)	-46.5 to 30.5
Sita 50 mg bid + Met 1000 mg bid	159	127.4 (14.1)	126.2 (13.6)	-1.2 (1.0)	-35.0 to 37.0
Placebo	91	125.7 (15.5)	127.2 (19.1)	1.4 (1.4)	-29.0 to 46.0
Sita 50 mg bid + Met 1000 mg bid OLC	88	123.2 (13.0)	124.6 (12.9)	1.4 (1.2)	-26.0 to 30.0
<b>Mean Arterial Pressure (mm Hg)</b>					
Sita 100 mg qd	113	93.3 (10.1)	93.8 (9.8)	0.4 (0.8)	-28.5 to 21.3
Met 500 mg bid	129	94.2 (8.5)	95.1 (9.8)	0.9 (0.8)	-26.7 to 22.7
Met 1000 mg bid	138	95.1 (10.4)	94.4 (10.7)	-0.7 (0.8)	-39.3 to 22.8
Sita 50 mg bid + Met 500 mg bid	153	94.8 (9.8)	93.7 (9.5)	-1.1 (0.7)	-22.8 to 28.0
Sita 50 mg bid + Met 1000 mg bid	159	94.8 (9.4)	94.4 (9.1)	-0.4 (0.7)	-27.0 to 29.0
Placebo	91	93.7 (9.7)	94.9 (11.0)	1.2 (0.9)	-19.7 to 24.3
Sita 50 mg bid + Met 1000 mg bid OLC	88	91.8 (8.6)	92.8 (9.0)	1.0 (0.9)	-22.7 to 20.0
<b>Pulse Rate (beats / min)</b>					
Sita 100 mg qd	113	72.7 (9.1)	73.3 (7.9)	0.6 (0.7)	-20.0 to 18.0
Met 500 mg bid	129	72.7 (9.9)	72.9 (10.4)	0.3 (0.8)	-28.0 to 24.0
Met 1000 mg bid	138	73.0 (9.7)	74.3 (9.1)	1.3 (0.8)	-24.0 to 30.0
Sita 50 mg bid + Met 500 mg bid	153	72.5 (9.2)	73.0 (9.7)	0.5 (0.7)	-21.0 to 32.0
Sita 50 mg bid + Met 1000 mg bid	159	73.7 (8.9)	75.0 (9.7)	1.3 (0.7)	-26.0 to 25.0
Placebo	91	74.5 (9.7)	74.3 (8.4)	-0.1 (1.0)	-31.0 to 28.0
Sita 50 mg bid + Met 1000 mg bid OLC	88	75.8 (10.2)	75.1 (9.6)	-0.7 (1.1)	-24.0 to 30.0

Adapted from the applicant's Tables 14-86 through 14-91, reference p036v1

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**Table 49. Mean changes in body weight from baseline to week 24 in Study P036**

Treatment Group	N	Baseline	Week 24	Change from baseline	
		Mean (SD)	Mean (SD)	Mean (SE)	Range
<b>Body weight (kg)</b>					
Sita 100 mg qd	175	85.9 (22.1)	85.9 (22.2)	0.1 (0.2)	-8.9 to 11.4
Met 500 mg bid	179	88.1 (22.0)	87.2 (21.5)	-0.9 (0.2)	-13.0 to 5.8
Met 1000 mg bid	175	89.4 (22.9)	88.3 (22.8)	-1.1 (0.2)	-13.4 to 5.7
Sita 50 mg bid + Met 500 mg bid	184	90.0 (23.3)	89.4 (23.1)	-0.6 (0.2)	-13.1 to 9.4
Sita 50 mg bid + Met 1000 mg bid	178	88.2 (21.2)	86.9 (21.0)	-1.3 (0.3)	-19.6 to 6.1
Placebo	167	90.1 (21.7)	89.2 (21.5)	-1.0 (0.2)	-14.4 to 7.0
Sita 50 mg bid + Met 1000 mg bid OLC	112	88.3 (23.9)	89.6 (24.0)	1.3 (0.3)	-5.8 to 21.2

### **Study P024**

A slight decrease in mean blood pressure parameters in the sitagliptin group occurred compared to glipizide, but the difference appeared only at the last 2 visits (weeks 46 and 52). These were not clinically significant changes (Table 50). On the other hand, mean changes in body weight were statistically (pre-defined and adequately powered analysis) and clinically significant between the sitagliptin group and glipizide group. This finding is not unexpected, since sulfonylureas are known to cause weight gain, and sitagliptin alone or in combination with metformin has been shown to be weight neutral (Table 51).

**Table 50. Mean changes from baseline to week 52 in vital signs in Study P024**

Treatment Group	N	Baseline	Week 24	Change from baseline	
		Mean (SD)	Mean (SD)	Mean (SE)	Range
<b>Systolic Blood Pressure (mm Hg)</b>					
Sitagliptin 100 mg	390	130.5 (15.0)	130.0 (14.2)	-0.4 (0.7)	-44.0 to 45.0
Glipizide	417	129.7 (13.4)	130.9 (14.4)	1.2 (0.7)	-39.0 to 40.0
<b>Diastolic Blood Pressure (mm Hg)</b>					
Sitagliptin 100 mg	390	78.4 (9.0)	78.3 (9.0)	-0.1 (0.5)	-37.0 to 30.0
Glipizide	417	78.6 (8.5)	79.4 (8.8)	0.8 (0.4)	-42.0 to 28.0
<b>Mean Arterial Pressure (mm Hg)</b>					
Sitagliptin 100 mg	390	95.8 (9.6)	95.5 (9.3)	-0.2 (0.5)	-31.0 to 28.3
Glipizide	417	95.7 (8.8)	96.6 (9.3)	0.9 (0.4)	-39.7 to 29.7
<b>Pulse Rate (beats / min)</b>					
Sitagliptin 100 mg	390	72.7 (9.7)	73.0 (9.9)	0.2 (0.5)	-26.0 to 50.0
Glipizide	417	72.7 (9.5)	73.5 (10.3)	0.8 (0.5)	-24.0 to 34.0
<b>Respiratory rate (breaths / min)</b>					
Sitagliptin 100 mg	369	16.7 (3.2)	16.6 (2.8)	-0.1 (0.2)	-20.0 to 12.0
Glipizide	393	16.2 (2.6)	16.3 (2.8)	0.0 (0.1)	-10.0 to 12.0
<b>Body Temperature (degree centigrade)</b>					
Sitagliptin 100 mg	349	36.4 (0.4)	36.4 (0.4)	-0.1 (0.0)	-1.7 to 1.3
Glipizide	371	36.4 (0.5)	36.4 (0.5)	0.0 (0.0)	-3.8 to 1.5

Adapted from the applicant's Tables 12-25 through 12-28 and 14-60 and 14-61 in reference p024v1

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**Table 51. Mean changes in body weight from baseline to week 52 in Study P024**

Body weight (kg)							
Treatment	N	Baseline	Week 52	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	389	89.4 (16.9)	88.0 (17.1)	-1.4 (0.2)	-1.5 (0.3)	(-2.0, -0.9)	<0.001
Glipizide	416	89.5 (17.1)	90.6 (17.6)	1.1 (0.2)	1.1 (0.3)	(0.5, 1.6)	<0.001
<b>Between Treatment Difference</b>		<b>Difference in LS Means (95% CI)</b>				<b>p-Value</b>	
Sitagliptin 100 mg vs. Glipizide		-2.5 (-3.1, -2.0)				<0.001	

Adapted from the applicant's Table 12-29, in reference p024v1.

#### 7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

##### **Study P024**

One subject (0.2 %) in the sitagliptin group and 2 subjects (0.3%) in the glipizide group had the clinical AE of hypotension. No other changes in vital signs resulted in shifts from normal to abnormal.

##### **Study P036**

One subject (0.5%) in the sitagliptin 50 mg / metformin 1000 mg bid had the clinical AE of hypotension. No other changes in vital signs resulted in shifts from normal to abnormal.

#### 7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no subjects discontinued due to vital signs abnormalities or marked outliers for vital sign abnormalities.

#### 7.1.8.4 Additional analyses and explorations

Not necessary.

### 7.1.9 Electrocardiograms (ECGs)

#### 7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The development program for sitagliptin phosphate, described in NDA 21995, included Study PN032 (a positive-controlled QTc study in healthy subjects), which demonstrated small mean increases (maximum 8.2 msec above a mean of 406 msec) in QTc intervals following administration of a single sitagliptin dose of 800 mg (8-fold the clinical dose of 100 mg qd). Subsequently, Phase 3

studies incorporated ECG assessments pre-dosing and 2 and 6 hours post-dosing at the final controlled study visit, which failed to demonstrate any meaningful prolongation of the QTc interval.

### 7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Under NDA 22044, ECG assessments were conducted at baseline and at weeks 24 and 52 in Study P024, and at baseline and week 24 in Study P036 and analyzed changes from baseline to these timepoints for PR, QRS, QTc and uncorrected QT intervals in the ITT population. A thorough QT study was conducted in support of approval of sitagliptin, and that study was reported under NDA 21995.

### 7.1.9.3 Standard analyses and explorations of ECG data

#### 7.1.9.3.1 Analyses focused on measures of central tendency

##### **Study P024**

There were no meaningful differences in change from baseline in QTc at Week 24 or Week 52 in the sitagliptin compared to the glipizide treatment group (Table 52). Similarly, there were no meaningful differences in the sitagliptin treatment groups compared with glipizide in mean change from baseline in other ECG intervals including PR, QRS, and uncorrected QT values (data not shown).

**Table 52. Mean Changes from baseline to weeks 24 and 52 in QTc intervals (msec) in Study P024**

Treatment	N	Baseline	On Treatment	Change from Baseline	
		Mean (SD)	Mean (SD)	Mean (SE)	Range
At week 24					
Sitagliptin 100 mg	474	416.3 (24.1)	415.1 (23.4)	-1.2 (1.0)	-105.0 to 78.0
Glipizide	476	417.1 (23.4)	416.2 (23.7)	-0.9 (1.0)	-75.0 to 107.0
At week 52					
Sitagliptin 100 mg	375	415.6 (24.2)	413.9 (23.2)	-1.7 (1.1)	-74.0 to 68.0
Glipizide	395	416.0 (22.4)	413.9 (22.8)	-2.2 (1.0)	-48.0 to 84.0

Adapted from the Applicant's Tables 12-31 and 12-32, in reference p024v1

##### **Study P036**

For the active treatment groups (including the OLC) at Week 24, there were no meaningful differences in change from baseline for QTc either compared with placebo or between-groups (Table 53). Similarly, for the active treatment groups at Week 24, there were no meaningful differences in change from baseline for other ECG intervals (including PR, QRS, and uncorrected QT).

**Table 53. Mean changes in QTc interval (msec) from baseline to week 24 in Study P036**

Treatment Group	N	Baseline	Week 24	Change from baseline	
		Mean (SD)	Mean (SD)	Mean (SE)	Range
Sita 100 mg qd	107	414.2 (23.6)	416.0 (21.6)	1.8 (1.9)	-53.0 to 53.0
Met 500 mg bid	123	411.3 (24.4)	410.9 (22.2)	-0.4 (1.6)	-62.0 to 41.0
Met 1000 mg bid	127	416.7 (28.5)	414.2 (23.5)	-2.5 (2.0)	-60.0 to 51.0
Sita 50 mg bid + Met 500 mg bid	145	410.7 (24.8)	412.3 (23.0)	1.6 (1.7)	-57.0 to 62.0
Sita 50 mg bid + Met 1000 mg bid	148	418.7 (25.9)	418.0 (22.9)	-0.7 (1.8)	-69.0 to 90.0
Placebo	85	414.4 (27.2)	417.7 (23.2)	3.2 (2.5)	-51.0 to 74.0
Sita 50 mg bid + Met 1000 mg bid OLC	83	412.6 (22.3)	411.7 (23.0)	-0.9 (2.2)	-60.0 to 46.0

Adapted from the applicant's Table 2.7.4:74, in Reference Summary of Clinical Safety

*7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal*

**Study P024**

Three subjects (0.6%) in the sitagliptin treatment group had at least one trough QTc value meeting the PDL of =500 msec. For each subject, the Week 52 value was similar to or below the baseline (randomization visit) value and <500 msec. One subject (0.2%) in the glipizide treatment group had one trough QTc value meeting the pre-defined limit of change of  $\geq 500$  msec. This subject had a QTc measurement at baseline (randomization visit) of 490 msec and a Week 24 QTc interval of 536 msec. The patient died at Week 51 (Day 357) due to an SAE experience of sudden cardiac death. (Table 54).

**Table 54. Subjects exceeding pre-defined limits of change in QTc from baseline in Study P024**

ECG parameter	Predefined Limits of Change†	Treatment	n/N (%)	% Difference with Glipizide % (95% CI)§
QTc (milliseconds)	One value $\geq 500$ msec	Sitagliptin 100 mg Glipizide	3/542 (0.6) 1/532 (0.2)	0.4 (-0.6, 1.4)
	One value with an increase $\geq 30$ msec	Sitagliptin 100 mg Glipizide	52/528 (9.8) 42/516 (8.1)	1.7 (-1.8, 5.2)
	One value with an increase $\geq 30$ msec and > gender specific ULN‡	Sitagliptin 100 mg Glipizide	35/528 (6.6) 21/516 (4.1)	2.6 (-0.2, 5.4)
	One value with an increase $\geq 60$ msec	Sitagliptin 100 mg Glipizide	7/528 (1.3) 8/516 (1.6)	-0.2 (-1.9, 1.4)
	One value with an increase $\geq 60$ msec and > gender specific ULN	Sitagliptin 100 mg Glipizide	6/528 (1.1) 6/516 (1.2)	-0.0 (-1.5, 1.4)

Copied from the applicant's Table 12-33, in Reference p024v1