CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-995

MEDICAL REVIEW

ODE Decisional Review Memorandum

Date	Monday, October 16, 2006
From	Robert J. Meyer, MD
Subject	Summary Review, Office Director
NDA/BLA # **Supp #**	21-995
Proprietary / Established (USAN) names	Januvia (sitagliptin phosphate) Tablets from Merck Laboratories
Dosage forms / strength	25, 50 and 100 mg tablets (expressed as the sitagliptin base)
Proposed Indication(s)	Januvia is indicated as an adjunct to diet and exercise to improve glycemic control in paitnets with type 2 diabetes. Januvia is indicated for: • Monotherapy • Combination therapy with metformin or PPARgamma agonists when diet and exercise plus the single agent do not provide adequate glycemic control *[Note: This is very similar to other drugs more recently approved for use in type 2 DM]*
Action:	**Approval**

1. Introduction to Memorandum

This is the first cycle review for this first in class agent. Sitagliptin phosphate is from a drug class called dipeptidyl peptidase (or DPP)-4 inhibitors. Amongst other actions, DPP-4 breaks down incretins, which are short-lived intestinal peptides released in response to food ingestion, which have an inhibitory effect on glucagon (and hence on hepatic glucose synthesis) and an enhancing effect on insulin secretion when serum glucose is elevated (not when it is normal or low). Hence agents to augment incretin activity are of considerable interest in type 2 diabetes (DM), since both insulin and incretin secretion are disregulated in that disease, yet there are still clinically functional islet cells in type 2 DM to affect with this mechanism (as opposed to type 1 DM, where sitagliptin would be largely, if not entirely, ineffective). FDA recently approved a glucagon-like peptide-1 (GLP-1) analogue, exenatide [GLP-1 is one of the incretins prolonged by DPP-4 inhibition]. However, that agent is an injection and is more targeted in its actions than a DPP-4 inhibitor, which affects other incretins, including glucose-dependent insulinotropic polypeptide (GIP). Sitagliptin, therefore, represents a new means of treating type 2 DM, a disease with many currently available treatment options, but one that is expanding in prevalence and in which satisfactory glucose control still eludes many patients.

There are relatively few controversies for this signatory review to address. The primary review team has recommended approval of this drug as safe and effective for its proposed indications. The clinical efficacy and safety data are robust in amount and

duration (though the systematic study of this drug with the full range of potential concomitant therapies is lacking, including concomitant use of insulin or sulfonylureas with sitagliptin), with acceptable dose-finding and a reasonable set of confirmatory studies. Note that there is some disagreement amongst the team on the optimal dosing of renally sufficient patients, and this will be discussed further. There is a broader issue in terms of toxicology of the DPP-4 agents under development that will be dealt with in the pharm/tox section of the memo (section 4).

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Per the primary MO review, the IND for this drug (65,495) was submitted August of 2002. There was an EOP2 meeting on June 9, 2004 that I attended. At that meeting, the FDA encouraged the inclusion of a 50 mg dose in the pivotal studies, but in fact, the sponsor chose rather to study 100 and 200 mg. The reasoning for the FDA recommendation is that there was not much additional efficacy shown in the phase 2 studies above 50 mg, yet there were dose-related tolerance issues. We felt, therefore, that if an important dose-related safety issue were to crop up in phase 3, it would be best for the company to have the data to support approval of the 50 mg dose. Merck chose not to follow this advice (more discussion on dosing follows). Note that sitagliptin has not been approved previously in other markets, so there is no foreign post-marketing data available to inform FDA decision making.

3. CMC/Microbiology/Device

3.1. General product quality considerations

This is a relatively straight forward, solid oral dosage form with immediate release characteristics. The drug has a chiral center, with no issues of chemical (or biologic) conversion. It is notable that the drug appears quite well-behaved pharmacokinetically, with all the clinical trials formulations being bioequivalent as subsequent formulations were developed, so the clinical trials results should be representative of those from the final, to-be-marketed formulation.

3.2. Facilities review/inspection

The facilities review/inspections were all satisfactory and there is an overall recommendation for approval.

3.3. Notable issues

The only notable issue is a disagreement between OCP and ONDQA on whether the proposed disintegration method is adequate to assure the quality of the product as a part of batch testing. ONDQA has ultimately deferred to OCP's recommendation for the need for dissolution testing and Merck has agreed to institute such testing post-approval.

4. Nonclinical Pharmacology/Toxicology

4.1. General nonclinical pharmacology/toxicology considerations

The preclinical review was done by Dr. Bourcier, with Dr. Davis-Bruno doing the supervisory concurrence. The preclinical testing for this drug is relatively unremarkable. The drug does show kidney and liver damage/necrosis at very high chronic doses (at > 150 of times the human exposure) in rats, but dog studies did not

show consistent toxicity patterns and 5-fold exposures in dogs for 1 year showed no significant toxicities.

4.2. Carcinogenicity

In rats, sitagliptin led to hepatic adenomas/carcinomas at high doses (62 fold above human exposures). Since the drug is not genotoxic, but is hepatotoxic, the sponsor feels this may be due to chronic hepatotoxicity. The mouse studies showed no evidence of carcinogenicity. Given the lack of genetic toxicity, these rat findings at very high multiples of human exposure, are felt to be of no significant clinical consequence, but deserve mention in labeling.

4.3. Reproductive toxicology

Reprotox studies were largely unremarkable, with only some resorption and post-implantation losses in rabbits at high human dose multiples (25x). At maternally non-toxic doses, no clear signal of teratogenicity emerged. The pregnancy category designation will therefore be category B. As with other NMEs, Merck plans to initiate a pregnancy registry to better assess maternal-fetal issues post-marketing.

4.4. Notable issues

Data from multiple DPP-4 programs, many of which are less selective to DPP-4 than sitagliptin, have shown the development of skin/vascular lesions in rhesus monkeys at relevant doses and durations of treatment. Merck has performed studies to assess this in sitagliptin and did not find any such effects at doses up to 25 fold the human dose. Merck provided some mechanistic data to suggest these skin effects are related to agents affecting other DPP subtypes (e.g., 8 and/or 9). While this vascular effect of other DPP-4 agents would raise concern about clinical relevance for diabetics (who already have both microvascular and macrovascular complications of their disease), these effects do not appear to be an issue for sitagliptin.

A second preclinical issue is that combination studies of sitagliptin with metformin (done for the combination product NDA) showed excess deaths in high dose metformin and sitagliptin, which appears most clearly related to the metformin itself. There was no excess in deaths at more relevant doses of metformin.

Lastly, it is notable that the preclinical pharmacology models for sitagliptin-mediated DPP-4 inhibition suggests that 80% inhibition of the DPP-4 enzyme is needed for a satisfactory pharmacodynamic effect. This information has relevance to the choice of dose discussed further in the next section.

5. Clinical Pharmacology/Biopharmaceutics

5.1. General – See Dr. Wei's primary review for details (Dr. Ahn did the secondary review). Sitagliptin is highly bioavailable (87%) and excreted largely unchanged in the urine, so there is little metabolism of any note. It is a substrate for p-glycoprotein. The peak serum concentration occurs at approximately 1 – 4 hours post-dose and the terminal half-life is approximately 12 hours. There is no apparent food-effect in its absorption.

5.2. Drug-drug interactions – noting that with cyclosporine (a p-glycoprotein inhibitor), there are increases in exposure to sitagliptin by only 30%, there are no remarkable DDIs, including other oral hypoglycemic agents, digoxin, warfarin and oral contraceptives.

5.3. Pathway of Elimination – being renally excreted, it is not surprising that renal impairment prolongs sitagliptin's elimination and hence exposure. This is important, given the prevalence of renal impairment in long-term DM. Dose adjustments are needed for renal impairment/failure and have been appropriately addressed by the OCP reviewers and the labeling. Hepatic impairment does not seem to be clinically important in sitagliptin's PK or dosing.

5.4. Demographic interactions/special populations – no important issues identified.

5.5. Thorough QT study or other QT assessment – Sitagliptin inhibits the hERG channel in vitro, though not at low, relevant levels. The IC_{50} is 147 microM (IC_{20} about 50 mM), with relevant human Cmax being approximately 1 microM. The canine safety pharmacology study did not show remarkable findings on cardiac intervals at many fold the human exposure, however. The sponsor did conduct a thorough QT study with a positive control of moxifloxacin 400 mg. The sitagliptin doses were 100 mg and 800 mg per day (the clinical dose and 8 times the clinical dose). The clinical dose of sitagliptin had no significant effect on cardiac intervals/QT, while both moxifloxacin and, to a lesser degree, the high dose of sitagliptin did prolong QT. The prolongation pattern with sitagliptin 800 followed serum kinetics, with a peak mean effect at approximate C_{max} of about 8 msec prolongation (compared to approximately 14 seconds with moxifloxacin). While the QT effect of the 800 mg dose is approaching a level of some clinical concern, there are very few things outside of renal failure (which has modified dosing instructions in the label) that will appreciably raise drug levels with sitagliptin. Severe renal failure only leads to about a 5 fold increase in exposure, an exposure still less than that expected from 800 mg given this drug's linear dose-proportionality. These data support that QT prolongation should not be a concern with clinically recommended doses. Even if the drug were to be given to renally impaired patients at "normal doses" inadvertently or intentionally, the expected consequences on cardiac conduction are expected to be small.

5.6. Notable issues – in multiple dose studies, 100 mg per day is needed to keep the percent DPP-4 inhibition above 80% throughout the 24-hour dosing interval, including at C_{min}. This, combined with the preclinical data suggesting the importance of 80% inhibition to clinical effect, is a part of the sponsor's rationale to focus on the 100 mg dose as the preferred dose. The OCP reviewer agrees with this assessment. Given the fact that a 100 mg dose is expected to maintain a level of drug that would lead to 80% or more inhibition of DPP-4 throughout the dosing interval and given the fact that the sponsor did not specifically instruct timing of the sitagliptin dose to meals or to morning, the dosage and administration section will not recommend a specific time for dosing either.

6. Clinical/Statistical

6.1. **General Discussion** – This drug development program was quite complete, as mentioned above and there are no major issues related to deviation from expectations. Please see Dr. Irony's primary review and Dr. Park's summary memorandum for details of the clinical program. There is a "dispute" between the statistical team's conclusions (see Drs. Pian's and Sahlroot's review) and the medical/OCP reviews on optimal dosing recommendations, but the statistical reviewer's input is largely based on a statistical finding from the phase 2 study and does not take into account other

information. I believe 100 mg once daily is an appropriate recommended dose. Whether 50 mg would have worked as well in replicate studies is an unknown, but with no overriding safety issues to limit dosing and with theoretic reasons (based on PD assessments) for the 100 mg dose, I believe the sponsor has provided adequate support for this proposed dosing.

6.2. Efficacy

6.2.1. Dose identification/selection and limitations – as above, this area of sitagliptin has led to disparate recommendations of the review team. There were two main phase 2 studies (P010 and P014). P010 was a 12 week study of 5, 12.5, 25 and 50 mg BID (total daily doses of 10, 25, 50 and 100) of sitagliptin with a positive control of glipizide. P014 examined 12 weeks of therapy with 25, 50, 100 mg QD and 50 mg BID. These data show a dose related increase in effects on HgbA1c up to 50 mg QD, with no further gain in efficacy at 100 mg QD or 50 mg BID. Therefore, there is not a clear statistical rationale for dosing higher and in fact, this was noted by FDA at the EOP2 meeting. Merck was warned that if untoward dose-related safety issues were found, their strategy of only examining 100 mg and 200 mg daily in phase 3 could be risky. However, Merck went forward with these doses, in part presumably based on modeling of DPP-4 inhibition and serum concentrations, and no untoward events are seen. The clinical team and OCP team feels the 100 mg daily dose for patients with full renal function is appropriate and I agree with them.

6.2.2. Phase 3/essential clinical studies, including design and analytic features
The sponsor conducted 4 phase 3 trials, 2 as monotherapy (one 24 weeks, one 12 weeks – both examining 100 and 200 mg) and 2 trials as add-on therapy, one for metformin and one for pioglitizone (as a demonstration for coadministration with PPARs in general), both add-on studies were of 100 mg only. The details of these studies can be found in the medical officer's and stastical reviewer's reviews, but these studies showed consistent efficacy for the 100 mg dose with approximately 0.5 – 0.6 % mean absolute lowering of HgbA1c irrespective of monotherapy or add-on. (Note that glipizide showed a mean effect of about 1.0% lowering in the phase 2 study.) The 200 mg dose did not show a clinical advantage on this endpoint. Secondary endpoints also supported evidence of efficacy.

Secondary assessments in the efficacy trials were numerous and typical of agents for type 2 DM, including effects on fasting plasma glucose, post-prandial glucose excursions, serum fructosamine and need for rescue glycemic therapy. These secondary endpoints generally supported efficacy in a pattern not inconsistent with the primary endpoint.

Given the clinically advantageous effects of the GLP-1 analogue – exenatide – on weight and appetite, these parameters were assessed in the clinical trials for sitagliptin. However, unlike exenatide, there does not seem to be a meaningful effect of sitagliptin on either satiety and weight. On the other hand, since some agents for type 2 DM appear to increase weight (irrespective of effects in some in causing edema), a neutral effect is not itself a negative, as further weight gain in type 2 DM is not helpful in controlling the underlying pathophysiology.

Finally, the assessment of efficacy by demographic subpopulations, while not always definitive due to low numbers of some ethnic groups, does not suggest any notable differences in response by gender, age or race for sitagliptin either as monotherapy or in combination.

6.2.3. Other efficacy studies – a study of reduced dosing strategies in renally impaired patients showed similar magnitude reductions in HgbA1c compared to renally sufficient patients given 100 mg daily. This study, along with the PK data in the impaired population, establishes the support for the proposed dosing recommendations for renal impairment in the labeling.

6.2.4. Both the medical and statistical team support approval based on robust data showing evidence of efficacy with sitagliptin and I agree with their recommendations.

6.2.5. Pediatric use/PREA waivers/deferrals

Pediatric studies were, appropriately, not initially done with sitagliptin until safety and efficacy were better examined in adults. The population down to age 11 will need to be studied clinically. Ages 10 and below are generally waived for drugs targeting type 2 DM due to the relatively few numbers of children with type 2 DM in this age range. The conduct of the studies in 11 to 17 year olds will be a required phase 4 commitment under PREA.

6.2.6. Notable issues – no additional issues, other than those discussed above.

6.3. Safety

6.3.1. General safety considerations

The safety database was reasonably sized, with over 2650 patients exposed in total, and approximately 2400 patients exposed to 100 mg or higher in phase 3 studies. For longer term exposures, 444 subjects were treated with sitagliptin at 100 mg or higher for at least 365 days, with some data out to beyond two years (164 patients). With this database, there is no clear signal of concern. Common AEs that were numerically higher with sitagliptin compared to placebo include nasopharyngitis, nausea, vomiting, diarrhea and arthralgias. Importantly, the rate of hypoglycemia, which one would predict would be low given the incretin's glucose dependant effects on the beta cells, was indeed low with only a mild increase relative to placebo (1.2% overall compared to 0.9% with placebo).

Twelve deaths were seen in phase 2 and 3 studies, with 10 of these being cardiovascular deaths. Of these 10, 7 patients were receiving sitagliptin, 3 were not on drug but in the run-in period, and 2 were on glipizide. Factoring in time of exposure and numbers of patients exposed to sitagliptin vs. controls, there is no clear signal of concern here. The rate of serious cardiac AEs in the long-term safety data showed the number of patients experiencing such AEs being numerically lower with sitagliptin than the non-exposed patients (1.2% vs. 2.6%). Otherwise, the safety findings were relatively benign.

One notable issue is the effect of sitagliptin on serum creatinine levels. There is a small, dose-related mean increase in serum creatinine out to week 24 in subjects given sitagliptin that seems isolated (i.e., not reflected by other indicators of renal disease). These changes amount to very small deviations (about 0.01 to 0.03 mg/dL above placebo), but are fairly consistent. The

sponsor feels that this is not a result of toxicity, but rather due to altered creatinine excretion due to the tubular handling of the drug, similar to what is seen with cimetidine. This supposition seems plausible and consistent with the observations and pharmacology (and the preclinical renal toxicity, which only showed pathologic renal changes at very high multiples above human exposure in a single species). While there is no signal of overt clinical renal toxicity and many patients with prespecified "notable" creatinine rises spontaneously resolved while continuing on drugs, the sponsor has not rigorously established this purported mechanism to explain the small, dose related changes in creatinine either. Specifically, direct assessment of GFR has not been conducted. The character of all the available renal data does not suggest a significant cause for concern, nonetheless, this issue will deserve some tracking and further assessment post-approval.

6.3.2. Discussion of primary and secondary reviewers' comments and conclusions
The primary and secondary reviewers feel the safety database is adequate and the findings allow for a favorable risk-benefit determination. I agree with this assessment.

6.3.3. Notable issues - none

6.4. Clinical Microbiology *(where relevant)*

Not relevant

7. **Advisory Committee Meeting**

No AC was scheduled or held due to the fact that, while this is an NME of a new class, this mechanism of action has in fact been the target of therapy (exenatide) and this drug present no daunting efficacy or safety issues requiring advisory committee deliberation, considering the resources needed to conduct such a meeting.

8. **Risk Minimization Action Plan *(where relevant)***

8.1. No specific RiskMAP is needed for Januvia at this time, since no outstanding risks necessitating specific management have been identified in the pre-marketing database.

9. **Other Regulatory Issues**

9.1. Application Integrity Policy (AIP) – no outstanding issues

9.2. Exclusivity/patent issues – no outstanding issues

10. **Financial Disclosure** – No issues, see Dr. Irony's review for details.

11. **Labeling**

11.1. Proprietary name – The division has disagreed with the DMETs assessment that Januvia represents a substantial risk for confusion with Tarceva when written out in script (these two drugs do have overlapping dosage strengths). The division feels that the likelihood of confusion is low, since the directions for use differ and due to inherent differences in the spelling and therefore find Januvia acceptable. I agree with the Division on this. I would note further that the likely extreme differential in price (Tarceva is very expensive) and indication would make the chances of Tarceva being dispensed for a Januvia prescription

quite low. Since the drug does not cause hypoglycemia in normal patients, Januvia dispensed for Tarceva would not be of important short-term consequence (although clearly an oncologic patient prescribed Tarceva would need their drug properly dispensed in the long-run).

11.2. Physician labeling – No major issues. The sponsor was requested to submit in PLR format and they did so.

11.3. Carton and immediate container labels

One issue that arose with the labeling, particularly for these portions of labeling, is how to represent the milligram strength. The established name of the product is sitagliptin phosphate, so the dosage strength would most correctly be in total milligrams of the drug substance as the salt (not as the base, which is the case for the 100 mg designation). I believe there are a number of ways to address this, but clearly the labeling of Januvia Tablets (sitagliptin phosphate) 100 mg is incorrect and should not be allowed without some clarification. This will be resolved with ONDQA taking the lead.

11.4. Patient labeling/Medication guide – none planned

12. DSI Audits

These audits were done and showed no evidence of data integrity issues or systematic study conduct issues (see Dr. Irony's review and DSI report for details).

13. Conclusions and Recommendations

13.1. Regulatory action

Like most recent therapies for DM, this drug will be approved on the basis of a very well accepted and characterized surrogate for improved outcomes – the HgbA1c. This endpoint essentially integrates glycemic control over time and lowering of HgbA1c has been shown repeatedly to predict better outcomes of microvascular and even macrovascular complications in DM, both type 1 and 2. However, as it is a surrogate, it is incumbent on the FDA to assure that the safety database is robust and relatively clean of serious concerns that would make the value of this surrogate questionable. I believe that Merck has presented such a safety database for sitagliptin (both preclinical and clinical). While the drug has a fairly modest effect on HgbA1c lowering, it is additive to metphormin or a PPAR agent and the drug does not appear to have significant adverse effects of concern, including weight gain. Overall, I find the efficacy and safety data compelling for approval without a specific Risk MAP being needed.

13.2. Safety concerns to be followed postmarketing

The one concern that deserves some monitoring post-approval, but not an active intervention, is the issue of the creatinine rise seen in the clinical studies. I understand the sponsor's argument that this is likely related to tubular secretion alterations, but I don't think we can definitively say there is no reason to give this further attention or thought. The sponsor does have ongoing studies that will further clarify this effect. It is important to realize, however, that periodic monitoring of renal function is recommended in patients on sitagliptin because

of the need to dose titrate for any significant reductions in renal function, which is, unfortunately, a common consequence of advancing DM. So, presumably, if this labeling advice is followed (and good care of DM patients would argue for periodic monitoring of kidney function), there may be additional sensitivity to detect any unanticipated untoward effects of sitagliptin on renal function in the larger population of use.

13.3. Risk Minimization Action Plan, if any - None

13.4. Postmarketing studies *(rationale, questions to be addressed)*

13.4.1. Required studies – Pediatric safety and efficacy studies in ages 11 and above will be needed to fulfill PREA. These may be conducted under a written request, as appropriate.

13.4.2. Commitments (PMCs)

The sponsor will need to commit to study this drug with other likely concomitant antidiabetic agents in type 2 patients, including insulin and insulin secretagogues, including the sulfonylurea agents. The main concern here would be to demonstrate safety (e.g., no unreasonable potentiation of hypoglycemic effects), as well as to demonstrate added efficacy from such combination therapy. A study of concomitant sulfonylurea treatment with sitagliptin has been recently completed and the commitment for this combination therefore will really be a commitment for timely reporting of these data (as an efficacy supplement).

13.4.3. Other agreements

None

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/s/

Robert Meyer
10/16/2006 09:18:05 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

DIVISION DIRECTOR'S MEMO

NDA #	21-995
Drug name	Januvia® (sitagliptin phosphate) - dipeptidyl peptidase IV inhibitor
Formulation and Dosage Strengths	25, 50, and 100 mg tablets
Sponsor	Merck Laboratories
Indication	Treatment of Type 2 diabetes mellitus as monotherapy as combination therapy with metformin or a PPAR-gamma agonist
Date of submission	December 16, 2005
Date review completed	October 13, 2006
Primary medical reviewer	Ilan Irony, MD

I. CLINICAL SUMMARY

A. Background and Product Description

Januvia® (sitagliptin phosphate), hereafter referred to as sitagliptin in this memo, is an inhibitor of the serine protease, dipeptidyl peptidase IV (DPP-IV), which is the enzyme responsible for the metabolism of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).

Incretin hormones are gastrointestinal hormones which increase insulin secretion in response to food ingestion. These hormones contribute to the control of postprandial glucose excursions, and their actions are dependent upon the level of plasma glucose. As opposed to other anti-diabetic therapies that stimulate pancreatic insulin release regardless of plasma glucose levels, this glucose-dependent effect of incretin hormones provides an internal safeguard against hypoglycemia. The release of incretin hormones in response to meal ingestion is illustrated in studies comparing insulin secretion after an oral glucose load versus an intravenous glucose load, with a larger insulin response observed in the former study condition. Studies comparing the incretin-mediated release of pancreatic hormones in Type 2 diabetics versus non-diabetics show a decreased incretin effect in patients with T2DM suggesting a deficiency or defective incretin effect contributing to the poor glycemic control over time in these patients.

In addition to enhanced postprandial insulin release, incretin hormones reduce glucagon release from pancreatic alpha cells thereby reducing hepatic glucose production. Again, this effect of incretin hormones is glucose-dependent such that under normoglycemic or more importantly, hypoglycemic conditions, the counter-regulatory response of glucagon release is not impaired. Finally, GLP-1 has

effects on food intake and gastric emptying as observed in clinical studies in which intravenous infusions of GLP-1 have shown reduced appetite and enhanced satiety.

GLP-1 is a product of the glucagon gene, expressed both in pancreatic alpha cells and in specialized intestinal endocrine cells called L cells, located in the lower small intestine and colon. Proglucagon is cleaved primarily to glucagon in alpha cells and to GLP-1 in the L cells. GIP is produced by K cells from the upper small intestine. Both these hormones are rapidly metabolized by DPP-IV, resulting in a half-life of only 1 to 2 minutes. Therapeutic use of native incretin hormones would therefore require continuous infusion or frequent injections, presenting practical challenges to their clinical use. The recently approved exenatide or Byetta® is a 34-amino acid GLP-1 analogue produced in the saliva of the Gila monster lizard. Exenatide has 53% homology with human GLP-1 but retains agonistic activity at the GLP-1 receptor. It is naturally resistant to DPP-IV allowing for a half-life of approximately 4 hrs. It is approved for the treatment of Type 2 diabetes in combination with metformin or sulfonylureas and is available as twice daily subcutaneous injections.

Inhibiting DPP-IV represents another measure in which to improve glycemic control through prolonging the half-life of endogenous incretin hormones and their effects. In the sitagliptin clinical development program, the applicant investigated whether prolonging the effect of endogenous GLP-1 and GIP activity through DPP-IV inhibition would enable its use as monotherapy or in combination with a PPAR-gamma agonist or metformin in the treatment of Type 2 diabetes mellitus.

B. Summary of Clinical Development Program

Please see Tables 5 and 6 from Dr. Irony's review for a summary of the Clinical Studies conducted in support of this NDA.

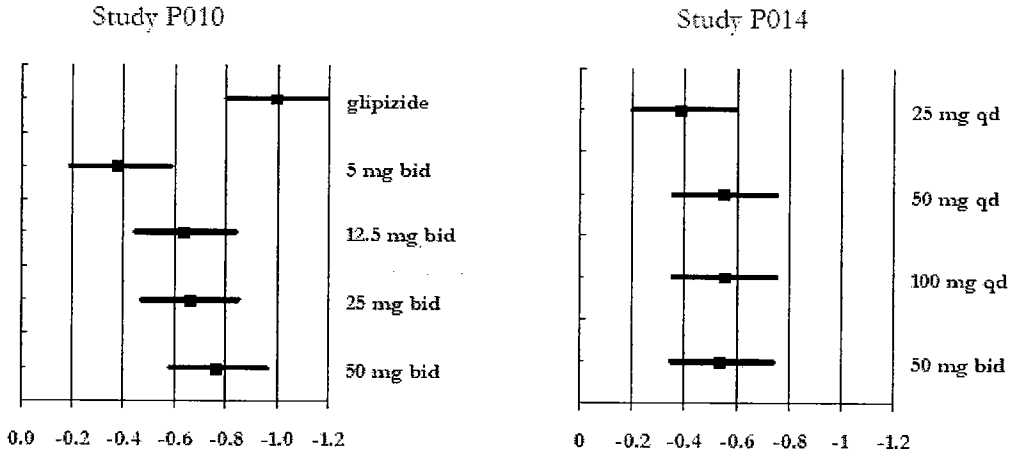
B1. Phase 1 and 2 Programs

Phase 1 studies have been reviewed by Drs. Wei and Bhattaram from the Office of Clinical Pharmacology. Key findings from these studies are summarized under the Clinical Pharmacology section of this memo.

Three Phase 2 dose-finding studies were conducted which evaluated sitagliptin 5, 12.5, 25, 50, and 100 mg administered as single or divided doses. These studies were placebo-controlled (one study included glipizide as an active control group) and were 12 weeks in duration; two of them have a 40-week extension period that is currently on-going. The results of these studies are discussed under Section 5.3 of Dr. Irony's review and Section 3.1.5 of Dr. Pian's statistical review. These studies demonstrated that there was no difference in efficacy with bid versus qd dosing of sitagliptin thereby supporting the applicant's recommendation for once-daily dosing. Daily doses of 25, 50, and 100 mg lowered HbA1c significantly compared to placebo.

Dr. Pian noted that there did not appear to be significant differences in efficacy between the 50 mg and 100 mg daily doses as illustrated in the following figure obtained from her review.

Figure 34 LSM Difference from Placebo (95% CI) – Phase 2 Studies



Nevertheless, the applicant evaluated only the 100 mg and 200 mg once daily doses in their Phase 3 program, despite advice at the EOP2 meeting that they focus on the 100 mg and 50 mg dosing in phase 3, due to theoretic concerns over potential dose-related serious toxicities.

The applicant conducted one study in a special population of type 2 diabetic patients with varying degrees of chronic renal impairment. Study 028 was a 12-week, double-blind, placebo-controlled study evaluating two lower doses of sitagliptin in patients with moderate (CrCl ≥30 to <50 mL/min), severe (<30 mL/min), or ESRD (on dialysis). Patients were eligible if they had the following baseline HbA1c values:

- not receiving AHA or on AHA prior to study with HbA1c ≥ 6.5% to ≤ 10%
- stable insulin monotherapy with HbA1c ≥ 7.5% and ≤ 10%

Patients were randomized to receive sitagliptin or placebo and were further stratified based on renal impairment. Patients with moderate renal insufficiency received either placebo or sitagliptin 50 mg daily while those with severe renal impairment or were on dialysis received placebo or sitagliptin 25 mg daily.

Efficacy was analyzed in all patients with no imputation for missing data. Efficacy at the two dose groups were combined as summarized in the following table obtained from the applicant's study report.

Analysis of Change From Baseline in HbA1c (%) at Week 12
All-Patients-as-Treated Population

Treatment	N	Mean (SD)		Change from Baseline	
		Baseline	Week 12	Mean (SE)	95% CI for Mean
MK-0431	55	7.60 (0.95)	7.01 (0.83)	-0.59 (0.08)	(-0.76, -0.42)
Placebo	25	7.81 (0.90)	7.63 (1.05)	-0.18 (0.13)	(-0.44, 0.08)

Between Treatment Difference	Difference in Means (95% CI)
MK-0431 vs. Placebo	-0.41 (-0.71, -0.11)

CI=Confidence Interval; SD=Standard Deviation; SE=Standard Error.

Data Source: [16.4.2.4]

B2. Phase 3 Program

Monotherapy
Two Phase 3 studies were conducted to support an indication for the monotherapy use of sitagliptin in T2DM. These two studies are briefly summarized in the following table:

Phase 3 Monotherapy Studies

Study No.	Design	Duration	Doses	Extension Phase
P021	multicenter, double-blind, randomized, placebo-controlled, parallel treatment	24 weeks	100 mg and 200 mg	80-wk, single-blind, uncontrolled treatment period – *ongoing*
P023	multicenter, double-blind, randomized, placebo-controlled, parallel treatment	18 weeks	100 mg and 200 mg	36-wk, double-blind, active-controlled treatment period – *ongoing*

Both studies P021 and P023 had a 1-week screening period and a diet run-in period that could last up to 12 weeks, depending upon whether the patients were naïve to drug treatment or required wash-out of current oral anti-diabetic therapy. Patients had to have had a HbA1c $\geq$ 7% and $\leq$ 10% while off any anti-diabetic therapy for at least 8 weeks. Patients with a HbA1c > 10% at the screening visit were considered eligible for study enrollment if the investigator expected this value to fall within a lower range during the diet/exercise run-in period.

In the extension phase of P021, patients assigned to placebo originally were re-randomized to sitagliptin 100 mg or 200 mg daily while those originally assigned to sitagliptin 100 or 200 mg daily remained on these treatments. In the extension phase of P023, patients assigned to placebo originally were switched to pioglitazone 30 mg daily while those originally assigned to sitagliptin 100 mg or 200 mg daily remained on these treatments. Any patient requiring glycemic rescue therapy during the first phase of the study was excluded from the extension phase.

Combination Therapy
This applicant is also seeking an indication for the combined use of sitagliptin with metformin or a PPAR-gamma agonist for the treatment of patients with T2DM who are not adequately controlled with either drugs administered as a single agent. Two Phase 3 studies were conducted in support of this indication. Study P020 evaluated combination therapy with metformin and Study P019 evaluated combination therapy with pioglitazone. Similar to the monotherapy study designs, studies evaluating combination therapy employed extensive screening and run-in periods that varied depending upon previous anti-diabetic therapies and screening HbA1c levels. Only the 100 mg daily dose of sitagliptin was evaluated in the combination trials.

<u>Study P020 - Combination with Metformin</u>
This was a 24-week, randomized, double-blind, placebo-controlled study in patients who had been on a stable dose of metformin (at least 1500 mg daily) with a HbA1c level between 7 and 10%. A metformin dose-stabilization/titration run-in period was allowed for patients not on metformin, on metformin but not meeting the entry criteria, or were on another oral agent. Patients were randomized in a 2:1 fashion to receive either sitagliptin 100 mg daily or placebo. After 24 weeks, patients assigned to placebo were

switched to glipizide while those patients originally assigned to sitagliptin remained on this therapy for an extension period that was 80 weeks in duration. Rescue therapy with pioglitazone was allowed if protocol-specified thresholds defining poor glycemic control were met by any patient.

Study P019 - Combination with Pioglitazone
This was a 24-week, randomized, double-blind, placebo-controlled study in patients who were on either pioglitazone 30 or 45 mg daily and had a HbA1c of 7 to 10%. A pioglitazone dose-stabilization/titration run-in period was allowed for patients not on any anti-diabetic therapy or if on pioglitazone and not meeting entry criteria. Patients were randomized in a 1:1 fashion to receive either sitagliptin 100 mg daily or placebo. Rescue therapy with metformin was allowed if protocol-specified thresholds defining poor glycemic control were met by any patient.

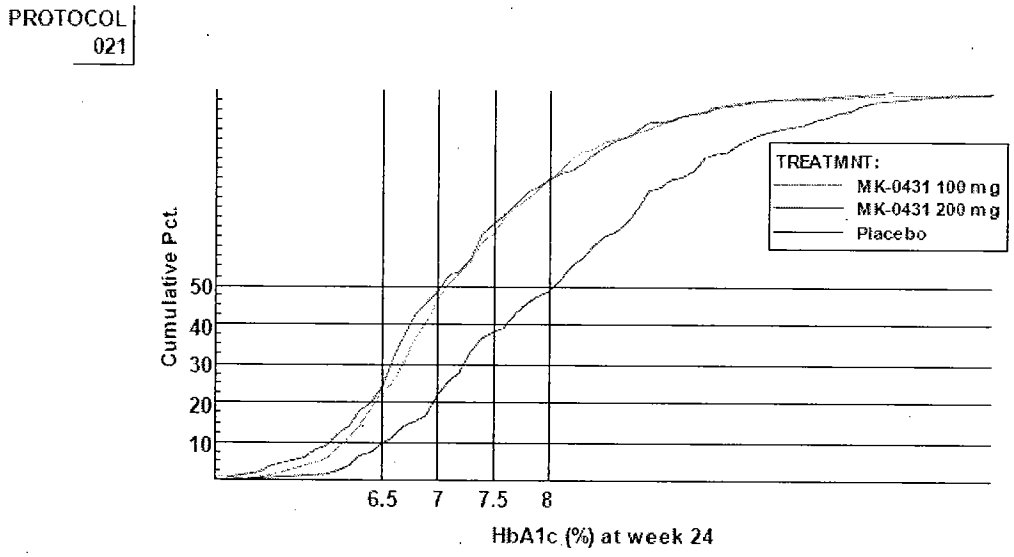
C. Clinical Efficacy Findings
In all studies, change in mean HbA1c from baseline at study endpoint was the primary efficacy variable. The primary analysis was conducted on the modified-ITT population which was defined as all randomized patients who had a baseline and at least one post-randomization HbA1c measurement. Missing values were imputed by LOCF and for patients requiring rescue treatment with another anti-diabetic agent, the HbA1c value prior to rescue therapy was carried forward in the analysis. Dr. Irony has summarized the secondary efficacy variables and the results in his review.

Monotherapy
A total of 741 patients were randomized to P021, of which 711(96% of randomized) were included in the ITT analysis. A total of 521 patients were randomized to P023, of which 495 were included in the ITT analysis. Baseline demographics and characteristics were similar across treatment groups in both of these studies. The mean age of randomized subjects was 54.2 and 55.1 years in P021 and P023, respectively. The mean duration of diabetes was approximately 4.4/4.5 years and the mean baseline HbA1c was 8.0/8.1% in these two studies. See Tables 14 and 15 from Dr. Irony's review for a more comprehensive summary of baseline demographics and characteristics in P021 and P023.

Sitagliptin 100 mg and 200 mg daily doses lowered HbA1c significantly compared to placebo; however, the two monotherapy studies gave disparate results with respect to a dose-response and the magnitude of efficacy. In Study P021, the 24-week study, a clear dose response was observed between the 100 and 200-mg doses with the least square mean difference from placebo being -0.79 in the 100 mg dose group and -0.94 in the 200 mg dose group. In contrast, in Study P023, the 18-week study, the 200 mg dose group had lower efficacy than the 100 mg dose group and in both groups, the placebo-subtracted treatment effect was lower than observed in P021. The LSM difference from placebo was -0.60 and -0.48 for the 100 and 200 mg doses, respectively, in P023.

The applicant is proposing the maximum daily dose for approval to be 100 mg. Given the absence of consistent further improvement in HbA1c reduction with higher doses, I agree with the applicant that there is insufficient evidence to recommend treatment at doses beyond 100 mg daily. In addition, Dr. Pian's review includes a cumulative distribution plot for HbA1c at Week 24 in Study 021 (see below) which shows nearly super-imposable effects of the 100 and 200 mg daily dose groups with respect to achieving selected HbA1c cut-points.

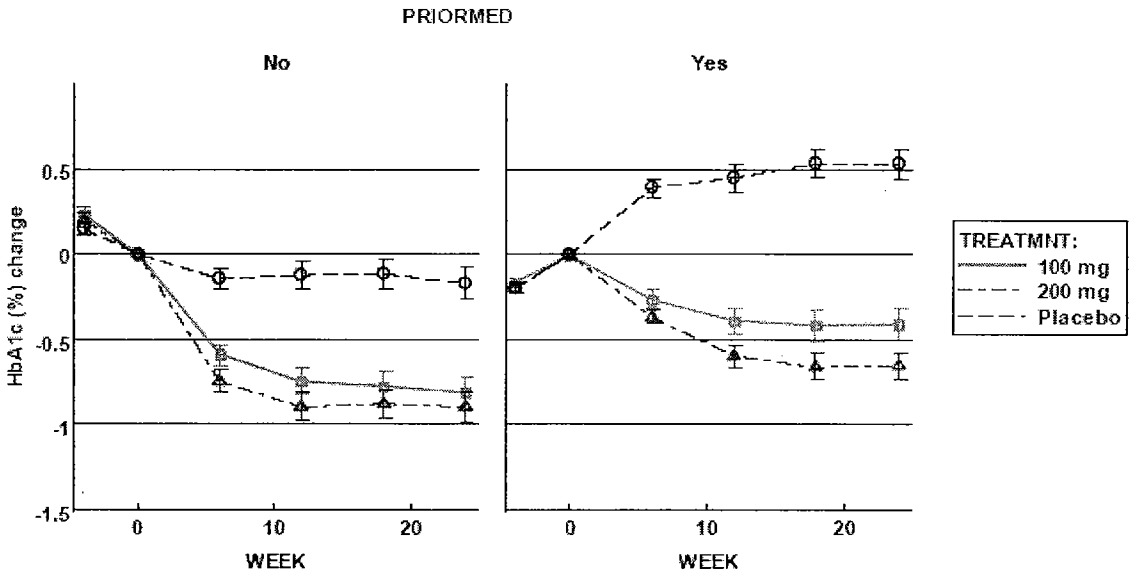
Figure 10 Cumulative distribution functions: HbA_{1c} (%) at week 24



In both studies, an interaction between baseline HbA1c and prior treatment with anti-diabetic therapy with efficacy of treatment was observed. Treatment difference between drug and placebo increased with increasing baseline HbA1c; however, this finding was not consistently observed in all studies. Patients without prior use of anti-diabetic therapy had a greater magnitude of HbA1c reduction but the treatment difference compared to placebo was not increased. On the contrary, the treatment difference was slightly higher in the subgroup of previously treated patients which may reflect the worsening glycemic control in the placebo-assigned patients as they were taken off prior therapies.

From Dr. Pian's review, the following figure compares treatment effects by prior use of anti-diabetic therapy(ies).

Appears This Way
On Original



Combination with Metformin
A total of 701 patients were randomized to Study P020: 464 received sitagliptin 100 mg daily and 237 received placebo. Six hundred seventy-seven (96.6%) were included in the MITT analysis. The mean age of the randomized population was 54.5 years; 57.1% were males; and the mean duration of diabetes was 6.2 years with a mean HbA1c of 8.0%.

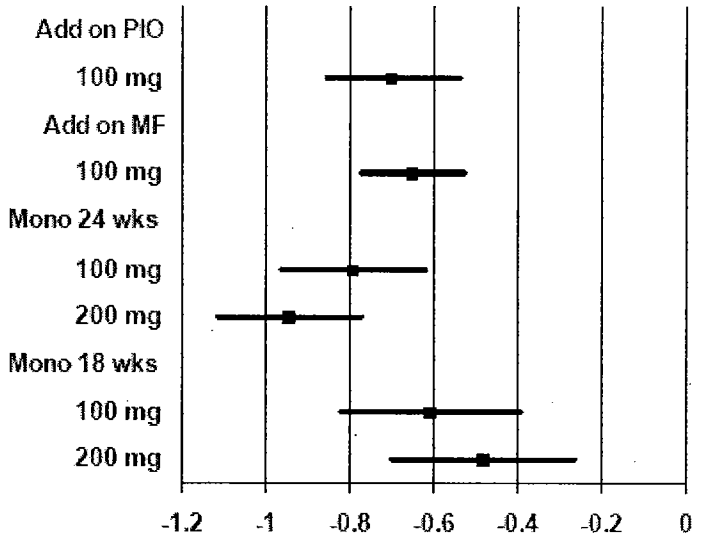
Sitagliptin 100 mg daily added onto metformin in Type 2 diabetics who have not achieved adequate glycemic control resulted in greater HbA1c reduction than placebo. The LSM difference from placebo was -0.65 ($p<0.001$).

Combination with Pioglitazone
A total of 353 patients were randomized to sitagliptin 100 mg plus pio 30/45 (n=175) or placebo plus pio 30/45 (n=178). Three hundred thirty-seven (95.5%) were included in the MITT analysis. The mean age was 56.2 years; 55.5% of the cohort was male. Mean baseline HbA1c was 8.0% with an average duration of diabetes of 6.1 years.

Sitagliptin 100 mg daily added onto pioglitazone in Type 2 diabetics who have not achieved adequate glycemic control resulted in greater HbA1c reduction than placebo. The LSM difference from placebo was -0.70 ($p<0.001$).

Conclusions on Efficacy
Sitagliptin 100 mg once daily achieved significant reductions in HbA1c when used as monotherapy or as add-on to metformin or pioglitazone in patients with Type 2 diabetes mellitus. The following figure from Dr. Pian's review summarizes the mean difference between sitagliptin treatmeng groups and placebo across the different Phase 3 trials.

Figure 1 LSM difference (C.I.) between MK-0431 and placebo by study - APT



In all the studies, a reduction in HbA1c was observed with the earliest time point of assessment (6 weeks) and sustained for the duration of the double-blind treatment (18 to 24 weeks).

Significant reductions in fasting plasma glucose and post-prandial glucose levels were also observed. There were no clinically meaningful changes in lipid parameters and no significant difference in these changes when compared to placebo. Unlike exenatide, which had an effect on weight reduction, treatment with sitagliptin did not result in any clinically meaningful reductions in weight nor did it contribute further to weight gain observed with a PPAR-gamma agonist.

Improvements in HbA1c associated with sitagliptin therapy were not affected by gender, age, race, or baseline BMI.

D. Clinical Safety Findings

Dr. Irony has extensively summarized the safety program under Section 7 of the primary medical review. Both he and the applicant categorized the safety population into the Pooled Phase 3 population, which was comprised of patients in common dose groups from four Phase 3 studies (P019, P020, P021, and P023), and the Pooled Long-term Safety Population. This memo will only highlight any clinically relevant findings that merit further study or discussion in labeling.

Drug Exposure

A total of 2719 patients were exposed to sitagliptin: 1116 in the Phase 2 program at doses ranging from 10 to 100 mg per day and 1538 in the Phase 3 program at 100 mg or 200 mg per day. In addition, 65 patients with varying degrees of chronic renal impairement were exposed to doses of 25 or 50 mg per day. The following table summarizes the average duration of exposure by dose in the completed periods of the Phase 3 monotherapy program. (Note: some patients took more than one of the assigned doses hence a few were exposed to doses > 200 mg/day)

Number of Patients on Study Drug by Dose and Actual Duration of Treatment
MK-0431 Pooled Phase III Monotherapy Studies (P021 and P023 Phase A)
Excluding Data After Initiation of Glycemic Rescue Therapy

MK-0431	<2 weeks	>=2 weeks to <6 weeks	>=6 weeks to <12 weeks	>=12 weeks to <16 weeks	>=16 weeks to <22 weeks	>=22 weeks	Total	Range of Days on Drug	Mean Number of Days on Drug
ANY DOSE	12	32	47	31	380	397	899	1 to 189	134.8
100 mg	25	10	19	15	199	192	460	1 to 183	130.7
200 mg	23	22	29	17	179	205	475	1 to 189	128.6
300 mg	4	0	0	0	0	0	4	1 to 2	1.3
400 mg	7	0	0	0	0	0	7	1 to 2	1.3

Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row.

Similarly, in the completed double-blind treatment periods of the combination trials, 464 patients received sitagliptin in combination with metformin. Of these, 397 received combination therapy for ≥ 22 weeks and the mean duration of exposure was 157.8 days. One hundred seventy-five patients received sitagliptin in combination with pioglitazone. Of these, 136 received combination therapy for ≥ 22 weeks and the mean duration of exposure was 146.5 days.

Exposures to sitagliptin beyond one year came from the extension studies to the Phase 2 studies, P010 and P014, and the Phase 3 studies, P020 (add-on to metformin) and P021 (monotherapy). These studies were evaluated in the Pooled Long-Term Safety population. From Table 75 in Dr. Irony's review, there were 429 patients contributing long-term safety data to the 100 mg dose group, 241 patients had at least one year exposure and 164 had ≥ 540 days of exposure to sitagliptin 100 mg once daily. The limitation of evaluating safety from this population is the absence of a concurrent control group.

These patient exposures are comparable to other new molecular entities that have been approved by the agency recently for the treatment of type 2 diabetes mellitus.

Deaths
Table 76 from Dr. Irony's review summarizes 12 deaths reported in the clinical development program up to the cut-off date of October 18, 2005. Three of these were reported prior to randomization. Seven occurred in sitagliptin-treated patients and two occurred in glipizide-treated patients. The predominant cause of death was cardiovascular-related in patients with established histories for CVD or risk factors for CVD. No clear signal of increase mortality related to sitagliptin treatment was detected from this NDA review.

Nonfatal Serious Clinical Adverse Events
Table 78 from Dr. Irony's review summarizes the nonfatal SAEs in the Pooled Phase 3 population by System Organ Class (SOC). The SOC with the highest incidence of nonfatal SAEs was "Neoplasms Benign, Malignant and Unspecified". The incidence of neoplasms was 0.7%, 0.9%, and 0.5% in the sitagliptin 100 mg, 200 mg, and placebo groups, respectively. However, there was no single cancer type that was predominant over the others.

Dr. Irony queried further the incidence of SAEs categorized as infections, cardiovascular, neoplastic, and psychiatric based on preclinical signals or common events occurring in the diabetic population. No notable imbalances were consistently observed in his analysis.

Other Adverse Events of Interest
Hypoglycemia
In Study P010, the 12-week Phase 2 study that included a glipizide active control group, the incidence of hypoglycemia (both investigator and subject-determined) was greater in the glipizide group (17.1 to 28.5%) compared to any dose of sitagliptin (0.8 to 8.1%). The incidence of hypoglycemia was 2.4% in

placebo. Another placebo-controlled Phase 2 study (Study P014) showed a higher rate of hypoglycemia in the sitagliptin-treated groups than placebo that might be dose-related; however, none of the events was considered serious. In the Pooled Phase 3 program, the incidence of hypoglycemia in both the sitagliptin 100 and 200 mg dose groups was not significantly greater than the control group. In many of these cases, fingerstick glucose values were > 65 mg/dL. It is possible that the higher reporting of hypoglycemic symptoms without objective evidence of hypoglycemia may reflect patient perception of hypoglycemia as a result of improvements in glycemic control. That is, a reduction in plasma glucose levels, while still in normal range may be perceived as a hypoglycemic episode by the study subject.

Gastrointestinal
GLP-1 has been associated with certain GI symptoms including nausea and abdominal pain. Indeed, GI-related side effects necessitate slow upward titration of exenatide to lessen these effects of treatment. In the Pooled Phase 3 population, the incidence of GI disorders was higher in the sitagliptin dose groups than control groups but did not appear dose related. A statistical comparison of the incidence of nausea between the two sitagliptin dose groups and placebo revealed a statistically significant difference only at the 200 mg dose groups.

Recent post-marketing reports of pancreatitis associated with exenatide use (without established causality) have also prompted this reviewer to look at any specific reports of pancreatitis associated with sitagliptin therapy. Only one case of pancreatitis was reported in this NDA involving a 57-year old woman treated with sitagliptin 100 mg daily. The event occurred on D37, requiring hospitalization, and resolved 7 days after study drug discontinuation. The patient was discharged on D43 and restarted on sitagliptin 100 mg daily on D44 but had to be re-hospitalized on D50 due to ileus. Study drug was discontinued and further investigation into the etiology of her worsening ileus revealed an adenocarcinoma of the colon which had extended beyond the wall of the colon. The study investigator considered the pancreatitis, ileus, and colon cancer unrelated to study drug.

Urticaria, angioedema, and skin lesions
The applicant had identified these events of "special interest" because *in vitro* tests show Substance P, neurogenic inflammatory mediator, to be a substrate for the DPP-IV enzyme. In the Pooled Phase 3 population, the incidence of urticaria was reported as 0.4%, 0.2%, and 0.3% in the 100 mg, 200 mg, and control groups, respectively. All these cases were reported as mild-to-moderate in intensity. Dr. Irony reported only one case of angioedema occurring in a patient treated with sitagliptin 100 mg daily for 79 days. The event was preceded by exposure to a toxic disinfectant at home. The patient required treatment with antihistamines and corticosteroids and was hospitalized for one day. She was discontinued from study on D94 and did not appear to have been re-challenged. Only one report of skin necrosis was noted in this NDA. The patient had a history of right toe amputation and the event was reported as "necrosis lesion in skin of first toe of left foot". The event resolved 22 days after despite continuation of therapy.

Laboratory Adverse Events
Dr. Irony noted slight increases in serum creatinine in the Pooled Phase 3 population in all three treatment groups. Although the increases were higher in the sitagliptin 100 and 200 mg groups than placebo, the mean change appeared of little clinical significance. Similarly, the decrease in creatinine clearance of 3.0 to 3.1 mL/min is of unknown clinical relevance.

In Study 028, the 12-week study in patients with chronic renal impairment, Dr. Irony noted a greater increase from baseline in serum creatinine in the two sitagliptin dose groups compared to placebo/active controls. It should be noted that the number of patients in each group is small and the baseline mean serum creatinine levels were not similar across the three groups. However, the magnitude of the increases was higher in this patient population than observed in patients with baseline normal renal function. These laboratory findings were not accompanied by any clinical adverse event. Some patients had their sitagliptin dose reduced from 50 mg to 25 mg daily with subsequent improvements in serum creatinine

levels. The applicant is proposing lower dosage strengths for patients with moderate to severe renal impairment. In addition to their proposal, labeling should include a discussion of the laboratory changes and recommendations for routine monitoring in patients with underlying renal disease.

Conclusions on Safety
Overall, the safety and tolerability of sitagliptin, as established in this NDA, is acceptable and does not counterbalance the efficacy findings. The slight increase in serum creatinine levels associated with sitagliptin therapy in patients with baseline renal impairment did not result in any serious clinical sequelae and the recommended lower dosage strengths for patients with moderate to severe renal impairment and recommendations for laboratory assessment upon initiation and periodically in these patients appear to be an acceptable risk management plan. The applicant has informed the agency that there are ongoing studies in patients with renal impairment and such data will be provided to the agency when available. No recommendations for Phase 4 commitments will be made to characterize the mechanism for these mild increases in serum creatinine associated with sitagliptin use.

II. CLINICAL PHARMACOLOGY SUMMARY
The clinical pharmacology reviewers have recommended approval of Januvia® with no requests for Phase 4 clinical studies although OCP is recommending that a dissolution method, not disintegration, be employed as a post-approval test method. The applicant has agreed to conduct post-approval drug product quality tests using a dissolution method.

Key findings from the clinical pharmacology are highlighted in this memo.

Pharmacokinetics
The pharmacokinetics of sitagliptin appear similar in healthy nondiabetic and type 2 diabetic patients based on several Phase 1 studies summarized under Section 2.2.1 of the OCP review. The Tmax ranges from 1 to 4 hours and the terminal half-life is approximately 12 hrs.

Pharmacokinetics of single doses of sitagliptin of 25 mg, 50 mg, 100 mg, 200 mg, and 400 mg reveal that AUC levels increase in a dose-proportional manner.

Food Effect
There was no effect on the pharmacokinetics of sitagliptin when co-administered with a high-fat meal. Labeling will recommend that Januvia® can be taken with or without food.

Metabolism and Elimination
The major pathway of elimination for sitagliptin is via urinary excretion and involves active tubular secretion. The majority of sitagliptin is eliminated unchanged. In vitro assays reveal that sitagliptin does not inhibit cytochrome P450s or PgP nor is it an inducer of CYP3A4. It is a substrate of the human PgP and renal oranic anion transporter hOAT3.

Renal Impairment
A single-dose study was conducted in 24 patients with varying degrees of renal insufficiency and in 6 healthy control subjects. AUC was increased approximately 2-fold with mild renal insufficiency and increased further with declining creatinine clearance. See Table 9 from OCP review. Recommendations for dosage adjustments are included in labeling for patients with moderate or severe renal insufficiency.

Hepatic Impairment
A single-dose study was conducted in patients with moderate hepatic impairment and healthy controls. AUC was increases 21% (see Table 10) and was not considered clinically relevant to recommend dose adjustments for patients with mild to moderate hepatic impairment. There are no clinical data for patients

with severe hepatic impairment (Child-Pugh score >9) and this will be reflected in labeling; however, there is no specific recommendation to avoid use in these patients.

Drug-Drug Interactions
Several DDI studies were performed with NTI drugs or drugs that have a high likelihood of co-administration with sitagliptin. The results of these studies are summarized under section 2.4.1 of the OCP review and will be reflected in labeling. No dose adjustments have been recommended based on the results of these studies including co-administration with digoxin, warfarin, and cyclosporine.

III. NONCLINICAL SUMMARY

The pharmacology/toxicology reviewers have recommended approval of Januvia® with no additional nonclinical studies required.

Carcinogenicity Studies
Two 2-year carcinogenicity studies were conducted in rats and mice. There was an increased incidence of combined liver adenoma/carcinoma in rats at approximately 60 times the maximum recommended daily adult human dose (MRHD) based on AUC. No increase in tumor incidence was observed in mice exposed to approximately 70 times the MRHD. Since the drug was not genotoxic/mutagenic, an exposure approach can be applied to the interpretation of the carcinogenicity studies and hence this finding at supermaximal doses in one species does not appear relevant for humans, but will be appropriately described in labeling.

Specific Nonclinical Toxicology Concerns of DPP-IV Inhibitors
Several DPP-IV inhibitors in development have been associated with vascular and necrotic skin lesions in preclinical models, particularly primates. The mechanism for these lesions is not known; however, there is speculation that the risk may be increased with less selectivity of the drug for DPP-IV and some cross-reactivity with other serine proteases such as DPP-VIII/IX. As a result of these findings in several compounds, the agency has requested that all sponsors of DPP-IV inhibitors conduct 3-month oral toxicity studies in monkeys to assess their compound's potential for necrotic skin lesion. This request was not made until later in the clinical development program for Januvia®. As a consequence, the applicant was asked to submit an amendment to its NDA no later than July 16, 2006, three months before the user fee goal date. The results of this study were submitted prior to this date and the review of this study showed that sitagliptin did not produce vascular/skin lesions in rhesus monkeys after 3 months of administration at doses up to 25 times the MHRD.

Reproductive Toxicology
Pregnancy Category B is recommended. Sitagliptin was not found to be teratogenic. Resorption and post-implantation losses were reported in animal studies but at doses of 25 times the MHRD. A pregnancy registry will be maintained by the applicant.

IV. CHEMISTRY, MANUFACTURING, AND CONTROL
The CMC review is still pending at present; however, issues raised by CMC have been discussed with the applicant and to my knowledge, there are no outstanding matters that will preclude an approval action with this review cycle. Please see Dr. Meyer's Office Director memo.

V. CONSULTS
A. DMETS
The Division of Medication Errors and Technical Support (DMETS) has raised objections to the proposed trade name, Januvia®, citing orthographic similarity with Tarceva®, a drug indicated for the treatment of advanced or metastatic non-small cell lung cancer. Dr. Irony has reviewed DMETS objections and the

applicant's counter-arguments and has concluded that Januvia® is an acceptable tradename. While there can never be 100% assurance of no medication errors resulting from approval of this drug name/product, the likelihood for this error is sufficiently low based on the reasons stated in section 1.2.4 of Dr. Irony's review. I concur that the proposed tradename should be accepted.

Another applicant for a DPPIV-inhibitor has raised concerns for possible medication errors between Januvia® and Enjuvia®, an oral contraceptive. DMETS has addressed this in their consult and found that these two products had sufficient differences to allow pharmacists to make distinctions between them. I concur with this finding. In particular, there are no overlapping dosage strengths and the package presentation for an oral contraceptive (28-day packages) versus those to be available for Januvia® are substantially different.

B. DDMAC

The Division of Drug Marketing, Advertising, and Communications had not objections to the proposed tradename, Januvia®. Specific recommendations regarding the professional labeling and patient package insert have been incorporated into the labeling negotiations with the applicant.

C. Office of Surveillance and Epidemiology

No specific risk management plan is proposed other than routine measures such as FDA-approved professional labeling and routine post-marketing surveillance. At present, no different recommendations are proposed by OSE.

D. DSI

Several investigator sites involved in Studies 020, 021, and 023 were selected for DSI inspection. DSI found the sites acceptable and no evidence noncompliance noted. (see letter issued on August 16, 2006 by Constance Lewin for details of the inspection).

V. PEDIATRICS

Based on the efficacy and safety data derived from the adult studies reviewed in this NDA, I concur with Dr. Irony that it would be appropriate to investigate the clinical efficacy and safety of sitagliptin in the pediatric population given the rise in obesity and diabetes in this population. The prevalence of diabetes secondary to obesity is greater in the adolescent patient population. Consequently, I would recommend that the company be granted a waiver from investigating sitagliptin therapy in the pediatric population ranging in age from newborn to [redacted] years of age. A deferral can be granted for [redacted] to 18 yrs age with approval of this NDA but the applicant will need to address the study design and plans for implementing such a study as a Phase 4 commitment.

VI. OTHER ADMINISTRATIVE/REGULATORY ISSUES

A. Financial Disclosure

Submitted documents have been reviewed by Dr. Irony under Section 4.6 of his review. He has found no evidence of financial arrangements which might impact the integrity of the clinical data.

B. Phase 4 Commitments

In his review, Dr. Irony has recommended the applicant conduct a specific study in African -Americans to evaluate efficacy and safety of sitagliptin in a controlled study design. His rationale is based on the observation that the clinical development program did not include sufficient Blacks to represent the prevalence of diabetes in this racial subgroup. Subgroup analyses by Dr. Pian and pharmacometrics review by race did not show a significant effect of race on efficacy/pharmacokinetics. While the proportion of certain racial and ethnic groups in this clinical development program may be lower than the prevalence of the condition in the general population, there is insufficient evidence to conclude that

sitagliptin is neither efficacious nor safe for use in African-Americans or other racial/ethnic subgroups to request a dedicated study as a Phase 4 commitment.

Dr. Irony has also recommended that the applicant study the co-administration of sitagliptin with insulin or sulfonylureas. Given the progressive deterioration in glycemic control over time in Type 2 diabetics and the high likelihood of concomitant insulin or SU use, these studies should be conducted to adequately assess efficacy and safety, especially risk of hypoglycemia. The applicant has already submitted a special protocol assessment for combined use with insulin; however, the division is recommending that both insulin and SU be formally studied with sitagliptin under Phase 4 agreements. The applicant has agreed to these Phase 4 agreements and timelines for study protocol submission, study start date and completion will be summarized in the approval letter.

VII. LABELING

CMC and DMETS raised objections to the applicant's presentation of the drug product as Januvia® (sitagliptin phosphate) tablets, xx mg, where the xx refers to the amount of the active ingredient (25, 50, or 100 mg of sitagliptin) and not the salt (sitagliptin phosphate). The applicant has agreed to modify their package inserts, carton labels, and professional samples to describe the product as Januvia® (sitagliptin) tablets, xx mg, and a qualifying statement will follow the trade/nonproprietary name describing that the tablet contains xx amount of the salt. This change will be implemented as a supplement to the NDA in January 2007 as labels have been printed in preparation for approval. Applicants are discouraged from such practice and are often informed that this is done at their risk should the agency recommend substantial changes to labeling. In this setting, I have no objections to allowing the change to take place in January 2007 as this name change does not present any safety concern.

Package Insert

The applicant has submitted labeling in the new Physician Labeling Rule (PLR) format. Please see final agreed-upon labeling attached to approval letter.

Patient Package Insert

Please see recommendations made to the PPI made by the Division of Surveillance, Research, and Communication Support (DSRCS). This is currently be modified by the applicant.

CONCLUSIONS AND RECOMMENDATIONS

Pending mutually acceptable language for the professional labeling, cartons, and patient package insert, this application should be approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
10/13/2006 04:13:42 PM
MEDICAL OFFICER

Robert Meyer
10/16/2006 08:00:36 AM
MEDICAL OFFICER

Date: September 19, 2006

From: Ilan Irony, M.D.

Subject: NDA21-995, Original Submission; Merck and Company, Inc.
Product: sitagliptin phosphate

Through: Mary Parks, M.D., director, DMEP/ODE2

To: NDA 21-995 File in DFS

Background

After the DFS filing of the Medical Officer's review of sitagliptin phosphate original New Drug Application 21-995, the statistical review team made a recommendation for labeling that requires additional clarification.

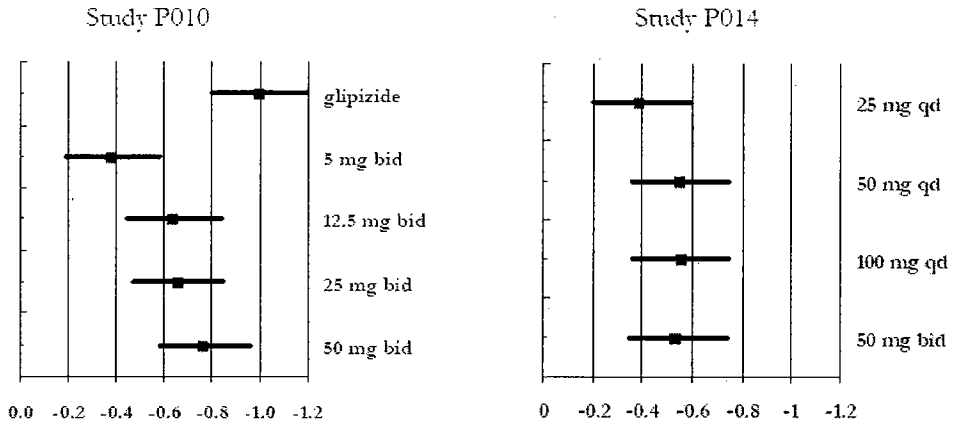
The applicant's recommended dose for all patients with normal renal function is 100 mg once daily. The statistical review team for this application recommended that the Section on Dosage and Administration in the sitagliptin labeling be revised to allow for either 50 mg or 100 mg daily doses of sitagliptin in monotherapy in the treatment of patients with T2DM.

"I recommend that, based on the Phase 2 efficacy results showing no clear lessening of clinical benefit for 50 mg compared to the proposed 100 mg dose, daily doses of 50 mg and 100 mg should both be made available to patients with Type 2 diabetes and normal renal function as monotherapy."

The statistical reviewer made the recommendation to add the 50 mg dose based on glycemic changes in the Phase 2 studies P010 and P014. These were dose ranging studies, testing the effect of sitagliptin on glycemic parameters in 12-week, placebo-controlled, parallel-group, studies.

Figure 1 copied from the statistical review document, shows that the least square means differences from placebo (and 95 % confidence intervals) between the sitagliptin 25 mg bid dose and the 50 mg bid dose in Study P010 overlap, and the same is observed among the groups treated with sitagliptin 50 mg qd, 50 mg bid and 100 mg qd in Study P014.

Figure 1. LSM Difference from Placebo (95% CI) – Phase 2 Studies



Tables 33 and 34 (from the statistician's review document) show numerically the same overlap

Table 33 Analysis of Change from Baseline in Hemoglobin A1c(%) at Week 12
Modified Intention-To-Treat With Data Carried Forward – Study 010

		Mean		Change From Baseline			
Treatment	N	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
MK-0431 5 mg b.i.d.	122	7.89 (0.94)	7.77 (1.22)	-0.13 (0.82)	-0.15	(-0.29, -0.01)	0.031
MK-0431 12.5 mg b.i.d	122	7.85 (0.88)	7.48 (0.98)	-0.38 (0.71)	-0.41	(-0.55, -0.27)	<0.001
MK-0431 25 mg b.i.d.	120	7.89 (0.94)	7.50 (1.14)	-0.39 (0.84)	-0.43	(-0.56, -0.29)	<0.001
MK-0431 50 mg b.i.d.	121	7.83 (0.95)	7.34 (1.01)	-0.49 (0.66)	-0.54	(-0.68, -0.40)	<0.001
Glipizide	119	7.82 (0.95)	7.11 (0.91)	-0.72 (0.84)	-0.76	(-0.90, -0.62)	<0.001

Table 34 Analysis of Change from Baseline in Hemoglobin A1c(%) at Week 12
Modified Intention-To-Treat With Data Carried Forward – Study 014

		Mean		Change from Baseline			
Treatment	N	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
MK-0431 25 mg q.d.	107	7.71 (0.91)	7.47 (1.30)	-0.23 (0.87)	-0.28	(-0.42, -0.14)	<0.001
MK-0431 50 mg q.d.	107	7.60 (0.94)	7.22 (1.02)	-0.38 (0.68)	-0.44	(-0.58, -0.30)	<0.001
MK-0431 100 mg q.d.	106	7.78 (0.90)	7.38 (1.11)	-0.40 (0.81)	-0.44	(-0.58, -0.30)	<0.001
MK-0431 50 mg b.i.d.	108	7.79 (0.85)	7.41 (1.10)	-0.38 (0.76)	-0.43	(-0.56, -0.29)	<0.001

The Clinical Review team decision regarding this labeling revision proposal

After consideration of the point made by our statistical colleagues, the clinical reviewer decided to maintain the recommended dose as 100 mg once daily only for diabetic patients treated with sitagliptin in monotherapy. This decision is based on the following reasons:

- The Phase 2 studies were 12 weeks in duration, while the Phase 3 studies, supporting the recommended dose of 100 mg once daily, were 24 or 18 weeks in duration. The Phase 3 studies provided experience and data with longer exposure to sitagliptin treatment.
- The magnitude of mean HbA1c reduction seen with either 25 mg bid, 50 mg bid, 50 mg qd or 100 mg qd seen in either Study P010 or P014 was similar to the magnitude of HbA1c reduction observed in the first 12 weeks of the Phase 3 monotherapy studies, but was lower than the mean reduction observed with 100 mg from baseline to week 24 in the Phase 3 studies (LS mean placebo-subtracted change of 0.8% and 0.6% for Studies P021 and P023, respectively). While it is possible that 24-week treatment with 50 mg qd or 25 mg bid of sitagliptin would result in similar improvement in HbA1c, the absence of 24-week data on HbA1c reduction with these doses precludes any conclusion related to the magnitude of improvement in glycemic control.
- The mean baseline HbA1c was lower in the Phase 2 studies compared to the Phase 3 studies, making any efficacy comparison even more inappropriate between these studies.
- The Phase 2 studies were thoroughly designed and conducted, thus allowing conclusions regarding dose-response among the doses tested (or lack of dose-response). The applicant has not studied the effect of up-titration from 50 mg to 100 mg of sitagliptin (either as forced titration or titration based on glycemic parameters), so any additional benefit from raised the dose from 50 mg to 100 mg for a particular patient remains unknown. Thus, we are unable to provide clear directions for use of either dose of sitagliptin, such as initiating treatment with 50 mg daily then titrating to 100 mg, as an example.
- There are no safety issues associated with the 100 mg dose of sitagliptin that are absent with the 50 mg dose; therefore we have no basis to request from the applicant a Phase 4 study commitment related to the 50 mg dose at this time.

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/s/

Ilan Irony
9/19/2006 05:11:15 PM
MEDICAL OFFICER

Mary Parks
9/20/2006 06:07:27 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type: NDA
Submission Number: 21-995
Submission Code: S

Letter Date: 2005-12-16
Stamp Date: 2005-12-16
PDUFA Goal Date: 2006-10-16

Reviewer Name: Ilan Irony
Review Completion Date: 2006-08-30

Established Name: Sitagliptin phosphate
(Proposed) Trade Name: Januvia
Therapeutic Class: Dipeptidyl peptidase IV inhibitor
Applicant: Merck and Company, Inc.

Priority Designation: S

Formulation: Oral Tablets
Dosing Regimen: 25, 50 or 100 mg once daily
Indication: Improve Glycemic Control
Intended Population: Adult patients with Type 2 diabetes mellitus

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1. EXECUTIVE SUMMARY

This document is the Medical Officer's Clinical Review of sitagliptin phosphate, a new molecular entity. The indications sought are "as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus" (use in monotherapy) and "to improve glycemic control in combination with metformin or a PPAR γ agonist (e.g., thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control".
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. The New Drug Application reviewed in this document describes the development program for sitagliptin phosphate. A total of 2719 subjects with T2DM were exposed to this product in Phase 2 and Phase 3 studies, lasting from 12 weeks to more than 1 year. Two Phase 3 studies were conducted to examine the safety and efficacy of sitagliptin in monotherapy; one Phase 3 study was conducted to examine the safety and efficacy of sitagliptin in combination with pioglitazone, while another Phase 3 study examined the effects of sitagliptin in combination with metformin.

1.1 Recommendation on Regulatory Action

The NDA contains reports of clinical studies which demonstrate substantial evidence of improved glycemic control in patients with T2DM treated with sitagliptin as a single agent or in combination with metformin or pioglitazone. Review of the safety profile did not identify risks associated with sitagliptin therapy to offset its efficacy profile. This reviewer recommends approval of sitagliptin for the indications sought.

1.2 Recommendation on Postmarketing Actions

Please refer to Sections 1.2.1 to 1.2.3 below for this reviewer's recommendations.

1.2.1 Risk Management Activity

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 during pregnancy will be monitored by routine

pharmacovigilance and by establishment of a pregnancy registry. 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.
The Division of Medication Errors and Technical Support (DMETS) in the Office of Surveillance and Epidemiology found the trade name JANUVIA unacceptable due to its similarity in orthographic appearance and overlapping product characteristics with Tarceva, a drug indicated for the treatment of cancer. The Division of Metabolism and Endocrinology Products (DMEP) in the Office of New Drugs took into account the arguments submitted by the applicant and by DMETS, and consider the trade name JANUVIA acceptable.
This reviewer agrees with the risk management plan proposed by the applicant, but would in particular request rigorous monitoring of serum creatinine in subjects with chronic renal insufficiency participating in ongoing and future clinical studies.

1.2.2 Required Phase 4 Commitments

1) The applicant will need to conduct clinical studies to determine both the efficacy and the safety of sitagliptin when added on to therapeutic regimens employing insulin and insulin secretagogues. The main issue with this combination is to determine the risk of hypoglycemia and its severity.
2) African-Americans were underrepresented in the clinical studies (6.2 % of 1538 subjects participating in Phase 3 studies). The proportion of African-Americans with T2DM in the United States is far greater. The response in this subset of the population to exenatide has been noted to be of a lesser magnitude than for other racial groups. A controlled study of safety and efficacy in African-American diabetics will provide safety and efficacy data on sitagliptin for this population.
3) The recent rise in the proportion of children and adolescents with T2DM requires demonstration of the safety of sitagliptin in this population, particularly in its effects on linear growth. The present application contains sufficient safety information on the use of sitagliptin in adult diabetics to allow initiation of clinical studies in children and adolescents.

1.2.3 Other Phase 4 Requests

1. There is evidence of mild increase in mean serum creatinine during treatment with sitagliptin, without clinical significance in diabetics with normal renal function. The magnitude of increase in serum creatinine was larger in a small study of sitagliptin therapy in subjects with both T2DM and varying degrees of chronic renal insufficiency, without other indicators of worsening renal function. The applicant attributed the increase to a sitagliptin-induced reduction in creatinine tubular secretion. Characterization of sitagliptin effects on serum creatinine and glomerular function

would be desirable and clinically relevant: this request could be satisfied by, among other options, a pharmacokinetic dose-response study to investigate whether the increase in serum creatinine found in clinical studies is related to inhibition of active tubular secretion or to a decrease in glomerular filtration rate, the latter being clinically relevant.

2. Clinical studies also indicated a trend in decreasing mean serum alkaline phosphatase (of liver and bone origin) over time, without evidence of stabilization or reversal of this trend at one year. Continuous monitoring of serum levels of alkaline phosphatase in ongoing and future studies may determine whether alkaline phosphatase becomes stable with treatment periods longer than 1 year or whether it continues to decrease. If the latter is true after a period of one or two years of treatment, additional studies may be recommended to investigate the clinical significance of these findings.

1.2.4 Recommended Trade Name:

Januvia is the proposed Trade Name. DMETS/OSE/CDER was consulted regarding the trade name and considered Januvia unacceptable due to similarities with Tarceva (erlotinib), when the prescription is scripted, and both an overlapping dose (100 mg) as well as oral administration. DMETS maintained the same argument despite the applicant's reply that an extensive search through the United States Patent and Trademark Office did not identify Tarceva as a potential for confusion, nor did 23 other countries where Januvia has been registered and erlotinib is marketed under the trade name Tarceva. In addition, the Safe Medication Practices Consulting, Inc. did not identify any source of confusion or error in their analyses of Januvia, the overlapping strength of 100 mg which is administered orally has a different direction for use (with or without food for Januvia, without food for Tarceva, and Januvia and Tarceva tablets have different physical characteristics. DMEP considers the trade name Januvia adequate, and unlikely to result in prescribing or dispensing error.

1.3 Summary of Clinical Findings

The Phase 2 and Phase 3 studies that generated data to support the safety and efficacy of sitagliptin included 2719 subjects with T2DM, treated with doses ranging from 10 mg to 200 mg once daily or in 2 divided doses, for periods of 12 weeks to one year. Two Phase 2 studies and two Phase 3 studies provided most of the experience with sitagliptin treatment as a single anti-diabetic agent. One Phase 2 study (sitagliptin combined with metformin) and two Phase 3 studies (one in combination with metformin and one in combination with pioglitazone) provide data to support the use of sitagliptin with these anti-diabetic agents.

1.3.1 Brief Overview of Clinical Program

The clinical program was designed to demonstrate the safety and efficacy of sitagliptin in improving glycemic control as a single agent (monotherapy) or in combination with insulin sensitizers (metformin or pioglitazone). The study design in the Phase 3 studies was similar, with a period of titration and dose stabilization of the add-on therapy, a single-blind placebo run-in period of 2 weeks and a randomized, placebo-controlled period of 12 weeks (Phase 2 studies), 18 or 24 weeks (phase 3 studies). In the studies conducted to support the use of sitagliptin in monotherapy, the applicant studied 2 doses of sitagliptin: 100 mg and 200 mg daily. In a placebo-controlled study of diabetic subjects with chronic renal insufficiency, the applicant tested doses of 50 mg or 25 mg daily depending on the calculated creatinine clearance. These doses were derived from the expected drug exposure based on pharmacokinetic characteristics. The outcome of interest was the change in HbA1c from baseline to study endpoint, as compared to the placebo group. A subset of the subjects in these studies elected to participate in extension studies, where they continue to be treated with sitagliptin. Subjects who remain under poor glycemic control after pre-specified timepoints in these studies were treated with additional, protocol-specified, anti-diabetic agents (glycemic rescue therapy). The applicant conducted a study to assess the safety of sitagliptin in diabetic subjects with chronic renal insufficiency. The development of sitagliptin also included studies conducted to assess dose response relationships, pharmacokinetic characteristics, drug interactions, and effects on the electrocardiographic QT interval.

1.3.2 Efficacy

The applicant is seeking approval of sitagliptin for 2 indications: improvement of glycemic control when used in monotherapy and improvement of glycemic control when used in patients not adequately controlled with insulin sensitizers: metformin and pioglitazone.

1.3.2.1 Use in monotherapy

To support the indication of sitagliptin use in monotherapy, the data in the following table show the effect of sitagliptin on the primary endpoint: a change in HbA1c from baseline to the study endpoint. Lack of HbA1c values or HbA1c data obtained after initiation of glycemic rescue therapy were treated similarly as missing data, and were imputed by the "last observation carried forward" method. Group means were compared after adjustment (least square means) for baseline HbA1c and/or prior treatment with anti-diabetic agents.

Table 1. Change from baseline to study endpoint in serum HbA1c (%) in Studies P021 and P023

Treatment	N	Mean (SD)		Change from baseline			
		Baseline	Study Endpoint	Mean (SE)	LS Mean (SE)	95 % CI for LS Mean	LS Mean Difference from Placebo (95% CI)
P021 (Study Endpoint = Week 24)							
Sitagliptin 100 mg	229	8.0 (0.9)	7.4 (1.2)	-0.6 (0.1)	**-0.61** (0.1)	(-0.7, -0.5)	**-0.79** (-1.0, -0.6)
Sitagliptin 200 mg	238	8.1 (0.9)	7.3 (1.1)	-0.8 (0.1)	**-0.76** (0.1)	(-0.9, -0.6)	**-0.94** (-1.1, -0.8)
Placebo	244	8.0 (0.8)	8.2 (1.4)	0.2 (0.1)	*0.18* (0.1)	(0.1, 0.3)	-
P023 (Study Endpoint = Week 18)							
Sitagliptin 100 mg	193	8.0 (0.8)	7.6 (1.2)	-0.5 (0.1)	**-0.48** (0.1)	(-0.6, -0.4)	**-0.60** (-0.8, -0.4)
Sitagliptin 200 mg	199	8.1 (0.9)	7.8 (1.3)	-0.3 (0.1)	**-0.36** (0.1)	(-0.5, -0.2)	**-0.48** (-0.7, -0.3)
Placebo	103	8.0 (0.9)	8.2 (1.4)	0.2 (0.1)	0.1 (0.1)	(0.0, 0.3)	-
Numbers in **bold** are associated with p<0.001 and in *italic* are associated with p<0.05							

Adapted from the applicant's Table 2.7.3:11 in Reference 2.7.3 Summary of Clinical Efficacy

Although in Study P021 the 200 mg dose of sitagliptin appeared to be more effective in reducing mean HbA1c during the base study (placebo-controlled), the other study (P023) showed the opposite: a greater reduction in HBA1c with the 100 mg dose compared to the 200 mg dose. Both doses tested were superior to placebo.
In the study of subjects with both T2DM and chronic renal insufficiency, a smaller placebo-subtracted effect was observed in the combined 25- and 50 mg groups, compared to the effects of 100 mg or 200 mg in the subjects with normal renal function (Table 2).

Table 2. Change from baseline in HbA1c for the combined sitagliptin groups (25 and 50 mg) in Study P028 of subjects with T2DM and chronic renal insufficiency

			Baseline	On treatment	Change from baseline	Placebo-subtracted difference in mean change in HbA1c (%) (95 % CI)
Week	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	
6	Sitagliptin	61	7.6 (1.0)	7.2 (0.9)	-0.4 (0.1)	
	Placebo	25	7.8 (0.9)	7.7 (1.1)	-0.1 (0.1)	
12	Sitagliptin	55	7.6 (1.0)	7.0 (0.8)	-0.6 (0.1)	**-0.41 (-0.71, -0.11)**
	Placebo	25	7.8 (0.9)	7.6 (1.0)	-0.2 (0.1)	

Adapted from the applicant's Table 14-8, reference P028v1

The effect on HbA1c persisted for at least 1 year, as demonstrated through the extension studies of pooled Phase 2 studies testing the 100 mg daily dose (Figure 1) and in the extensions of Study P021, one of the Phase 3 studies with 1-year data submitted by the applicant at the time of the 4-month safety update report (Figure 2).

Figure 1. Mean change in HbA1c in the base studies P010 and P014 and in their extension studies among subjects receiving a total daily dose of 100 mg of sitagliptin versus glipizide

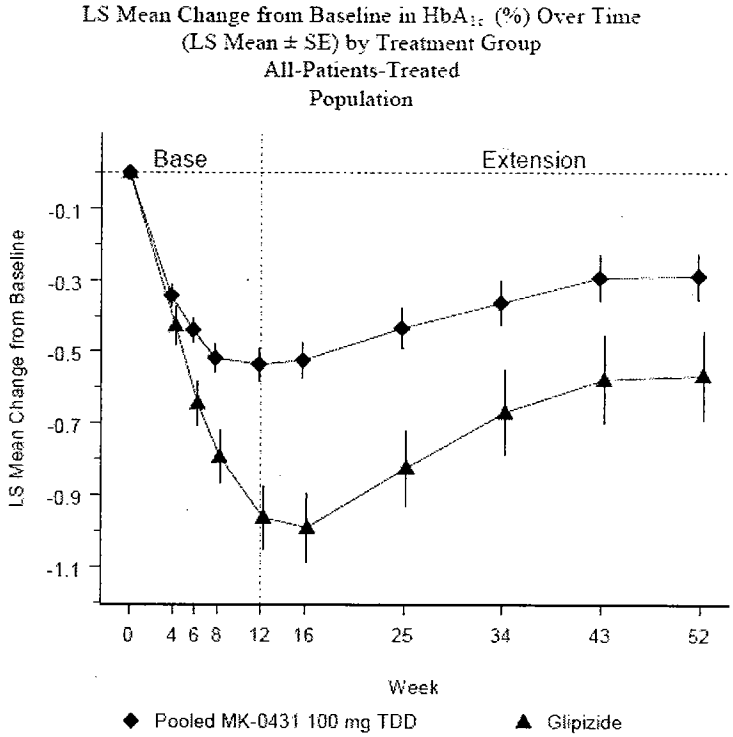
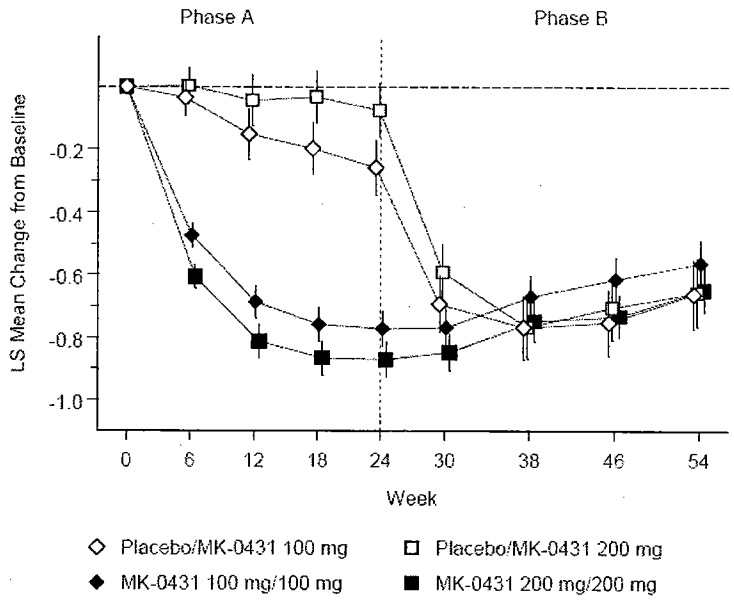


Figure 4 copied from the applicant's report, reference R23 Memo to Gertz B. Bain R. Amatruda J from Lunceford J. Stein P: Integrated Summary of Efficacy Results, 2005.

Figure 1 shows a rapid reduction (nadir reached at week 12) in mean HbA1c for both the sitagliptin- and the glipizide-treated groups, albeit the latter had a greater magnitude of effect. Most of the sitagliptin treatment effect persisted for a period of 1 year.

Figure 2. LS Mean change from baseline in HbA1c (%) over time by treatment group (LS Mean ± SE) in Study P021



Copied from the applicant's Figure 8-1, reference r0027 from the 4-Month Safety Update Report

Figure 2 shows the sitagliptin-induced glycemic effect in Study P021, similar to that seen in the Phase 2 studies and their extensions. In Study P021, after the placebo-controlled phase (noted in the figure as Phase A), subjects who had been randomized to placebo were re-randomized to either 100 mg or 200 mg of sitagliptin daily until week 54. A similar effect on glycemia was then seen in those 2 groups: placebo → sitagliptin 100 mg and placebo→ sitagliptin 200 mg. Moreover, the effect on HbA1c in the 2 original sitagliptin groups persisted for the 54 weeks of the study.
The treatment effect on HbA1c was consistent across different age categories, races and baseline characteristics, except for a greater effect in subjects with higher HbA1c at baseline. Treatment with sitagliptin had favorable effects on both fasting and post-prandial glucose levels. The placebo-subtracted reduction in post-prandial plasma glucose in the sitagliptin groups was greater than the effect on fasting plasma glucose, which is consistent with the incretin mechanism.

1.3.2.2 Use of sitagliptin as add-on to metformin treatment

The Phase 3 study to investigate the efficacy of sitagliptin as add-on to metformin was of similar design as the studies performed to support use in monotherapy, with the exception of:

- Subjects needed to be on stable metformin doses of at least 1500 mg daily and have HbA1c between 7 and 10 % at randomization.
- Only the sitagliptin 100 mg dose was being tested, and 701 subjects were randomized 2:1 favoring sitagliptin 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.

Table 3 summarizes the data on the primary endpoint: change in HbA1c from baseline in the ITT population.

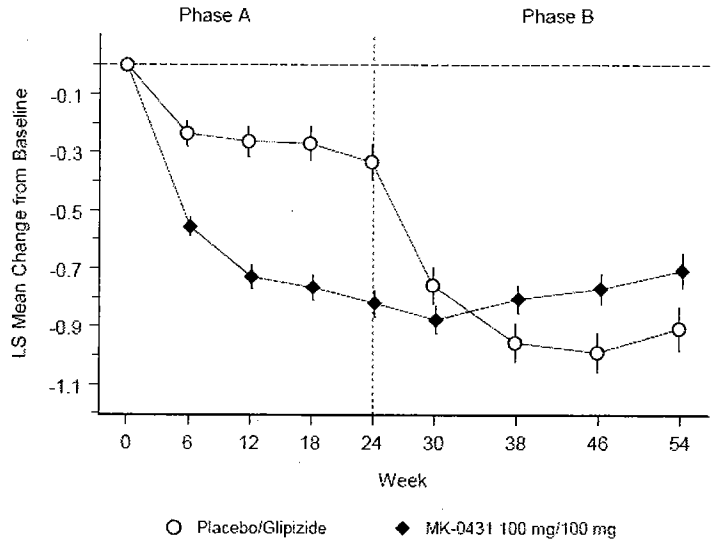
Table 3. Change of HbA1c from baseline to week 24 in Study P020 (ITT population)

		Mean (SD)		Change from baseline			
					LS Mean	95% CI for LS	p-Value
Treatment	N	Baseline	Week 24	Mean (SE)	(SE)	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 P021v1

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. Figure 3 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.

Figure 3. LS Mean change from baseline in HbA1c (%) over time by treatment group (LS Mean ± SE)



Copied from the applicant's Figure 8-1 in reference r0026 from the 4-month Safety Update Report

The significant reduction in HbA1c, with favorable effects on fasting plasma glucose and on the 2-hour post-meal glucose (data not shown), provide evidence of the benefit in adding sitagliptin to the treatment regimen of patients not adequately controlled with metformin alone.

1.3.2.3 Use of sitagliptin as add-on to pioglitazone treatment

Study P019 was conducted to support use of sitagliptin as add-on therapy for patients not adequately controlled with pioglitazone at doses of 30 or 45 mg daily. The design

was similar to that of Study P020, with the only sitagliptin dose tested being the 100 mg dose given daily, and the 353 eligible subjects were randomized 1:1 to sitagliptin or placebo. Table 4 shows the results of the study regarding the primary efficacy endpoint.

Table 4. Change in HbA1c from Baseline to week 24 in Study P019 (ITT Population)

Treatment	N	Mean (SD)		Change From Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	163	8.0 (0.8)	7.2 (0.9)	-0.9 (0)	-0.8 (0.1)	(-1.0, -0.7)	<0.001
Placebo	174	8.0 (0.8)	7.8 (1.1)	-0.2 (0.1)	-0.2 (0.1)	(-0.3, 0)	0.017

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-0.70** (-0.8, -0.5)	<0.001

Adapted from the applicant's Table 11-1, reference P019

Following sitagliptin treatment for 24 weeks, improvement in fasting plasma glucose levels was also observed, as compared to placebo.
There was no additional weight gain or edema when sitagliptin treatment was added on to pioglitazone.
These data also support approval of sitagliptin as a combination therapy with pioglitazone. Although no direct studies were conducted in combination with rosiglitazone, the other thiazolidinedione approved in the treatment of T2DM, there is no reason to believe that sitagliptin would yield results inconsistent with those observed in combination with pioglitazone.

1.3.3 Safety

The applicant's strategy to summarize the data demonstrating the safety of sitagliptin was to pool the safety findings from all the Phase 3 studies (termed Pooled Phase 3 Population) and from the long-term exposure (one year or more) in a subset of both Phase 2 and Phase 3 study populations that participated in the base studies and their extensions (termed Pooled Long-Term Safety Population). Summaries of the safety data in the application included events assessed after initiation of glycemic rescue therapy. The mean exposure to sitagliptin 100 mg (the dose proposed for marketing in this application) in the Pooled Phase 3 Population was 615.2 subject-years and the mean exposure in the Pooled Long-Term Safety Population was 577 subject-years.
The pattern of deaths and serious adverse events (SAEs) reported in the clinical studies was similar between treatment groups and controls and also consistent with the adverse events (AEs) usually observed in diabetic patients, with a predominance of cardiovascular deaths and SAEs. In addition, no specific adverse events resulted in drop outs or discontinuation of sitagliptin-treated subjects more frequently than in controls.
The following findings are relevant to be listed in this section:
Common AEs (at least 3% of subjects in the group) and present with higher incidence in sitagliptin-treated subjects than in control subjects include diarrhea, nasopharyngitis, upper respiratory tract infection, urinary tract infection, arthralgia and headache. Of note, nausea was more prevalent in those subjects treated with sitagliptin 200 mg daily, with incidence

statistically significantly higher than controls (the between-groups difference was 2.3%). The frequency of nausea was similar between controls and the sitagliptin 100 mg group.
Certain AEs were deemed by the applicant to be of special interest, based on either the sitagliptin mechanism of action or on findings from animal studies, as follows:
Hypoglycemia was monitored as a set of symptoms by the subject and / or the investigator and as events of blood glucose levels less than 60 mg/dL in self-assessed measurements. The frequency of hypoglycemic symptoms or events was similar in sitagliptin-treated subjects as in control-treated subjects and much lower than those treated with glipizide.
Gastrointestinal events, specifically nausea, vomiting, diarrhea, and abdominal pain were also monitored closely due to the known profile of exenatide (GLP1 analog). Both diarrhea and constipation were more commonly reported among subjects treated with sitagliptin, with incidences not proportional to the dose used.
Neurologic and skeletal muscle-related AEs were not more common in the sitagliptin group. Infections were slightly more common, but their severity, duration and frequency over time were similar to those of subjects not exposed to sitagliptin.
There were no increases in the incidence of cardiovascular events. Neoplastic AEs were slightly more common among sitagliptin subjects, but there was no specific pattern of neoplastic conditions that could raise the suspicion of causal relationship, and most of these events were observed in the first few weeks or months of exposure, making the assessment of causality less scientifically plausible.
Laboratory findings of interest include a dose-related decrease in serum levels of alkaline phosphatase, small and transient mean increases in serum uric acid and creatinine, white blood cell counts and absolute neutrophil counts, and small decreases in hemoglobin. The increases in serum creatinine were of a greater magnitude in subjects with chronic renal insufficiency treated with sitagliptin for 12 weeks.
Unlike the common and expected weight gain that follows treatment with sulfonylureas and insulin, treatment with sitagliptin did not cause any weight changes.
No drug-drug interactions or changes in vital signs were observed. No QT interval changes were detected in the thorough QT study.
The applicant categorized sitagliptin as Pregnancy Category B for labeling purposes.

1.3.4 Dosing Regimen and Administration

According to the label proposed, the recommended dose of sitagliptin is 100 mg once daily as monotherapy or as combination therapy with metformin or a PPAR γ agonist (e.g., thiazolidinedione). Sitagliptin can be taken with or without food.
For patients with mild renal insufficiency (creatinine clearance $\geq$ 50 mL/min, approximately corresponding to serum creatinine levels $\leq$ 1.7 mg/dL in men and $\leq$ 1.5 mg/dL in women), no dosage adjustment for sitagliptin is required.
For patients with moderate renal insufficiency (creatinine clearance $\geq$ 30 to < 50 mL/min, approximately corresponding to serum creatinine levels > 1.7 mg/dL and $\leq$ 3.0 mg/dL in men and > 1.5 and $\leq$ 2.5 mg/dL in women), the dose of sitagliptin is 50 mg once daily.
For patients with severe renal insufficiency (clearance < 30mL/min, approximately corresponding to serum creatinine levels > 3.0 mg/dL in men and > 2.5 mg/dL in women), the dose of sitagliptin is 25 mg once daily.

The conclusion supporting the once daily dosing is based on a head-to-head comparison of 50 mg twice daily against 100 mg daily that resulted in a similar pharmacodynamic profile. A comparison between effects of 100 mg or 200 mg in the 2 Phase 3 monotherapy studies was inconclusive with one study indicating a possible dose-proportional response and the other showing that 200 mg was worse than 100 mg daily in lowering one's plasma glucose.

1.3.5 Drug-Drug Interactions

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 probe 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 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.

1.3.6 Special Populations

Because of the renal elimination, renal function has the most impact on dosing, thus the recommendation for dose reductions in patients with moderate or with severe renal insufficiency. Sitagliptin is only modestly removed by hemodialysis, and can be given without respect to the timing of hemodialysis. Race, gender, age (within the range of age tested, with subjects 18 years or older, with a 20 % increase in C_{max} among those 65 to 80 years of age) and obesity do not have a clinically meaningful effect on PK (less than 2-fold exposure).
Moderate hepatic insufficiency in subjects without diabetes causes small changes in PK parameters (21 % increase in AUC and 13 % increase in C_{max}). This information may be useful for dosing sitagliptin in the population with T2DM, given the prevalence of various degrees of liver steatosis to hepatitis and cirrhosis.

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-[(3*R*)-3-amino-1-oxo-4-(2, 4, 5-trifluorophenyl) butyl]-5, 6,7,8-tetrahydro-3-(trifluoromethyl)-1, 2,4-triazolo[4,3-*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:

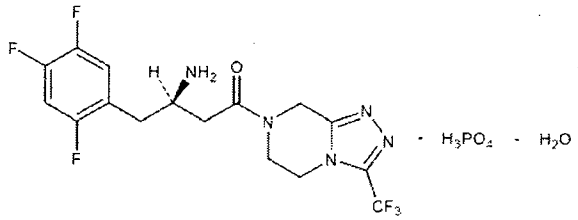


Figure copied from the applicant's structure. PDF under Quality – Drug Substance information in the application

2.1.2 Established name and proposed trade name

The established name used in the application is sitagliptin phosphate. The applicant has designated this product during development under the codes MK-0431 and L-224715. The proposed trade name is Januvia.

2.1.3 Chemical class

Sitagliptin is a new molecular entity, formulated as a monohydrate phosphate salt.

2.1.4 Pharmacological 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.

2.1.5 Proposed indications, dosing regimens and age groups

"Januvia is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus" and "Januvia is also indicated in patients with type 2 diabetes mellitus in combination with metformin or a PPAR γ agonist (e.g., thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control". The recommended dose is 100 mg once daily in monotherapy or in combination with metformin or a PPAR γ agonist. The dose should be reduced to 50 mg once daily for patients with moderate renal insufficiency (creatinine clearance between 30

and 50 mL / min) and should be further reduced to 25 mg once daily in patients with severe renal insufficiency (creatinine clearance less than 30 mL/min) or end stage renal disease. Januvia is taken orally, with or without food.
Sitagliptin should not be used in the pediatric population or during pregnancy and lactation.

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 (GLP-1)
- Synthetic analogs of human amylin

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 an active moiety that is not yet marketed in any country.

2.4 Important Issues With Pharmacologically Related Products

There are no pharmacologically related products, since sitagliptin is the first in its class being considered for marketing approval.
FDA has recently notified manufacturers 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 started an oral toxicity study in monkeys.

2.5 Presubmission Regulatory Activity

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.

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 (in type 1 diabetics) and Complications Trial 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 β-cells, and GLP1 lowers glucagon secretion from pancreatic α -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 GLP-1). 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. Such a new class of products may improve 2 of the 3 key defects underlying the pathogenesis of T2DM—reduced insulin secretion and, by lowering glucagon levels, excessive hepatic glucose production.

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 [redacted] capsule formulation (the Phase 1 formulation) containing the [redacted] phosphate salt form of sitagliptin as [redacted] in [redacted] cellulose capsules. Film-coated tablets containing the anhydrous phosphate salt 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 salt form of sitagliptin was used in the Phase 3 studies (P019, P020, P021, 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. Final market image film-coated tablet formulations include potencies of 25, 50, and 100 mg tablets.

On May 18, 2006, FDA requested additional information from the applicant regarding issues related to tablet content uniformity and other CMC issues. Per FDA request, the applicant submitted additional information and clarification of specific manufacturing methods on June 13, 2006. The CMC review is still ongoing.

3.2 Animal Pharmacology/Toxicology

The applicant has demonstrated that sitagliptin is a potent, selective DPP4 inhibitor based upon in vitro (human, mouse, rat and dog serum) and in vivo animal pharmacology studies. Importantly, sitagliptin is highly selective over DPP8/9 (>2500-fold); inhibition of these enzymes has been previously demonstrated to result in marked toxicity in preclinical species. The main issue related to the toxicity of this new class of drugs relates to the specificity of inhibition of DPP4. Sitagliptin is a highly selective inhibitor of DPP4 and has not been associated with the known toxicities encountered by this applicant and sponsors of other DPP4 inhibitors that are less selective. Five other compounds in this class tested in monkeys are associated with dose and duration-dependent necrotic skin lesions (tail, digits, ears, nose, and scrotum). Two of these 5 also produce lesions in dogs (footpad sores, edema, limping) and one produces lesions in rats and monkeys.
The concern around the drug class arose from the fact that the toxicities were not species specific, not related to molecular structure or to the type of inhibition (covalently bound irreversible or non-covalently bound reversible inhibition)
As of Nov 1, 2005, all sponsors were asked to conduct 3-month monkey toxicity study to identify whether their drug displays this toxicity (since monkeys are the most sensitive species).
The sitagliptin toxicity study conducted in monkeys was unrevealing, whereas another less potent and less specific compound tested concurrently by Merck revealed similar skin toxicities, renal toxicities and death.
With sitagliptin, DPP4 inhibition occurs at a concentration of 18 nM (IC_{50}) and DPP8/9 inhibition at 49,000 - 100,000 nM. The clinical exposure is 1000 nM, so sitagliptin would not inhibit DPP8/9 even with doses 10 times higher than the 100 mg daily dose proposed.
A theoretical liability of DPP4 inhibition is impaired immune function, in that DPP4 is identical to CD26, and because inhibitors have been shown to attenuate T cell activation in vitro. The applicant investigated the effect of sitagliptin on IL-2 production, MLR-induced or antigen-specific proliferation of T cells, or proliferation induced by PMA and IL-2. Sitagliptin has no activity in *in vitro* assays of T cell activation at concentrations up to 50 μM. LPS-induced B cell proliferation was also not inhibited by sitagliptin. The applicant found attenuation of T cell activation with less specific DPP4 inhibitors. Sitagliptin is well tolerated in vivo and targeted safety pharmacological studies focused on assessment of cardiovascular, respiratory, gastrointestinal, renal, and behavioral functions revealed no significant toxicities for sitagliptin.
Placental transfer was studied in pregnant rabbits and rats, and indicated that sitagliptin readily crosses the placenta.
The initial toxicology studies (prior to FDA's request for monkey toxicity studies) were conducted in mice, rats and dogs and reproductive and developmental toxicities were conducted in rabbits and rats. The toxicology program also included potential genotoxicity (in vitro in bacterial and mammalian cell assays and in vivo in the mouse micronuclear assay) and 2-year rat and mouse studies to determine the potential for carcinogenicity. Sitagliptin was not found to be genotoxic in vitro or in vivo as assessed by a battery of assays designed to detect mutagenicity, direct DNA damage, or clastogenicity.
In dogs, doses of 2, 10, and 50 mg/kg/day of sitagliptin were tested in the 2-, 14-, 27-, and 53-week oral toxicity studies. In each of these GLP dog studies, drug-related and dose-limiting physical signs of toxicity have been consistently noted at the highest dose of 50

mg/kg/day. These signs have included ataxia, trembling, decreased activity, and labored and/or abnormal respiration characterized by pronounced bronchial sounds associated with open-mouth breathing. These signs generally began in Drug Week 1 in each of the studies and were intermittently observed throughout the duration of the study. The onset of signs in affected dogs generally occurred about 30 minutes to 1 hour after dosing and lasted for from 1 to several hours after onset. In all cases, the affected dogs were normal by the end of the observation period each day indicating the transient nature of these signs. In addition to the physical signs produced in dogs at a dose of 50 mg/kg/day of sitagliptin, very slight to slight skeletal muscle degeneration was noted histologically at this dose in 2/8 and 1/8 dogs in the 14- and 27-week oral toxicity studies, respectively. However, no skeletal muscle changes were observed in any dogs treated with 50 mg/kg/day in the 53-week toxicity study, again supporting the conclusion that this effect does not progress with increased duration of treatment. Carcinogenicity studies in rats revealed an incidence of hepatic neoplasia higher (but not statistically significant) than that seen in control animals at doses approximately 19-fold higher than the human recommended dose. The incidence was higher at higher doses (500 mg/kg/day), but these cases were preceded by hepatotoxicity, known to induce hepatic neoplasia.
Sitagliptin improved glucose tolerance in lean and DIO mice and decreased glucose in db/db mice.
The maximal efficacy in lean mice (corresponding to a 2-fold increase in active GLP1) was achieved with 70 % inhibition of plasma DPP4 at a dose of 1 mg /kg given orally. In DIO mice, a dose dependent decrease in blood glucose excursion was also observed (0.3, 3, 30 mg/kg) Maximum efficacy was seen at the 3 mg/kg dose in this study, corresponding to a plasma concentration of approximately 700 nM.
Acute lowering of blood glucose was also demonstrated in diabetic db/db mice (3 to 30 mg/kg).

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. The NDA was submitted in the electronic Common Technical Document format, 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 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.
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 in the treatment of T2DM.

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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 [redacted] 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 ^{14}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 [redacted] 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

Table 6. Studies with Efficacy and Safety objectives in the sitagliptin development

Study Number	Study design	Number and type of subjects	Endpoints	Dose range	Duration of exposure
P010	DB, R, PC, AC, PG	743 M, F T2DM, HbA1c 6.5 to 10%	HbA1c, FPG, Fructosamine, PPG, 7-point glucose average	5, 12.5, 25, 50 mg bid or PBO or Glipizide 5-20 mg qd	12 weeks
P010X1	Extension to P010	509 M, F, T2DM who completed P010	HbA1c, FPG, 7-point glucose average	PBO subjects re-randomized to sitagliptin; glipizide subjects continued same; sitagliptin doses collapsed to 100 mg qd only	40 weeks
P014	DB, R, PC, PG	555 M, F T2DM, HbA1c 6.5 – 10%	HbA1c, FPG, Fructosamine, PPG, 7-point glucose average	25, 50, and 100 mg qd or 50 bid or placebo	12 weeks
P014X1	Extension to P014	338 M, F T2DM who completed P014	HbA1c, FPG, 7-point glucose average	PBO subjects switched to metformin 850 bid, sitagliptin subjects had dose collapse to 100 mg qd	40 weeks
P015	DB, R, PC, crossover study	28 M, F T2DM poor control on metformin alone	24 h weighted mean glucose, FPG, fructosamine	50 mg bid followed by PBO or PBO followed by sitagliptin 50 bid	4 weeks each period
P019	DB, R, PC, PG	353 M, F T2DM poor control on pioglitazone alone	HbA1c, FPG, beta cell function	Pioglitazone 30 or 45 mg and either sitagliptin 100 mg or PBO	24 weeks
P020	DB, R, PC, PG	701 M, F T2DM poor control on metformin alone	HbA1c, FPG, beta cell function	Metformin ≥ 1500 mg qd and either sitagliptin 100 mg qd or PBO	24 weeks (Phase A) and 80 weeks (Phase B)
P021	DB, R, PC, PG	741 M, F T2DM	HbA1c, FPG, beta cell function	100 mg or 200 mg or PBO	24 weeks (Phase A) and 80 weeks (Phase B)
P023	DB, R, PC, PG	521 M, F T2DM	HbA1c, FPG, beta cell function	100 mg or 200 mg or PBO (2:2:1 randomization)	18 weeks (Phase A) and 36 weeks (Phase B)
P028	DB, R, PC, PG	91 M, F T2DM and chronic renal insufficiency	HbA1c, FPG, fructosamine	25 or 50 mg qd depending on creatinine clearance OR PBO	12 weeks (Phase A) and 42 weeks (Phase B)
RC431A201	DB, R, PC, PG	151 M,F Japanese T2DM	HbA1c	100 mg or PBO	12 weeks

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

Other studies were described under NDA 022044. This NDA is for a fixed-dose combination of sitagliptin and metformin, as a second-line treatment for patients with inadequate glycemic control on either agent alone or who are already being treated with sitagliptin and metformin. The NDA was submitted to FDA on [redacted]

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 [redacted] tabs formulated with or without [redacted] 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 [redacted] 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

Under IND 70,934, Merck is studying the combination of sitagliptin and metformin for the treatment of T2DM. [redacted]

4.3 Review Strategy

The review of efficacy was conducted separately for each indication: use of sitagliptin as monotherapy or its use in combination with either metformin or pioglitazone. The main studies reviewed to investigate the efficacy of sitagliptin were the adequately powered and controlled Phase 3 studies. Wherever relevant, data from the pooled Phase 2 studies were reviewed, particularly looking for consistency of the treatment effect and durability of glycemic control in the extension studies.

The review of safety was conducted in 2 datasets of subjects enrolled in sitagliptin studies:
The pooled Phase 3 population, which pooled AEs, SAEs, study discontinuation rates and reasons, laboratory AEs from the 4 Phase 3 studies;
The Long-Term Safety Population, including the extension studies of both Phase 2 and Phase 3 studies, to investigate trends of safety signals that may manifest themselves over time.
In addition, relevant information on the efficacy and safety of sitagliptin were reviewed from the 4-month safety update report.

4.4 Data Quality and Integrity

This reviewer requested a routine site inspection at the National Research Institute (principal investigator: Dr. Andrew Lewin). The request was based simply on the fact that the site had the highest number of subjects randomized (61 subjects were enrolled in three of the four Phase 3 studies at this site, out of approximately 1300 subjects exposed to sitagliptin). The treatment effect observed at that site was similar to the average effect observed in the pooled sites for each study. Dr. Lewin's site was inspected for the 3 studies conducted and the final inspection report indicates that no major deviations from FDA regulations were observed and no FDA Form 483 was issued.
Between May 3rd and May 10th, 2006, Merck was also inspected and no major deviations from FDA regulations were observed and no FDA Form 483 was issued.
There was no 'for cause" reason for inspection identified and no "for cause" safety reason for inspection identified.

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 the investigator's Institutional Review Board or Ethics Committee.
Because many subjects with T2DM were already being treated with anti-diabetic 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, whether the study was investigating sitagliptin effects in monotherapy or in combination with metformin or pioglitazone. All studies also included a single-blind, placebo run-in phase, to ensure stability of glycemic control and subject compliance with protocol procedures.
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 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 not eligible to enter the extension studies.

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 as seen in the table below, and did not affect the studies conclusions regarding the efficacy or safety of sitagliptin.

Table 8. Protocol violations observed in the four Phase 3 studies

Study	% of violators	Protocol Violation	Number of subjects
P021	1.5%		
		Irregular anti-diabetic medication wash-off rule	1
		Drug compliance < 75%	7
		Use prohibited anti-diabetic medication for >14 day or > 7 consecutive days	1
		Use of glucocorticoids for > 14 days in the last 3 months of Phase A	2
P023	1 %		
		Irregular anti-diabetic medication wash-off rule	1
		Use prohibited anti-diabetic medication for >14 day or > 7 consecutive days	4
P019	1.4%		
		Drug compliance < 75 %	3
		Use prohibited anti-diabetic medication for >14 day or > 7 consecutive days	2
P020	0.8 %		
		Drug compliance < 75 %	4
		Use of glucocorticoids for > 14 days in the last 3 months of Phase A	2

Records of anti-diabetic medication use prior to randomization were collected by the investigators and were included in the model used for the analyses of efficacy.

The primary population set for analysis of efficacy was the "All Patients Treated" (APT) defined as all randomized subjects with a baseline measurement of the parameter being analyzed, at least one post-randomization measurement and consumption of at least one dose of double-blind study therapy. This strategy (a modified intent to treat population for analysis) is used frequently to minimize bias and preserve the power of randomization for statistical tests.

4.6 Financial Disclosures

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

Table 9 below lists all studies related to safety and efficacy considered "covered studies for the purpose of 21 CFR 54.2. FPI means First Patient In and LPO means Last Patient Out.

Table 9. Summary of Covered Clinical Trials as Defined by 21 CFR 54.2(e)

Protocol Number	Protocol Title	FPI	LPO	"Payments of Other Sorts" Range
010	A Multicenter, Double-Blind, Randomized, Placebo- and Active-Controlled Dose-Range Finding Study of L-000224715 in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control	18-Jul-2003	30-May-2005	18-Jul-2003 Through 30-Apr-2005
014	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Dose-Range Finding Study of Once-Daily Dosing of L-000224715 in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control	29-Sep-2003	09-May-2005	29-Sep-2003 Through 30-Apr-2005
015	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Crossover Study of L-000224715 in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin	10-Dec-2003	19-Jun-2004	10-Dec-2003 Through 30-Apr-2005
019	A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Pioglitazone Therapy	15-Jul-2004	28-Sep-2005	15-Jul-2004 Through 30-Apr-2005
020	A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin Therapy	13-Jul-2004	20-Jul-2005	13-Jul-2004 Through 30-Apr-2005
021	A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of MK-0431 Monotherapy in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control	08-Jul-2004	21-Jul-2005	08-Jul-2004 Through 30-Apr-2005
023	A Multicenter, Randomized, Double-Blind, Study of MK-0431 in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control	15-Oct-2004	17-Aug-2005	15-Oct-2004 Through 30-Apr-2005
028	A Multicenter Randomized, Double- Blind Study to Evaluate the Safety and Efficacy of MK-0431 Monotherapy in Patients With Type 2 Diabetes Mellitus and Chronic Renal Insufficiency Who Have Inadequate Glycemic Control	14-Dec-2004	18-Oct-2005	14-Dec-2004 Through 30-Apr-2005
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

Copied from the applicant's Table A-1 (Summary of Covered Clinical Trials) under Financial Disclosure

Table 10. Summary of Investigators that Meet the Definition of "Clinical Investigator"

Investigator Category	Total Number
Grand Total Number of Investigators/ Sub-investigators per Protocol and Site	2306
Total Number of Investigators/ Sub-investigators Who Are Certified Regarding an Absence of Financial Arrangements per Protocol and Site	2213
Total Number of Investigators/ Sub-investigators Not Providing Information and Not Certified per Protocol and Site	64 * (32 no longer at the site and Merck unable to obtain information) (32 not returning requested information)
Total Number of Investigators/ Sub-investigators Not Certified Due to "Significant Payments of Other Sorts" or Equity Interest per Protocol and Site	29 (Details of payments and equity are listed in the NDA from the investigators for the protocols in which they participated)
Total Number of Investigators/ Sub-investigators Receiving Payments Based on the Outcome of the Study per Protocol and Site	0
Total Number of Investigators/ Sub-investigators with Proprietary Interest in the Test Product or Company per Protocol and Site	0

Copied from the applicant's Table A-3 (Summary of Investigators that Meet the Definition of "Clinical Investigator") under Financial

Disclosure
*The applicant demonstrated due diligence by making multiple requests for the financial information (21 CFR Part 54.4).

In this reviewer's analysis, those investigators listed that had received significant payments and had results in their sites that were very favorable (both in primary endpoint efficacy and less SAEs reported) compared to the study mean estimate effect had enrolled too few subjects to influence the overall results.

5. CLINICAL PHARMACOLOGY

Please see Dr. Wei's Biopharmacology review for in depth pharmacokinetic and pharmacodynamic information on sitagliptin.

5.1 Pharmacokinetics

Sitagliptin has an absolute oral bioavailability of 87%. It is rapidly absorbed, reaching a T_{max} between 1 and 4 hours, with a C_{max} of 950nM after a single 100 mg dose and an apparent terminal half-life of 12.4 hours. In the therapeutic dose range, the pharmacokinetic parameters are dose proportional. Sitagliptin is primarily renally eliminated as unchanged drug (approximately 80%), with metabolism playing only a minor role. Formation of metabolites appears to be primarily mediated by CYP 3A4. Given a renal clearance of approximately 350 mL/min, active tubular secretion appears to be involved in the renal elimination of sitagliptin, but it is not definitively known which transporters are involved in this process in vivo. In vitro studies suggest that the organic anionic transporter-3 (OAT-3) may play a role. This is relevant as the applicant uses this explanation for the observed increase in serum creatinine (similar to the increase in creatinine with administration of cimetidine, without a real decrease in glomerular filtration or worsening of renal function). Sitagliptin is a human p-glycoprotein (PgP) substrate and thus p-glycoprotein may also influence the absorption and elimination of sitagliptin; however, the observed modest effects of cyclosporine A, a potent probe p-glycoprotein inhibitor (likely representing the worst case for PgP inhibitors), suggest that the potential for clinically meaningful p-glycoprotein mediated drug interactions is limited.
Consistent with dose-independent clearance, sitagliptin AUC increases dose proportionally with increasing dose while C_{max} increases modestly greater than dose proportionally and C_{24hr} increases modestly less than dose proportionally with increasing dose. Steady-state is generally reached by 3 days and the accumulation is slight, with an AUC accumulation index of 1.14 following a dose of 100 mg. There is no effect of food on sitagliptin pharmacokinetics; thus, sitagliptin can be dosed without regard to food.
Consistent with the characteristics of a drug that is primarily renally eliminated, renal function is the most significant factor impacting sitagliptin pharmacokinetics. Dosage reductions by 2-fold are recommended for subjects with moderate renal insufficiency (i.e., creatinine clearance ≥30 mL/min and <50 mL/min) and by 4-fold in severe renal insufficiency (i.e., creatinine clearance <30 mL/min) and subjects with end-stage renal

disease requiring hemodialysis in order to achieve similar exposures as subjects with normal renal function. Mild renal insufficiency (i.e. creatinine clearance ≥50 mL/min and <80 mL/min) does not have a clinically meaningful impact on sitagliptin pharmacokinetics and therefore no dosage alteration is necessary. Plasma protein binding is not meaningfully altered by renal insufficiency. Sitagliptin is modestly removed by dialysis and can be administered without respect to the timing of hemodialysis.
Race, gender, age and obesity do not have a clinically meaningful effect (i.e., a greater than 2-fold change in exposure) on sitagliptin pharmacokinetics. However, the pharmacokinetics of sitagliptin has not been investigated in children and adolescents with T2DM. Moderate hepatic insufficiency does not meaningfully affect sitagliptin pharmacokinetics. No dose adjustments of sitagliptin are needed based on these factors.
Sitagliptin has a low propensity to be involved in drug-drug interactions as either a perpetrator or a victim. In vitro, sitagliptin is not an inhibitor of cytochrome P-450 (CYP) enzymes and is not an inducer of CYP3A4. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, simvastatin, warfarin, oral contraceptives, rosiglitazone or glyburide providing further in vivo evidence for a low propensity for inducing drug interactions with substrates of human organic cation transporter (hOCT), CYP3A4, CYP2C8, and CYP2C9. Multiple doses of sitagliptin slightly increased plasma digoxin concentrations, however, these increases are not considered likely to be clinically meaningful. Sitagliptin concentrations are not meaningfully altered by metformin. In a population pharmacokinetic analysis of Phase 1 and Phase 2b studies, 83 concomitant medications were screened for potential effects on sitagliptin pharmacokinetics; sitagliptin plasma concentrations were not meaningfully altered by any of the medications that were evaluated. Sitagliptin concentrations were increased by approximately 29% by supratherapeutic single oral doses of cyclosporine, a potent p-glycoprotein inhibitor, although the renal clearance of sitagliptin was not decreased. The increases in sitagliptin plasma concentrations are not considered clinically meaningful and clinically meaningful interactions with other p-glycoprotein inhibitors are not expected.
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. The applicant did not have the opportunity to study potential interactions between sitagliptin and this class of drugs in their analysis of population PK conducted in the Phase 1 and Phase 2 studies. This potential interaction does not appear to exist. An analysis of sitagliptin effect on HbA1c in 5 subjects in 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.

5.2 Pharmacodynamics

The effects of sitagliptin on proximal biomarkers, plasma DPP4 activity and incretins (GLP1 and GIP levels, active and total), were assessed. Distal biomarkers assessed included glucose, insulin, C-peptide and glucagon levels. In preclinical rodent models,

near-maximal glucose lowering activity was associated with inhibition of plasma DPP4 activity of 80% or higher and enhancement of post-glucose challenge active GLP1 levels of 2-fold or higher.
Sitagliptin inhibits plasma DPP4 activity in a dose- and concentration-dependent manner. Doses of 100 mg once daily or higher are associated with approximately 80% DPP4 inhibition at steady-state trough or higher. Using an E_{max} model, the EC_{50} is approximately 25 nM and the EC_{80} is approximately 100 nM. For point of reference, the 100 mg dose at trough is associated with a plasma sitagliptin concentration of approximately 100 nM. Sitagliptin enhances post-meal and post-oral glucose tolerance test (OGTT) active GLP1 levels by approximately 2-3-fold, as compared to placebo. This magnitude of GLP1 increase is similar to that found in a DPP knock out mouse. Active GIP levels are similarly increased following an OGTT. In healthy subjects, sitagliptin has no consistent, treatment-related effect on fasting or post-meal levels of glucose, C-peptide, insulin or glucagon. The lack of a response on these endpoints is consistent with the observed low incidence of hypoglycemia in clinical studies in patients. In middle-aged obese individuals, sitagliptin reduces post-OGTT glucose excursion. In subjects with T2DM, single oral doses of sitagliptin reduce post-OGTT glucose excursion, enhance insulin / C-peptide levels and decrease glucagon levels. PK/PD analyses from the single dose study in subjects with T2DM suggest that near-maximal reduction of post-challenge glucose excursion is associated with sitagliptin plasma concentrations of approximately 100 nM or higher, plasma DPP4 inhibition of 80% or higher and augmentation of post-challenge active GLP1 levels of 2-fold or higher, thus corroborating targets from preclinical experiments. It was reasoned that for optimal chronic glucose lowering in patients with T2DM, that plasma DPP4 inhibition of 80% or greater at trough would be sought. This data served as the rational basis for selecting doses in the Phase 2b dose range finding studies (P010 and P014).

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 Phase 2 dose-range finding studies (P010 and P014) examined the efficacy and safety of sitagliptin doses from 10 mg per day to 100 mg per day. In P010, 100 mg per day (50 mg bid) provided greater reduction in both HbA_{1c} and FPG than 50 mg per day (25 mg bid), the next lower dose studied (Table 11).

Table 11. Change in mean HbA1c from baseline to week 12 in the dose ranging study P010 in the ITT population

		Mean		Change from baseline			
Treatment	N	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
Sita 25 mg bid	120	7.89 (0.94)	7.50 (1.14)	-0.39 (0.84)	-0.43	(-0.56, -0.29)	<0.001
Sita 50 mg bid	121	7.83 (0.95)	7.34 (1.01)	-0.49 (0.66)	-0.54	(-0.68, -0.40)	<0.001
Glipizide	119	7.82 (0.95)	7.11 (0.91)	-0.72 (0.84)	-0.76	(-0.90, -0.62)	<0.001

Adapted from the applicant's Table 7-1, reference P010

Table 12 shows the effect on HbA1c of once daily doses of sitagliptin in Study P014, with doses ranging from 25 mg to 100 mg, and compared a dosing regimen of 50 mg bid to the 100 mg qd dosing.

Table 12. Changes in HbA1c from baseline to week 12 in dose and regimen study P014

		Mean		Change from baseline			
Treatment	N	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
Sita 50 mg qd	107	7.60 (0.94)	7.22 (1.02)	-0.38 (0.68)	-0.44	(-0.58, -0.30)	<0.001
Sita 100 mg qd	106	7.78 (0.90)	7.38 (1.11)	-0.40 (0.81)	-0.44	(-0.58, -0.30)	<0.001
Sita 50 mg bid	108	7.79 (0.85)	7.41 (1.10)	-0.38 (0.76)	-0.43	(-0.56, -0.29)	<0.001

Adapted from the applicant's Table 7-1, reference P014

In P014, doses of 50 mg qd and 100 mg qd were not well separated in the primary analysis for HbA_{1c}; however, the preponderance of evidence, including the results from P010, the results from the extension study periods (P010X1, P014X1), the results from other glycemic endpoints in P014 (including FPG and fructosamine), and the secondary (per-protocol) analysis of the primary endpoint (HbA_{1c}) in P014, all supported the conclusion that 100 mg per day was more effective than 50 mg per day. With respect to the dosing regimen of sitagliptin, in P014, 100 mg per day administered with a twice-daily dose (50 mg bid) or with a once-daily dose (100 mg qd) provided similar reductions in glycemic endpoints.

Based upon these results, sitagliptin 100 mg qd was selected for further development and was included in Studies P019, P020, P021, and P023.

The lack of a clear plateau in glycemic efficacy between 50 and 100 mg per day in Study P010 raised the potential that the maximum effective dose of sitagliptin had not been established; thus, a 200 mg qd dose was also included in the 2 Phase 3 monotherapy studies (P021 and P023) to determine if a greater glycemic effect would be observed with this higher dose.

6. INTEGRATED REVIEW OF EFFICACY

The indications for sitagliptin proposed in this application are:

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

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

Sitagliptin development has been planned to provide evidence of efficacy to support these treatment indications in the population of patients with T2DM.

6.1 Indication

Use of sitagliptin in monotherapy

6.1.1 Methods

The development program to support the safety and efficacy of sitagliptin treatment in monotherapy included three Phase 2 studies and three Phase 3 studies (two of these in monotherapy for subjects with T2DM, and one in patients with T2DM who also had chronic renal insufficiency).
The studies had similar or identical designs, similar or identical endpoints and it is appropriate and useful to combine their data for a more robust conclusion regarding the efficacy of this product. This section will present the review of the Phase 3 studies, with integration of efficacy data from the studies of sitagliptin monotherapy.
The applicant conducted the study in subjects with T2DM and chronic renal insufficiency (Study P028) for the purpose of demonstrating the safety and tolerability of sitagliptin in that population. In that study, sitagliptin doses of 25 mg or 50 mg daily (depending on the creatinine clearance) were investigated in order to provide similar expected exposure as the proposed dose for patients without renal impairment. Study P028 was not intended to support efficacy, but rather to generate safety information on the use of sitagliptin in this special population. Since the applicant plans to market these reduced doses for patients with chronic renal insufficiency, this reviewer found it relevant to include the efficacy data from Study P028 in this section.
All studies had a placebo-controlled phase (referred in the study reports as base study or Phase A) followed by an active-controlled phase. The placebo-controlled period of the Phase 2 studies was 12 weeks in duration, while the placebo-controlled period of the Phase

3 studies was 18 weeks for one study and 24 weeks for the other. This study duration is sufficient to demonstrate an effect on glycemic control, and has been acceptable for other products in the Division of Metabolism and Endocrinology Products. However, for a chronic condition such as diabetes, with secondary failure of most (if not all) oral hypoglycemic agents, it is important to establish the durability of the treatment effect of the investigational product. Therefore, this clinical reviewer has included in this section summary analyses of data from the extension periods (active-controlled, or Phase B) of the Phase 2 studies and from the Phase 3 Study P021. This reviewer recognizes the limitations of establishing a long-term effect of treatment in studies that are not randomized (subjects self-selected to participate in the Phase 2 and Phase 3 extension studies) and not placebo-controlled; but these data are still important in the overall assessment of efficacy.
Details of the Phase 3 studies and a description and summaries of findings of the Phase 2 studies are described in Section 10.1 of this 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 18 in Study P023 and week 24 in Study P021). 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.
Other endpoints used in the Phase 3 efficacy studies are listed below. Their value is to establish mechanism of action and to provide support for the primary and secondary endpoints, but no regulatory action is based on effects of sitagliptin on these endpoints alone. Therefore, they are considered in this review as exploratory endpoints.

- Post-meal total and incremental glucose, insulin and C-peptide area under the curve (AUC): useful in the evaluation of beta cell function,
- Serum fructosamine: provides an integrated index of glycemic control that reflects changes occurring in days to weeks.
- Time to initiation of glycemic rescue therapy
- Pro-insulin to insulin ratio: high ratio reflects inefficient insulin processing and is a marker of beta cell dysfunction
- Homeostasis model assessment – beta (HOMA-beta): measures beta cell function, based on fasting insulin and glucose levels. In addition, beta cell function and insulin

sensitivity were further characterized in response to sitagliptin treatment with the frequently sampled meal tolerance testing.

- Homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI).
- Lipid endpoints

6.1.3 Study Design

6.1.3.1 General overview of study design

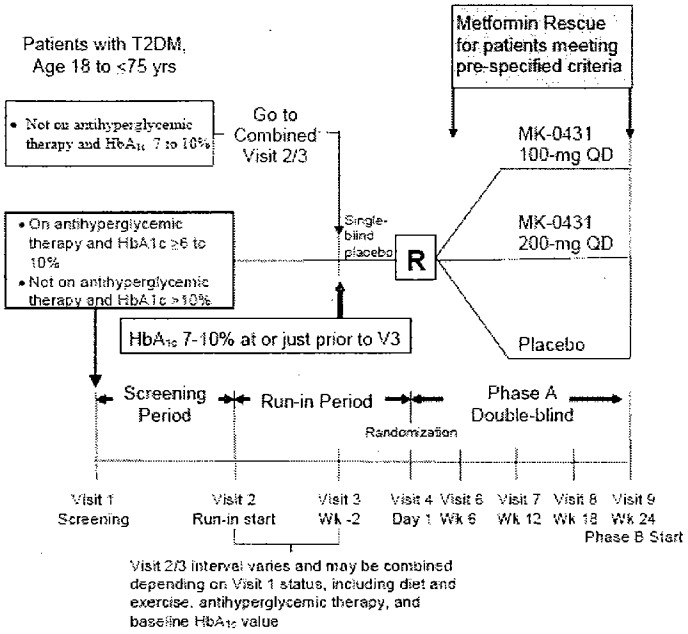
The study design for the two large Phase 3 monotherapy studies is similar. Their similarities and differences will be described. The applicant had selected sitagliptin 100 mg daily as the dose to be tested at these efficacy trials, based on both the pharmacokinetic / pharmacodynamic characteristics of this dose in normal volunteers, but also based on large numbers of subjects with T2DM exposed to 12 weeks of sitagliptin either as once daily or twice daily. However, the Phase 2 studies had not demonstrated a clear plateau of efficacy with 100 mg of sitagliptin administered daily. Therefore, the applicant decided to test the effect of 100 mg daily as compared to 200 mg daily in the two studies designed to demonstrate sitagliptin efficacy.

Studies P021 and P023 were multicenter, double-blind, randomized, placebo-controlled, parallel-group studies in subjects with T2DM with inadequate glycemic control (Figure 4 and Figure 5)

The studies had the following phases:

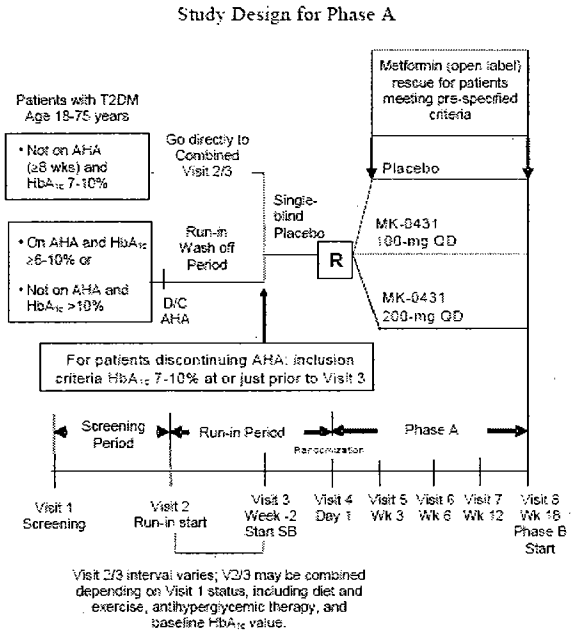
- A 1-week screening period (Visit 1 and 2)
- A diet / exercise run-in period of up to 12 weeks (Visits 2 to 3), depending on whether the subjects were being treated with anti-hyperglycemic agents (AHA) or not, to allow time for complete wash-off of the AHA effect.
- A 2-week, single-blind, placebo run-in (Visits 3 to 4)
- Randomization at Visit 4, followed by a 24-week (in Study P021) or 18-week (in Study P023), placebo-controlled, double-blind treatment period (Phase A)
- After completion of Phase A, subject could choose to enter an 80-week (in Study P021) or 36-week (in Study P023) extension study (Phase B). The Phase B for Study P021 was a single-blind, dose-controlled treatment period, in which subjects that had been randomized to placebo in Phase A were re-randomized to receive sitagliptin at either 100 or 200 mg daily dose, while subjects originally randomized to either 100 mg or 200 mg daily in Phase A remained on the same doses through Phase B. The Phase B for Study P023 was a double-blind, active-controlled period, in which subjects who were on sitagliptin treatment during Phase A continue to receive the same treatment with the same doses in Phase B, while subjects who were treated with placebo during Phase A were switched to pioglitazone 30 mg daily. Phase B for both studies is ongoing. The applicant submitted 1 year data for study P021 with the 4-month safety update report.

Figure 4. Design of Study P021 Phase A



Copied from the applicant's Figure 9-1, reference P021v1

Figure 5. Design of Study P023 Phase A



Copied from the applicant's Figure 9-1, reference P023v1

Subjects who did not meet protocol-specified progressively stricter thresholds for fasting plasma glucose during Phase A were treated with metformin, which was supplied open label by the applicant (glycemic rescue therapy). In Study P021 these subjects were not allowed to participate in the Phase B extension, while in Study P023, the subjects receiving glycemic rescue therapy were allowed to participate in the Phase B extension study.

The criteria for glycemic rescue in both studies were as follows:

- FPG (with value repeated after reinforcement of diet/exercise counseling) >270 mg/dL after Visit 4 / Day 1 through Visit 6 / Week 6,
- FPG (with value repeated after reinforcement of diet/exercise counseling) >240 mg/dL after Visit 6 / Week 6 through Visit 7 / Week 12,
- FPG (with value repeated after reinforcement of diet/exercise counseling) >200 mg/dL after Visit 7 / Week 12 up to (but not including) Visit 9 / Week 24.
- HbA1c > 8% after Visit 9 / Week 24 was also a rescue criterion in Study P023 only.

These studies were adequately designed and well controlled to allow demonstration of sitagliptin efficacy, if supported by data. It is unclear why the applicant has chosen to conduct Study P023 as an 18-week study, instead of the usually employed 24-week treatment period. This would somewhat impair the ability to assess durability of the effect, if not for the similarly conducted 24-week study P021, which was robust in its sample size. The issue of durability of the effect is extremely important in any chronic condition, such as T2DM. It is particularly relevant in T2DM because all anti-diabetic therapies tend to become less effective over time (secondary treatment failure) as the deterioration of beta cell function progresses or insulin resistance worsens. The typical duration of Phase 3 studies for other products intended for treatment of T2DM has been 24 to 26 weeks. Studies P021 and P023 are continuing through their Phase B and the 1-year data on HbA1c changes for Study P021 were included in the 4-month safety update report submitted by the applicant.

6.1.3.2 Subject eligibility

Subjects were eligible if they met the following conditions:

- Age ≥ 18 and ≤ 75 years of age, BMI between 20 and 43 kg/m^2
- HbA1c ≥ 7 % and ≤ 10 % not on anti-diabetic agents for at least 8 weeks by Visit 3 (This condition includes subjects not on anti-diabetic agents with HbA1c ≥ 10 % at the screening visit who the investigator expected to be within range after diet/exercise run-in, subjects with HbA1c ≥ 6% and < 10 % on an anti-diabetic agent, or subjects not on any anti-diabetic agent with HbA1c > 10 % at Visit 1, but likely to have HbA1c within inclusion range by Visit 3).
- If on AHA therapy at the time of screening, subjects had to be using either a single agent or low doses of a dual oral combination therapy (< 50 % of maximal doses of each of the component)
- ≥ 75 % compliance with placebo treatment during the placebo run-in
- None of the following: female subjects pregnant, lactating, or not on active contraception; any subject with uncontrolled thyroid function, viral hepatitis or liver dysfunction, kidney insufficiency or significant albuminuria, CPK > 2XULN or triglycerides > 600 mg/dL.

The criteria for entering into the studies were reasonable to ensure comprehensive assessment of sitagliptin efficacy in monotherapy for patients with T2DM, and could allow generalization of the findings to the target population of patients with T2DM who are not treated with other anti-diabetic agents.

The applicant's decision to exclude subjects with HbA1c > 10 % is based on the ethical issue of treating these subjects with placebo for periods of 4 months or longer. There is no reason to believe the data obtain from subjects with a range of HbA1c from 7 to 10 %

could not be extended to subjects with HbA1c > 10 %.
For eligibility into Study P028, subjects older than 18 years of age with T2DM had to have creatinine clearance < 50 mL/min or be on dialysis and HbA1c between 6.5 and 10 % (or between 7.5 % and 10 % if they were on stable insulin monotherapy).

6.1.3.3 Randomization

The randomization ratio in study P021 was 1:1:1 for sitagliptin 100 mg, sitagliptin 200 mg or placebo. The randomization ratio in Study P023 was 2:2:1 for sitagliptin 100 mg, sitagliptin 200 mg or placebo. There was no stratification in the randomization process. The randomization ratio in Study P028 was 2:1 favoring sitagliptin, and the subjects were stratified based on baseline creatinine clearance (moderate [≥ 30 and ≤ 50 mL/min] or severe [< 30 mL/min or on dialysis] strata).

6.1.3.4 Study Endpoints and Analyses

Primary Endpoint:
HbA1c was used to assess longer term glucose lowering efficacy of sitagliptin. For the primary analysis of efficacy, the population used was a modified ITT population, which included all randomized subjects with a baseline measurement, who took at least one dose of double-blind therapy, and had at least one post-randomization assessment.
This modified ITT complies with the Intent to Treat principle, and does not increase bias or contribute to inflate the type1 error (see ICH E9. Statistical Principles for Clinical Trials, Section 5.2.1. Full Analysis Set). The primary analysis was a comparison of mean change in HbA1c from baseline to study termination visit among the treatment groups.
A secondary analysis of the primary efficacy endpoint was conducted in the Completers subset, defined as all subjects in the ITT population who had both a baseline and a week 18 (Study P023) / week 24 (Study P021) assessment of HbA1c.
The values for comparison were the least squared means (LS) among the 3 treatment groups estimated by analysis of covariance (ANCOVA). The ANCOVA model included terms for treatment, prior anti-diabetic agent status (on or off treatment) and had baseline HbA1c as a covariate. Missing data were imputed by the Last Observation Carried Forward (LOCF) method for data that were either truly missing or for subjects that underwent glycemic rescue therapy before the end of Phase A of the studies.
A maximum likelihood approach for repeated measurements was used as a secondary approach for handling missing data (testing the sensitivity of the imputation method proposed). This secondary approach was a generalization of the ANCOVA model to account for the repeated measurements on each subject over time. The approach employed a longitudinal model having terms for the interactions between week (treated as a categorical variable) and the following: treatment, prior diabetes pharmacotherapy (on or off treatment), and baseline HbA1c value as a covariate. An unstructured variance/covariance model was used to capture the correlation between repeated measurements.

Secondary Endpoints:
In study P021 there were 2 supportive secondary endpoints: fasting plasma glucose and the 2-hour post meal plasma glucose. The 2-hour post-meal glucose is assessed during the meal

tolerance test (MTT). Sampling was performed at baseline, at 60 minutes and 120 minutes. The meal provided for testing was a standardized, predominantly solid, mixed meal consisting of 2 nutrition bars and 1 nutrition drink (about 680 kilocalories, including 111 grams of carbohydrates, 14 grams of fat, and 26 grams of protein).

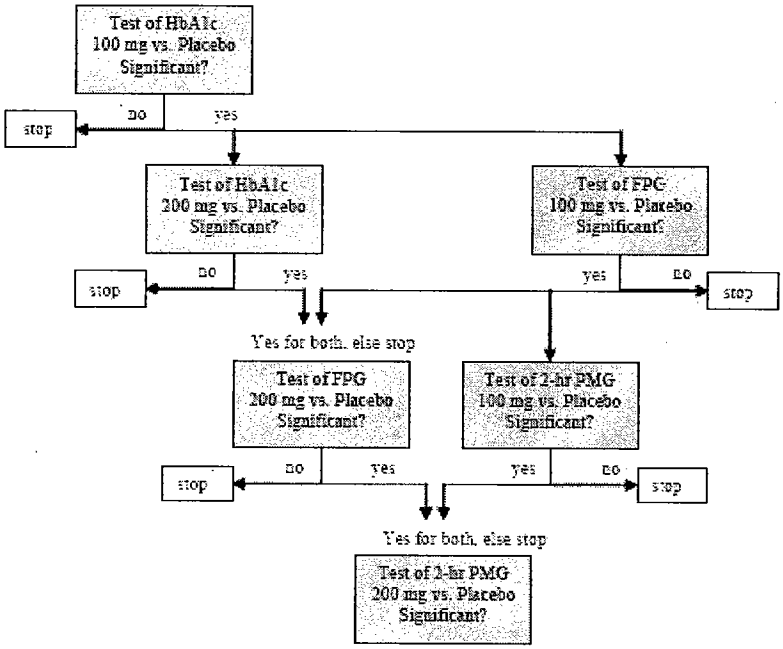
In Study P023, the only secondary efficacy endpoint is the fasting plasma glucose, as there was no systematic, protocol-guided assessment of post-prandial glucose. In Study P023, a modified, frequently sampled MTT (9-point MTT) was offered as a separate sub-study. In that study the meal used in the MTT consisted of 1 nutrition bar and 1 nutrition drink (460 kilocalories, 75 grams of carbohydrates, 9 grams of fat and 18 grams of protein).

These formulations were used in order to provide a better model of a patient's day to day food intake, compared to a standard liquid only nutritional challenge. However, it is not clear why the "standardized meal" was not standardized between the 2 protocols.

In the 9-point MTT, samples were collected at the following time points relative to the start of the meal: -10, 0, 10, 20, 30, 60, 90, 120, and 180 minutes at baseline and at Weeks 12 and 24 (Study P021) or at baseline and at week 18 (Study P023); glucose, insulin, and C-peptide concentrations were measured. The 9-point MTT allowed for a detailed description of the glucose and insulin area under the curves (AUCs) associated with a standard meal and thus allows an assessment of beta-cell function. A subset of the total study participants underwent the 9-point MTT: 55 of 238 randomized to sitagliptin 100 mg, 51 of 250 in the sitagliptin 200 mg and 54 of 253 subjects in the placebo participated in Study P021. In Study P023 82 of 205 subjects randomized to sitagliptin 100 mg, 77 of 206 subjects randomized to sitagliptin 200 mg and 38 of 110 subjects randomized to placebo took part in the 9-point MTT.

The applicant had proposed a sequential comparative analysis for study P021, with further comparisons depending on the statistical significance of the prior comparison. Thus, the first analysis was a comparison of change in HbA1c from baseline to study termination between sitagliptin 100 mg daily and placebo (the rationale being that the 100 mg is the primary dose in these studies). The sequential analysis was designed to control for the multiplicity of testings while preserving the type 1 error rate. For the sequence of analytic tests for both the primary and secondary endpoints, please refer to Figure 6, based on Figure 9-2 in the Reference P021V1.

Figure 6. Sequential analyses for the Primary and Secondary Endpoints



FPG = Fasting Plasma Glucose
PMG = Post-Meal Glucose

Copied from the applicant's Figure 9-2 in the Statistical and Analytical Plans to Address Study Objectives, Protocol P021V1

Many exploratory, sensitivity and subset analyses were proposed in the statistical analytical plan for these 2 studies.
In addition to the oral MTT administered to subjects in both studies, subjects in selected sites for Study P021 were also offered participation in the intravenous glucose tolerance test (IVGTT), performed at baseline and at week 24, in order to assess changes in beta cell function with sitagliptin treatment that are independent of the acute response to incretins.

6.1.4 Efficacy Findings

6.1.4.1 Subject disposition

Table 13 shows the numbers of subjects who were randomized in both Studies P021 and P023 included in the modified ITT analysis (designated by Merck as All Patients Treated). Study P021 investigators had screened 1807 subjects and excluded 1066 of these; 46.2 % were excluded because they did not meet HbA1c criteria prior to randomization. Study P023 investigators screened 1387 subjects and excluded 866 of these: 52.4% were excluded

because they did not meet HbA1c criteria. While the percentage of subjects excluded may call into question the ability of the studies' data to be extended to the overall population with T2DM, it is imperative to note that efficacy studies need to include subjects with a disease severity at the time of randomization that can reasonably be expected to respond (if such treatment effect exists) within the time frame of the study. Therefore, it is reasonable to include in the study subjects with HbA1c that falls within the 7 to 10 % range. However, it is interesting to note that about half of the patients with T2DM that are recruited or that volunteer for these studies have HbA1c outside of this range.

Table 13. Subject disposition for analyses of efficacy

		Study P021				Study P023			
		Sita 100	Sita 200	Placebo	Total	Sita 100	Sita 200	Placebo	Total
Total Randomized		238	250	253	741	205	206	110	521
Included in ITT analysis		229	238	244	711	193	199	103	495
Excluded from ITT analysis	No baseline data	2	0	0	2	3	1	1	5
	No on-treatment data	7	12	9	28	9	6	6	21
Included in Completers analysis		189	198	176	563	168	161	74	403
Excluded from Completers analysis	Rescued prior to study endpoint	17	10	45	72	13	17	15	45
	No data at study endpoint	23	30	23	76	12	21	14	47
ITT: modified ITT to represent all subjects randomized with baseline data and ≥ 1 post-randomization efficacy assessment and who took ≥ 1 dose of double-blind study agent									
Completers are a subset of ITT including all subjects with data at study endpoint without rescue glycemic therapy									

Adapted from the applicant's Table 10-3, reference P021V1 and Table 10-3, reference P023V1

6.1.4.2 Baseline and demographic characteristics

Demographic Characteristics

Study P021

The mean age of the randomized subjects in Study P021 was 54.2 years, 51.7 % were males and 49 % had been on prior anti-hyperglycemic medications prior to the study. The mean duration of T2DM was 4.4 years, and the mean baseline HbA1c was 8.0 %. The demographic characteristics were comparable among the 3 treatment groups (Table 14 and Table 15).

Study P023

The mean age of the randomized subjects in Study P023 was 55.1 years, 54.3 % were males, and 59.1 % had been on prior anti-hyperglycemic medications prior to the study. The mean duration of diabetes was 4.5 years, and the mean baseline HbA1c was 8.1 %. The demographic characteristics were comparable among the 3 treatment groups (Table 14 and Table 15).

Study P028

The mean age of the randomized subjects in Study P028 was 68 year, 51.6 % were males, and 68.1 % were on prior anti-hyperglycemic medications prior to the study. The mean duration of diabetes was 13.5 years, and the mean baseline HbA1c was 7.7%. The demographic characteristics were comparable among the 3 treatment groups, but were substantially different than those seen in the efficacy studies P021 and P023. In terms of baseline characteristics, there was a greater proportion of subjects with HbA1c < 8% and a lower proportion of subjects with baseline HbA1c ≥ 8 % and < 9 % in the sitagliptin groups, compared to placebo (71 % vs. 58% and 20 % vs. 35 %, respectively). The proportion of subjects with HbA1c ≥ 9% at baseline was similar across the treatment groups (9% in the sitagliptin group vs. 8% in the placebo group). It is unlikely that these imbalances would affect the interpretability of the efficacy results.

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Table 14. Demographic characteristics in subjects participating in Studies P021 and P023

	Study P021			Study P023		
Age (years)						
Treatment	N	Mean ± SD		N	Mean ± SD	
Sitagliptin 100 mg	238	53.4 ± 9.5		205	54.5 ± 10	
Sitagliptin 200 mg	250	54.9 ± 10.1		206	55.4 ± 9.2	
Placebo	253	54.3 ± 10.1		110	55.5 ± 10.1	
All	741	54.2 ± 9.9		521	55.1 ± 9.7	
Gender						
Treatment	Male N (%)	Female N (%)		Male N (%)	Female N (%)	
Sitagliptin 100 mg	136 (57.1)	102 (42.9)		110 (53.7)	95 (46.3)	
Sitagliptin 200 mg	117 (46.8)	133 (53.2)		104 (50.5)	102 (49.5)	
Placebo	130 (51.4)	123 (48.6)		69 (62.7)	41 (37.3)	
All	383 (51.7)	358 (48.3)		283 (54.3)	238 (45.7)	
Baseline Body Weight (kg)						
Treatment	N	Mean ± SD		N	Mean ± SD	
Sitagliptin 100 mg	238	85.0 ± 18.4		205	89.7 ± 19.1	
Sitagliptin 200 mg	250	83.7 ± 19.2		206	89.6 ± 19.4	
Placebo	253	85.0 ± 18.1		110	92.8± 18.8	
All	741	84.6 ± 18.5		521	90.3± 19.2	
Baseline Body Mass Index (kg/m2)						
Treatment	N	Mean ± SD		N	Mean ± SD	
Sitagliptin 100 mg	237	30.3 ± 5.2		205	31.8 ± 5.3	
Sitagliptin 200 mg	250	30.3 ± 5.4		205	32.0 ± 5.3	
Placebo	252	30.8 ± 5.5		110	32.5 ± 5.2	
All	739	30.5 ± 5.3		520	32.0 ± 5.3	
Race						
Treatment	Sitagliptin 100 mg N (%)	Sitagliptin 200 mg N (%)	Placebo N (%)	Sitagliptin 100 mg N (%)	Sitagliptin 200 mg N (%)	Placebo N (%)
White	122 (51.3)	132 (52.8)	127 (50.2)	142 (69.3)	146 (70.9)	68 (61.8)
Black	10 (4.2)	12 (4.8)	16 (6.3)	16 (7.8)	11 (5.3)	12 (10.9)
Hispanic	58 (24.4)	53 (21.2)	64 (25.3)	37 (18.0)	39 (18.9)	22 (20.0)
Asian	32 (13.4)	37 (14.8)	34 (13.4)	8(3.9)	7 (3.4)	5 (4.5)
Other	16 (6.7)	16 (6.4)	12 (4.7)	2 (1.0)	3 (1.5)	3 (2.7)

Adapted from the applicant's Table 10-4, reference P021V1 and Table 10-4, reference P023V1

Table 15. Baseline characteristics of subjects participating in Studies P021 and P023

Study P021				Study P023			
Baseline HbA1c (%)							
Treatment	**N**	**Mean**	**SD**	**Treatment**	**N**	**Mean**	**SD**
Sita 100 mg	236	8.0	0.9	Sita 100 mg	202	8.0	0.8
Sita 200 mg	250	8.1	0.9	Sita 200 mg	205	8.1	0.9
Placebo	253	8.0	0.8	Placebo	109	8.0	0.9
All	739	8.0	0.9	All	516	8.1	0.9
Baseline FPG (mg/dL)							
Sita 100 mg	238	170.7	43.0	Sita 100 mg	205	180.2	43.3
Sita 200 mg	249	174.2	46.2	Sita 200 mg	206	183.4	44.3
Placebo	253	176.1	41.8	Placebo	110	183.7	48.5
All	740	173.7	43.7	All	521	182.2	44.8
Baseline Fasting Insulin (microIU/mL)							
Sita 100 mg	233	14.5	13.1	Sita 100 mg	199	14.7	8.9
Sita 200 mg	247	14.1	11.8	Sita 200 mg	203	16.6	13.3
Placebo	252	14.9	10.8	Placebo	109	17.5	16.8
All	732	14.5	11.9	All	511	16.0	12.7
Duration of Type 2 Diabetes Mellitus (years)							
Sita 100 mg	238	4.3	4.9	Sita 100 mg	204	4.5	4.3
Sita 200 mg	250	4.3	4.7	Sita 200 mg	205	4.5	3.9
Placebo	252	4.6	4.7	Placebo	110	4.7	5.0
All	740	4.4	4.8	All	519	4.5	4.3
Use of Anti-Hyperglycemic Medication at Screening							
	Present	Absent	Total		Present	Absent	Total
Sita 100 mg	114 (47.9)	124 (52.1)	238	Sita 100 mg	118 (57.6)	87 (42.4)	205
Sita 200 mg	125 (50.0)	125 (50.0)	250	Sita 200 mg	120 (58.3)	86 (41.7)	206
Placebo	124 (49.0)	129 (51.0)	253	Placebo	70 (63.6)	40 (36.4)	110
All	363 (49.0)	378 (51.0)	741	All	308 (59.1)	213 (40.9)	521
Prevalence of Metabolic Syndrome†							
	Present	Absent	Total		Present	Absent	Total
Treatment	N (%)	N (%)	N	Treatment	N (%)	N (%)	N
Sita 100 mg	139 (58.4)	99 (41.6)	238	Sita 100 mg	130 (63.4)	75 (36.6)	205
Sita 200 mg	150 (60.0)	100 (40.0)	250	Sita 200 mg	132 (64.1)	74 (35.9)	206
Placebo	169 (66.8)	84 (33.2)	253	Placebo	81 (73.6)	29 (26.4)	110
All	458 (61.8)	283 (38.2)	741	All	343 (65.8)	178 (34.2)	521
Distribution of HbA1c at Baseline							
Number (%) of Subjects with Baseline HbA1c				Number (%) of Subjects With Baseline HbA1c			
Treatment	<8%	≥8 and <9%	≥9%	Treatment	<8%	≥8 and <9%	≥9%
Sita 100 mg	135 (57.2)	62 (26.3)	39 (16.5)	Sita 100 mg	103 (51.0)	70 (34.7)	29 (14.4)
Sita 200 mg	129 (51.6)	69 (27.6)	52 (20.8)	Sita 200 mg	99 (48.3)	62 (30.2)	44 (21.5)
Placebo	132 (52.2)	85 (33.6)	36 (14.2)	Placebo	63 (57.8)	26 (23.9)	20 (18.3)
All	396 (53.6)	216 (29.2)	127 (17.2)	All	265 (51.4)	158 (30.6)	93 (18.0)

Adapted from the applicant's Table 10-5, reference P021V1 and Table10-5, reference P023V1.

6.1.4.3 Primary efficacy endpoint: Change in HbA1c

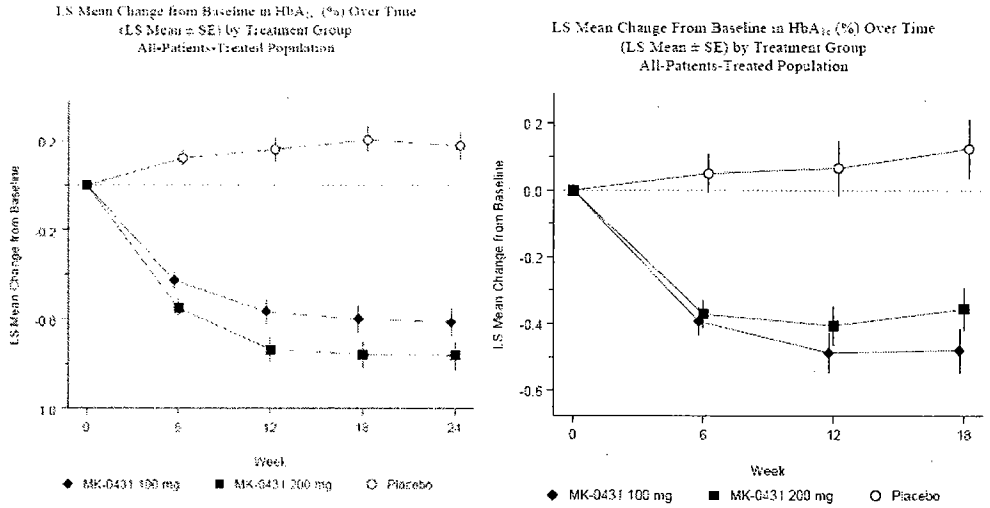
The results of the main analysis of the primary endpoint indicate a statistically and clinically significant effect of sitagliptin in lowering HbA1c by the study endpoint, compared to placebo (Table 16 and Figure 7). Using the least squared means of serum HbA1c in each treatment group, a difference from placebo of approximately 0.7 % is noted for the sitagliptin 100 mg group in both studies. The mean lowering effect of sitagliptin 200 mg in the 2 studies, while indicating an improvement in glycemic control, had discrepant magnitude between the 2 studies. In Study P021 the mean effect was greater in the sitagliptin 200 mg compared to sitagliptin 100 mg, while in Study P023 the mean HbA1c-lowering effect among subjects treated with sitagliptin 200 mg daily was smaller than that seen among those subjects treated with sitagliptin 100 mg daily. The reason for the lack of dose response in one study, while it is suggested in the other study, is unclear. These studies were not designed for dose titration, so we have no data to suggest that subjects treated with sitagliptin 100 mg would achieve further benefit by having a dose increase to 200 mg daily. There were no obvious differences in the demographic and baseline characteristics that could explain this finding, and the results of changes in HbA1c were consistent with changes in other markers of glycemic control, such as fasting plasma glucose and serum fructosamine (please see below). It is reasonable to speculate that the ability to inhibit DPP4 or the individual concentrations of endogenous endothelial or plasma DPP4 could predict a dose response; such studies, however, were not planned, and the data for dose selection in the phase 3 studies were based on pharmacodynamics in healthy volunteers. Regardless of a dose response, the studies indicate that sitagliptin used in monotherapy can improve glycemic control over an 18- or 24-week period, as manifested by lowering of the subject's baseline HbA1c.

Table 16. Change from baseline to study endpoint in serum HbA1c (%) in Studies P021 and P023

Treatment	N	Mean (SD)		Change from baseline			
		Baseline	Study Endpoint	Mean (SE)	LS Mean (SE)	95 % CI for LS Mean	LS Mean Difference from Placebo (95% CI)
P021 (Study Endpoint = Week 24)							
Sitagliptin 100 mg	229	8.01 (0.88)	7.39 (1.15)	-0.62 (0.07)	**-0.61** (0.06)	(-0.74, -0.49)	**-0.79** (-0.96, -0.62)
Sitagliptin 200 mg	238	8.08 (0.94)	7.31 (1.14)	-0.78 (0.06)	**-0.76** (0.06)	(-0.88, -0.64)	**-0.94** (-1.11, -0.77)
Placebo	244	8.03 (0.82)	8.20 (1.37)	0.17 (0.07)	*0.18* (0.06)	(0.06, 0.30)	-
P023 (Study Endpoint = Week 18)							
Sitagliptin 100 mg	193	8.04 (0.82)	7.58 (1.15)	-0.46 (0.06)	**-0.48** (0.07)	(-0.61, -0.35)	**-0.60** (-0.82, -0.39)
Sitagliptin 200 mg	199	8.14 (0.91)	7.81 (1.31)	-0.34 (0.07)	**-0.36** (0.06)	(-0.48, -0.23)	**-0.48** (-0.70, -0.26)
Placebo	103	8.05 (0.90)	8.21 (1.35)	0.16 (0.09)	0.12 (0.09)	(-0.05, 0.30)	-
Numbers in **bold** are associated with p<0.001 and in *italic* are associated with p<0.05							

Adapted from the applicant's Table 2.7.3:11 in Reference 2.7.3 Summary of Clinical Efficacy

Figure 7. Changes in HbA1c over time in Study P021 (on the left) and P023 (on the right)



Copied from the applicant's Figure 11-1 reference P021V1 and Figure 11-1, reference P023V1

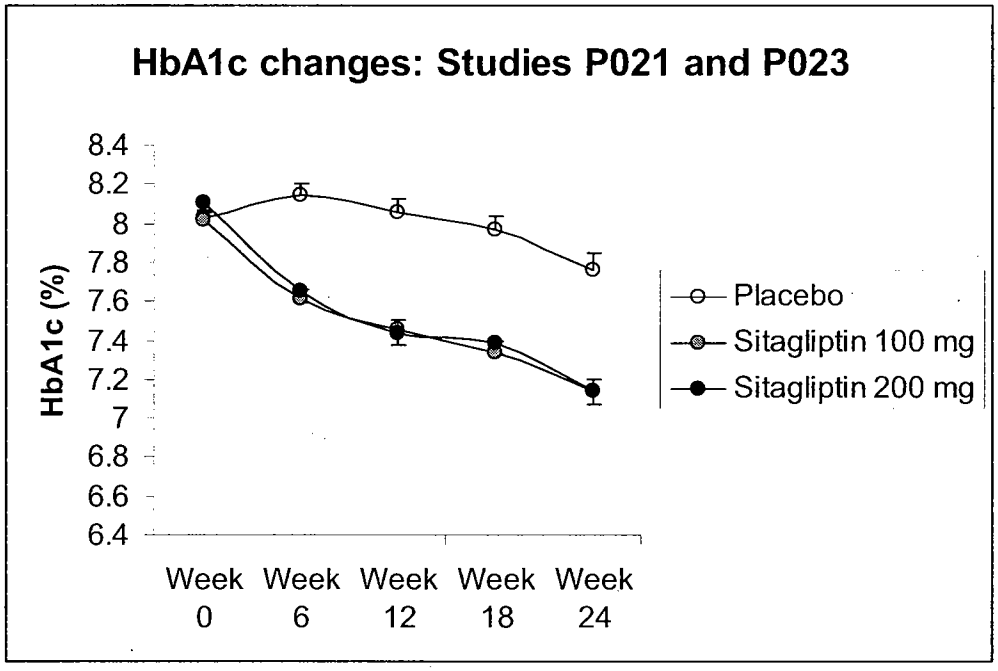
This reviewer combined the HbA1c data from baseline to week 18 (the last study timepoint common to the 2 studies) originated from Studies P021 and P023, to investigate the overall effect of sitagliptin 100 mg and 200 mg daily doses on the reduction in HbA1c (Table 17 and Figure 8) without excluding data due to glycemic rescue therapy.

Table 17. Mean change in HbA1c (%) from baseline to week 18 in the combined Monotherapy Studies by treatment group

Treatment	N at week 18	Mean change in HbA1c (± SD)
Placebo	363	0.05 ± 0.97
Sitagliptin 100 mg	443	-0.63 ± 0.88
Sitagliptin 200 mg	456	-0.66 ± 0.92

The overall placebo-subtracted reduction in HbA1c from baseline to week 18 in the 100 mg dose group was -0.72 %. This analysis, although useful in pooling results from studies with similar design, have the limitations of lack of randomization and the confounding effect of different proportions of subjects receiving glycemic rescue therapy with different magnitudes of effect. Despite the limitations, a difference favorable to sitagliptin-treated groups can be detected.

Figure 8. Mean changes in HbA1c (%) (± SE) by Study Visit in Studies P021 and P023 combined



* Week 24 data points reflect Study P021 data only.

In the combined studies, a substantial placebo-corrected reduction of HbA1c in the pooled sitagliptin treatment groups from baseline to week 18 is noted, of approximately 0.7 %. The mean treatment effect is similar among the 100 mg and the 200 mg dose cohorts, with a difference in HbA1c reduction between the 2 doses that does not reach statistical significance.

An analysis of changes in HbA1c among completers also showed significant reductions in HbA1c from baseline to study endpoint, but the treatment effect of sitagliptin compared to placebo was attenuated, in comparison with the treatment effect observed in the ITT population analysis (Table 18).

Table 18. Change from baseline to study endpoint in HbA1c (%) in completers in Study P021 and P023

Treatment	N	Mean (SD)		Change from baseline			
		Baseline	Study Endpoint	Mean (SE)	LS Mean (SE)	95 % CI for LS Mean	LS Mean Difference from Placebo (95% CI)
P021 (Study Endpoint = Week 24)							
Sitagliptin 100 mg	189	7.9 (0.9)	7.1 (0.9)	-0.8 (0.1)	**-0.8 (0.1)**	(-0.9, -0.6)	**-0.6** (-0.8, -0.5)
Sitagliptin 200 mg	198	8.0 (0.9)	7.1 (0.9)	-0.9 (0.1)	**-0.9** (0.1)	(-1.0, -0.7)	**-0.7** (-0.9, -0.6)
Placebo	176	7.9 (0.7)	7.8 (1.1)	-0.1 (0.1)	-0.1 (0.1)	(-0.2, 0)	-
P023 (Study Endpoint = Week 18)							
Sitagliptin 100 mg	168	8.0 (0.8)	7.4 (1.0)	-0.6 (0.1)	**-0.6** (0.1)	(-0.7, -0.5)	**-0.5** (-0.7, -0.3)
Sitagliptin 200 mg	161	8.0 (0.9)	7.6 (1.2)	-0.4 (0.1)	**-0.4** (0.1)	(-0.6, -0.3)	**-0.3** (-0.6, -0.1)
Placebo	74	7.9 (0.9)	7.8 (1.2)	-0.1 (0.1)	-0.1 (0.1)	(-0.3, 0.1)	-
Numbers in **bold** are associated with p<0.001 and in *italic* are associated with p<0.05							

Adapted from the applicant's Table 14-8, reference P021V1 and Table 14-8, reference P023V1

Even though the within-group decreases in HbA1c were larger in both sitagliptin groups in the analysis of completers, compared to the ITT analysis, the placebo-subtracted decrease in HbA1c was attenuated in the completers. More subjects in the placebo group than the sitagliptin groups were rescued with metformin and had their Week 24 HbA1c data imputed. Rescued / discontinued subjects generally had poorer HbA1c responses compared with subjects who completed without rescue therapy, and thus the completers placebo group showed a greater reduction from baseline when the imputed Week 24 values for the rescued/discontinued subset were removed.

6.1.4.3.1 Comparison of the treatment effect in Phase 3 studies to Phase 2 studies

The mean placebo-subtracted effect on HbA1c in the Phase 3 studies falls within the range of placebo-subtracted HbA1c changes from baseline to week 12 among subjects treated with sitagliptin 100 mg qd in the Phase 2 studies (Table 19). As expected, the mean estimates of HbA1c reduction vary more between studies and the confidence intervals are wider due to the smaller sample size in each study (121 subjects in P010, 214 subjects in P014 and 75 subjects in RC431201).

Table 19. Changes in mean HbA1c and fasting plasma glucose from baseline to week 12 in Phase 2 in the sitagliptin 100 mg daily groups in studies P010, P014 and RC431201

Study	Placebo-subtracted difference in LS Mean change in HbA1c (%) (95 % CI)	Placebo-subtracted difference in LS Mean change in Fasting Plasma Glucose (mg/dL) (95 % CI)
P010	-0.77 (-0.96, -0.58)	-26.1 (-34.9, -17.2)
P014	-0.56 (-0.75, -0.36)	-17.2 (-26.0, -8.4)
RC431201	-1.05 (-1.27, -0.84)	-31.9 (-39.7, -24.1)

In subjects with chronic renal insufficiency treated with sitagliptin 25 mg or 50 mg qd for 12 weeks, the magnitude of HbA1c reduction was more modest than that observed in 12 weeks of treatment with sitagliptin 100 mg in subjects with normal renal function in the Phase 2 studies (Table 20 and Table 21). The reason for the attenuated difference from placebo appears to be more related to some improvement in the mean glycemic control in the placebo group, rather than a smaller magnitude of reduction in HbA1c in the sitagliptin groups.

Table 20. Mean levels of HbA1c in Study P028 by treatment groups and study week

Treatment	**Sitagliptin 25 mg**			**Sitagliptin 50 mg**			**Placebo**		
	Baseline	Week 6	Week 12	Baseline	Week 6	Week 12	Baseline	Week 6	Week 12
N	29	25	24	36	36	34	26	25	25
Mean (SD) HbA1c	7.6 ± 0.7	7 ± 0.8	6.9 ± 0.8	7.6 ± 1.1	7.3 ± 1.0	7.1 ± 0.8	7.8 ± 0.9	7.7 ± 1.1	7.6 ± 1.0

Table 21. Change from baseline in HbA1c for the combined sitagliptin groups in Study P028

			Baseline	On treatment	Change from baseline	Placebo-subtracted difference in mean change in HbA1c (%) (95 % CI)
Week	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	
6	Sitagliptin	61	7.60 (0.95)	7.16 (0.93)	-0.44 (0.07)	
	Placebo	25	7.81 (0.90)	7.71 (1.07)	-0.10 (0.10)	
12	Sitagliptin	55	7.60 (0.95)	7.01 (0.83)	-0.59 (0.08)	**-0.41 (-0.71, -0.11)**
	Placebo	25	7.81 (0.90)	7.63 (1.05)	-0.18 (0.13)	

Adapted from the applicant's Table 14-8, reference P028v1

6.1.4.3.2 Exploratory analyses of efficacy in subsets based on demographic characteristics

Exploratory analyses of efficacy in the combined studies P021 and P023

In order to conduct integrated analyses of efficacy in the demographic subsets, this reviewer combined data from Studies P021 and P023, and calculated changes in HbA1c from baseline to week 18. These timepoints were chosen because only Study P021 has week 24 data. Table 22 and Table 23 show changes in HbA1c in the 3 treatment arms from baseline to week 18 in both Studies P021 and P023, by gender and by age categories, respectively. Missing data were not imputed in these analyses.

Sitagliptin effect on HbA1c by gender

Table 22. Mean (SD) changes in HbA1c (%) from baseline to week 18 in the combined Studies P021 and P023 by gender

	Females			Males		
Treatment	Mean (± SD)	N (week 0)	N (week 18)	Mean (± SD)	N (week 0)	N (week 18)
Placebo	0.1 ± 1.0	163	129	0 ± 0.9	199	152
Sitagliptin 100 mg	-0.5 ± 0.9	194	167	-0.7 ± 0.8	243	211
Sitagliptin 200 mg	-0.6 ± 0.9	235	196	-0.7 ± 1.0	220	183

Reductions in HbA1c from baseline were observed in both male and female subgroup analyses. The mean differences from placebo appear comparable in both genders without evidence of a dose-response.

Sitagliptin effect on HbA1c by categories of age

Table 23. Mean (SD) changes in HbA1c (%) from baseline to week 18 in the combined Studies P021 and P023 by age categories

Age categories (years)	Treatment	N at week 0	N week 18	Mean HbA1c change	SD
≤ 35	Placebo	12	9	-0.2	1.6
	Sitagliptin 100 mg	14	12	-0.6	0.7
	Sitagliptin 200 mg	15	11	-0.5	0.9
>35 to ≤ 60	Placebo	253	194	0.1	0.9
	Sitagliptin 100 mg	306	258	-0.6	0.9
	Sitagliptin 200 mg	303	252	-0.6	0.9
> 60	Placebo	97	78	0	0.9
	Sitagliptin 100 mg	117	108	-0.7	0.9
	Sitagliptin 200 mg	137	116	-0.7	0.9

The difference in sitagliptin effect on HbA1c from baseline to week 18 within each age group was similar in the 3 age categories. The placebo-subtracted effect appears attenuated in those subjects younger than 35 years of age, but the numbers are very small to reach any conclusion. The decrease in each age category was not proportional to the dose of sitagliptin used.

Exploratory analyses of efficacy in the individual studies

Sitagliptin effect on HbA1c by gender

Table 24 . Mean change in HbA1c (%) from baseline to week 24 in Study P021 by gender

Gender	Treatment	N	Mean (± SD) change in HbA1c
Female	Placebo	123	-0.1 ± 0.9
	Sitagliptin 100 mg	102	-0.7 ± 0.9
	Sitagliptin 200 mg	133	-0.8 ± 0.8
Male	Placebo	130	-0.2 ± 1.0
	Sitagliptin 100 mg	135	-0.8 ± 0.9
	Sitagliptin 200 mg	117	-1.0 ± 0.9

Relative to the mean changes observed in the placebo group, the reduction in HbA1c between males and females treated with either dose of sitagliptin in Study P021 was similar.

Table 25. Mean HbA1c change from baseline to week 18 in Study P023, by gender

Gender	Treatment	N	Mean (± SD) change in HbA1c
Female	Placebo	41	0.1 ± 1.0
	Sitagliptin 100 mg	95	-0.5 ± 0.8
	Sitagliptin 200 mg	102	-0.4 ± 0.9
Male	Placebo	69	-0.1 ± 0.8
	Sitagliptin 100 mg	110	-0.6 ± 0.8
	Sitagliptin 200 mg	104	-0.4 ± 0.9

In Study P023, gender did not influence the effect of sitagliptin on the reduction in HbA1c from baseline to week 18. The response was not proportional to the sitagliptin dose in neither males nor females.

Sitagliptin effect on HbA1c by categories of age

Table 26. Mean changes in HbA1c (%) from baseline to week 24 in Study P021 by age categories

Age categories	Treatment	N at week 0	N week 24	Mean (± SD) change in HbA1c
≤ 35	Placebo	8	5	-0.7 ± 1.2
	Sitagliptin 100 mg	10	10	-0.8 ± 0.8
	Sitagliptin 200 mg	10	8	-0.8 ± 0.5
>35 to ≤ 60	Placebo	182	123	-0.1 ± 1.0
	Sitagliptin 100 mg	172	133	-0.7 ± 0.9
	Sitagliptin 200 mg	165	135	-0.8 ± 0.9
> 60	Placebo	63	48	-0.1 ± 0.8
	Sitagliptin 100 mg	56	46	-0.9 ± 1.0
	Sitagliptin 200 mg	75	55	-1.0 ± 0.8

Table 27. Mean HbA1c change from baseline to week 18 in Study P023, by age categories

Age categories	Treatment	N	Mean (± SD) change in HbA1c
≤ 35 years	Placebo	4	-0.5 ± 0.8
	Sitagliptin 100 mg	5	-0.3 ± 0.6
	Sitagliptin 200 mg	5	0.3 ± 1.4
> 35 to ≤ 60 years	Placebo	71	0 ± 0.9
	Sitagliptin 100 mg	138	-0.6 ± 0.8
	Sitagliptin 200 mg	139	-0.4 ± 0.9
> 60 years	Placebo	35	-0.2 ± 0.9
	Sitagliptin 100 mg	62	-0.6 ± 0.7
	Sitagliptin 200 mg	62	-0.6 ± 0.8

The placebo-subtracted mean effect was similar among those subjects treated with sitagliptin at either 100 mg or 200 mg daily in both studies. The placebo-subtracted magnitude of glycemic improvement in response to sitagliptin appeared again attenuated in the group younger than 35 years of age primarily due to a reduction of HbA1c in the few placebo-treated subjects in that age category.

Sitagliptin effect on HbA1c by racial groups

Table 28. Mean change in HbA1c (%) from baseline to week 24 in Study P021 by racial groups *

Race	Treatment	N	Mean (± SD) change in HbA1c
Asian	Placebo	34	-0.2 ± 0.9
	Sitagliptin 100 mg	32	-0.7 ± 0.7
	Sitagliptin 200 mg	37	-0.9 ± 0.8
Hispanic	Placebo	64	-0.1 ± 0.9
	Sitagliptin 100 mg	58	-1.0 ± 1.1
	Sitagliptin 200 mg	53	-1.0 ± 0.9
Black	Placebo	16	0.1 ± 1.1
	Sitagliptin 100 mg	10	-0.9 ± 0.6
	Sitagliptin 200 mg	12	-1.0 ± 0.6
Multiracial	Placebo	11	-0.3 ± 1.3
	Sitagliptin 100 mg	13	-1.2 ± 1.0
	Sitagliptin 200 mg	14	-1.1 ± 1.1
White	Placebo	127	-0.1 ± 0.9
	Sitagliptin 100 mg	121	-0.6 ± 0.8
	Sitagliptin 200 mg	132	-0.8 ± 0.8

* excludes groups with ≤ 2 subjects each: European, Indian, Native American, and Polynesian

Table 29. Mean HbA1c change from baseline to week 18 in Study P023, by racial groups *

Race	Treatment	N	Mean (± SD) change in HbA1c
Asian	Placebo	5	0.3 ± 1.1
	Sitagliptin 100 mg	8	-1.0 ± 0.9
	Sitagliptin 200 mg	7	-0.6 ± 0.6
Hispanic	Placebo	22	-0.6 ± 1.1
	Sitagliptin 100 mg	37	-0.5 ± 0.9
	Sitagliptin 200 mg	39	-0.7 ± 1.0
Black	Placebo	12	-0.3 ± 1.0
	Sitagliptin 100 mg	16	-0.7 ± 0.8
	Sitagliptin 200 mg	11	0.3 ± 1.2
White	Placebo	68	-0.1 ± 0.8
	Sitagliptin 100 mg	142	-0.6 ± 0.7
	Sitagliptin 200 mg	146	-0.4 ± 0.8

* excludes groups containing ≤ 2 each: Indian, Native American, Polynesian, and Multiracial

Mean reductions in HbA1c were observed across all racial groups in both studies; however, too few subjects in certain racial groups preclude any definitive conclusions on efficacy subgroup analysis.

Sitagliptin effect on HbA1c by categories of body mass index

Table 30. Mean change in HbA1c (%) from baseline to week 24 in Study P021 according to categories of body mass index (lower or equal/greater than the study median)

BMI Categories	Treatment	N	Mean (± SD) change in HbA1c
< 30.15 Kg/m^2	Placebo	125	-0.1 ± 0.8
	Sitagliptin 100 mg	120	-0.8 ± 0.8
	Sitagliptin 200 mg	124	-1.0 ± 0.9
≥ 30.15 Kg/m^2	Placebo	127	-0.1 ± 1.0
	Sitagliptin 100 mg	116	-0.8 ± 1.0
	Sitagliptin 200 mg	126	-0.8 ± 0.8

Table 31. Mean HbA1c change from baseline to week 18 in Study P023, by categories of body mass index, (lower or equal/greater than the study median)

BMI categories	Treatment	N	Mean (± SD) change in HbA1c
< 32.15 Kg/m^2	Placebo	51	0 ± 1.0
	Sitagliptin 100 mg	105	-0.5 ± 0.8
	Sitagliptin 200 mg	104	-0.4 ± 0.8
≥ 32.15 Kg/m^2	Placebo	59	-0.1 ± 0.8
	Sitagliptin 100 mg	100	-0.6 ± 0.8
	Sitagliptin 200 mg	101	-0.4 ± 1.0

The mean effect of sitagliptin was consistent between subjects with BMI greater or smaller than the median in both studies.

The conclusions of these exploratory subset analyses based on demographic characteristics are consistent with those of the applicant.

Figure 9 and Figure 10 below, are provided by the applicant, plotting the point estimates for the treatment effect of sitagliptin 100 mg in different subsets, based on demographic and important disease characteristics that can affect outcome. The point estimates in subsets can be visually compared to the point estimate of the overall treatment effect for Studies P021 and P023.

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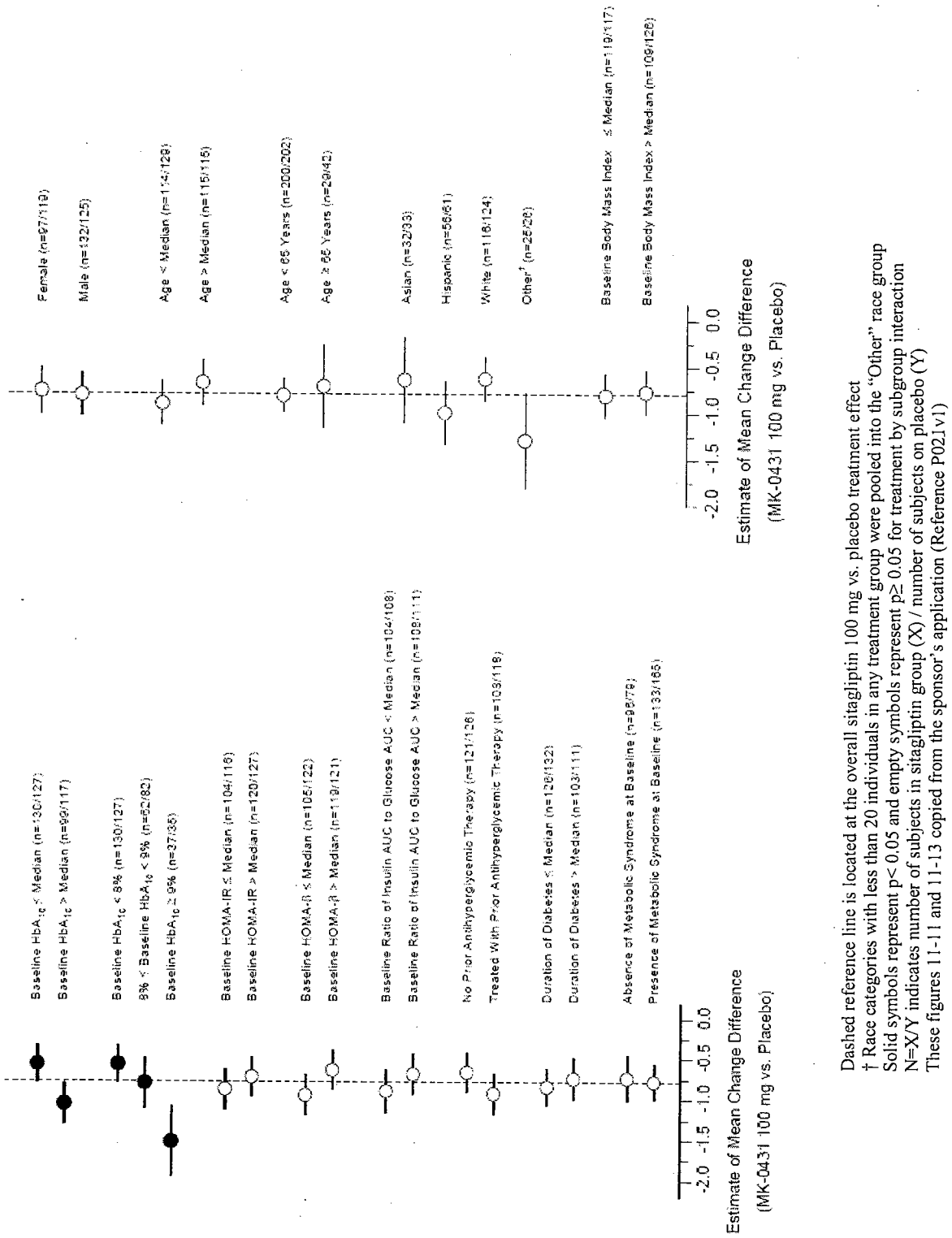
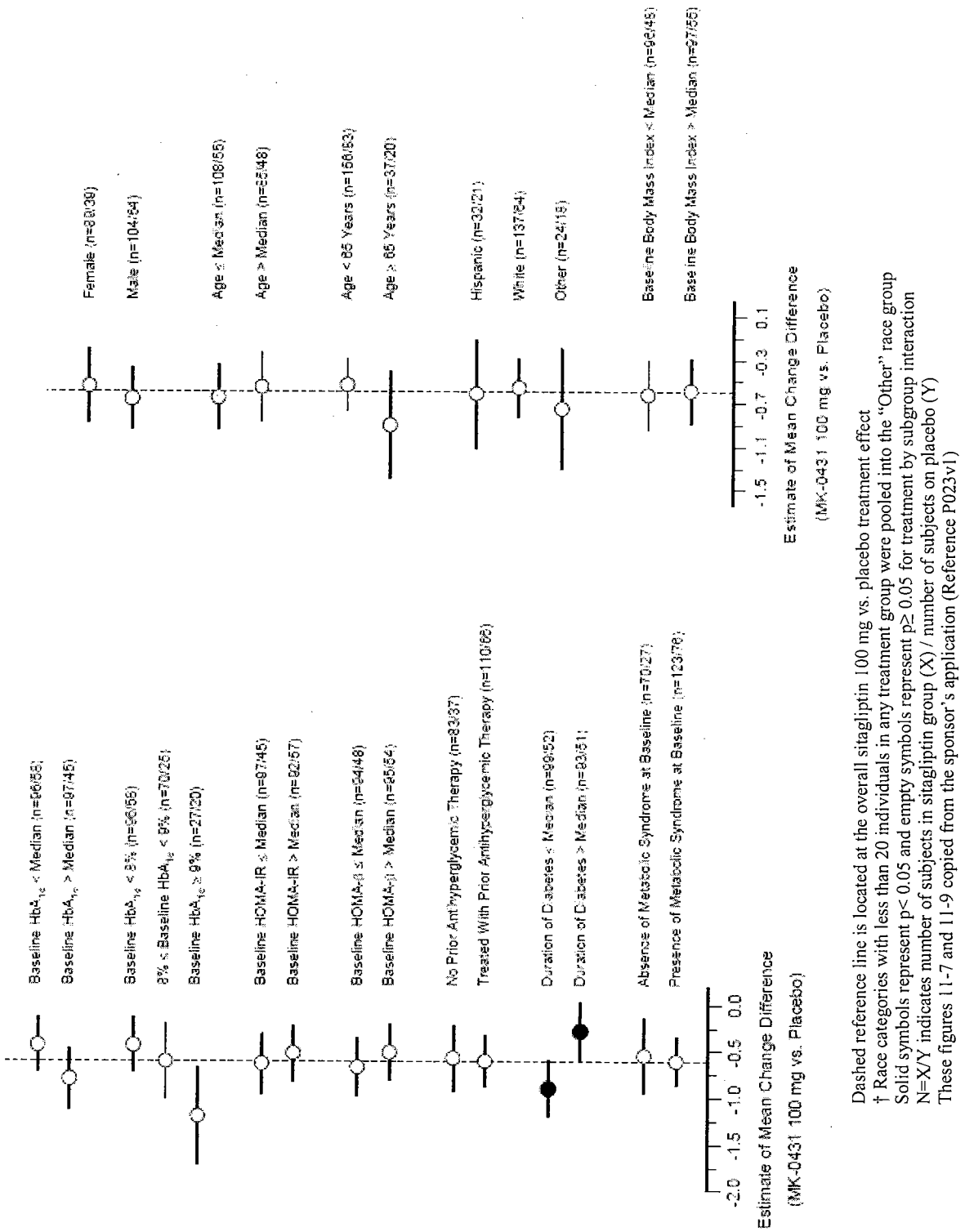
Figure 9. Point estimates (95% CI) of HbA1c mean change in study P021 by demographic / baseline subsets



Dashed reference line is located at the overall sitagliptin 100 mg vs. placebo treatment effect
† Race categories with less than 20 individuals in any treatment group were pooled into the "Other" race group
Solid symbols represent $p < 0.05$ and empty symbols represent $p \geq 0.05$ for treatment by subgroup interaction
N=X/Y indicates number of subjects in sitagliptin group (X) / number of subjects on placebo (Y)
These figures 11-11 and 11-13 copied from the sponsor's application (Reference P021v1)

Figure 10.Point estimates (95% CI) of HbA1c mean change in study P023 by demographic / baseline subsets



Dashed reference line is located at the overall sitagliptin 100 mg vs. placebo treatment effect
† Race categories with less than 20 individuals in any treatment group were pooled into the "Other" race group
Solid symbols represent p< 0.05 and empty symbols represent p≥ 0.05 for treatment by subgroup interaction
N=X/Y indicates number of subjects in sitagliptin group (X) / number of subjects on placebo (Y)
These figures 11-7 and 11-9 copied from the sponsor's application (Reference P023v1)

From Figure 9 above, a trend is noted in Study P021 for greater treatment effect in the subset with baseline HbA1c greater than the study median, and this statistical trend becomes more apparent by contrasting the HbA1c reduction among those subjects who had baseline HbA1c less than 9 % to those with baseline HbA1c greater than 9%.
A similar trend is seen in Figure 10, where subjects in Study P023 with baseline HbA1c greater than 9% had greater reduction of HbA1c at week 18 with sitagliptin 100 mg qd, compared to subjects with HbA1c of less than 9% at baseline. The analysis did not reach statistical significance, compared to equivalent data in Study P021. In Study P023, a statistical trend is also observed with greater treatment effect in subjects who had duration of disease less than the study median (3 years).

<u>Applicant's analyses of pooled studies P021 and P023 in subsets defined by demographic and by disease-specific baseline characteristics.</u>

In the pooled analyses of Studies P021 and P023, treatment effects on HbA1c were generally consistent between subsets defined by gender, age, race/ethnicity, and baseline body mass index at Week 18. Subsets defined by race were, however, of variable size, and this may have reduced the sensitivity to detect differences in response. In particular, there is a non-statistically significant trend towards greater placebo-subtracted HbA1c reduction in the Hispanic and Black subgroups. The largest subgroups were Whites and Hispanics where the estimated treatment effects were -0.61% and -0.89%, respectively.
Significant differences in the sitagliptin 100 mg effect among subsets defined by baseline HbA1c were observed, whether categorizing by baseline median HbA1c ($p = 0.008$) or by baseline categories: $< 8\%$, $\geq 8\%$ but $< 9\%$, and $\geq 9\%$ ($p < 0.001$). Most notable was the increased HbA1c-lowering efficacy for subjects whose baseline HbA1c was $\geq 9\%$ (placebo-adjusted lowering of -1.45%). The interaction test was also significant when subjects were grouped by both baseline HbA1c category and prior use of anti-hyperglycemic therapy status ($p < 0.001$); however, the notable difference was again between those subjects whose baseline HbA1c was $\geq 9\%$ and the rest, with relatively small effect differences between categories defined by prior anti-diabetic therapy (i.e., previously on or not previously on an anti-diabetic medications) within a given HbA1c category.
A significant interaction ($p = 0.032$) with treatment was also observed with subsets defined by the baseline tertiles of HOMA-β: a greater HbA1c-lowering was observed for the subjects in the lowest baseline tertile (lower baseline insulin secretion) relative to the other tertiles: patients in the lowest tertile of HOMA-β had nearly 1% reduction in HbA1c relative to placebo. No statistically significant treatment interactions were observed for subgroups defined by baseline tertiles of HOMA-IR or baseline tertiles of proinsulin to insulin ratio at Week 18; however, there is a trend towards greater HbA1c reduction in patients who have the highest proinsulin to insulin ratios. Increase in proinsulin secretion and an increase in the ratio of proinsulin to insulin are accepted markers of beta-cell dysfunction and are commonly observed in patients with T2DM. Hence, subjects with the highest ratio of proinsulin to insulin would be expected to have the greatest extent of beta-cell dysfunction. There is also a trend towards greater HbA1c reduction in patients with a lower HOMA-IR (i.e., less insulin resistant patients).
Treatment effects across subsets defined by factors related to diabetes disease history were explored. A significant interaction ($p < 0.05$) was observed for subsets defined by median

duration of diabetes (the median duration was 3 years), with efficacy at Week 18 greater in patients with shorter duration. When diabetes duration was categorized as ≤ 5 years, > 5 but ≤ 10 years, or > 10 years, the interaction test was not significant (p = 0.257); however, subjects with duration ≤ 5 years had numerically greater placebo-subtracted HbA1c reduction compared to subjects in the other duration categories. No statistically significant treatment interactions were observed for subgroups defined by prior anti-hyperglycemic therapy status or presence/absence of metabolic syndrome.

6.1.4.3.3 Other sensitivity and exploratory analyses of the primary endpoint data

Individual changes in HbA1c categories over time in Studies P021 and P023

Figure 11 shows the changes in HbA1c (HbA1c data being divided in 4 color-coded categories) occurring in each subject from baseline to the study endpoint (week 18 in P023 and week 24 in P021), with subjects sorted in ascending order according to their baseline HbA1c. Missing data were imputed by LOCF, according to the statistical analytical plan described in each of these study protocols.

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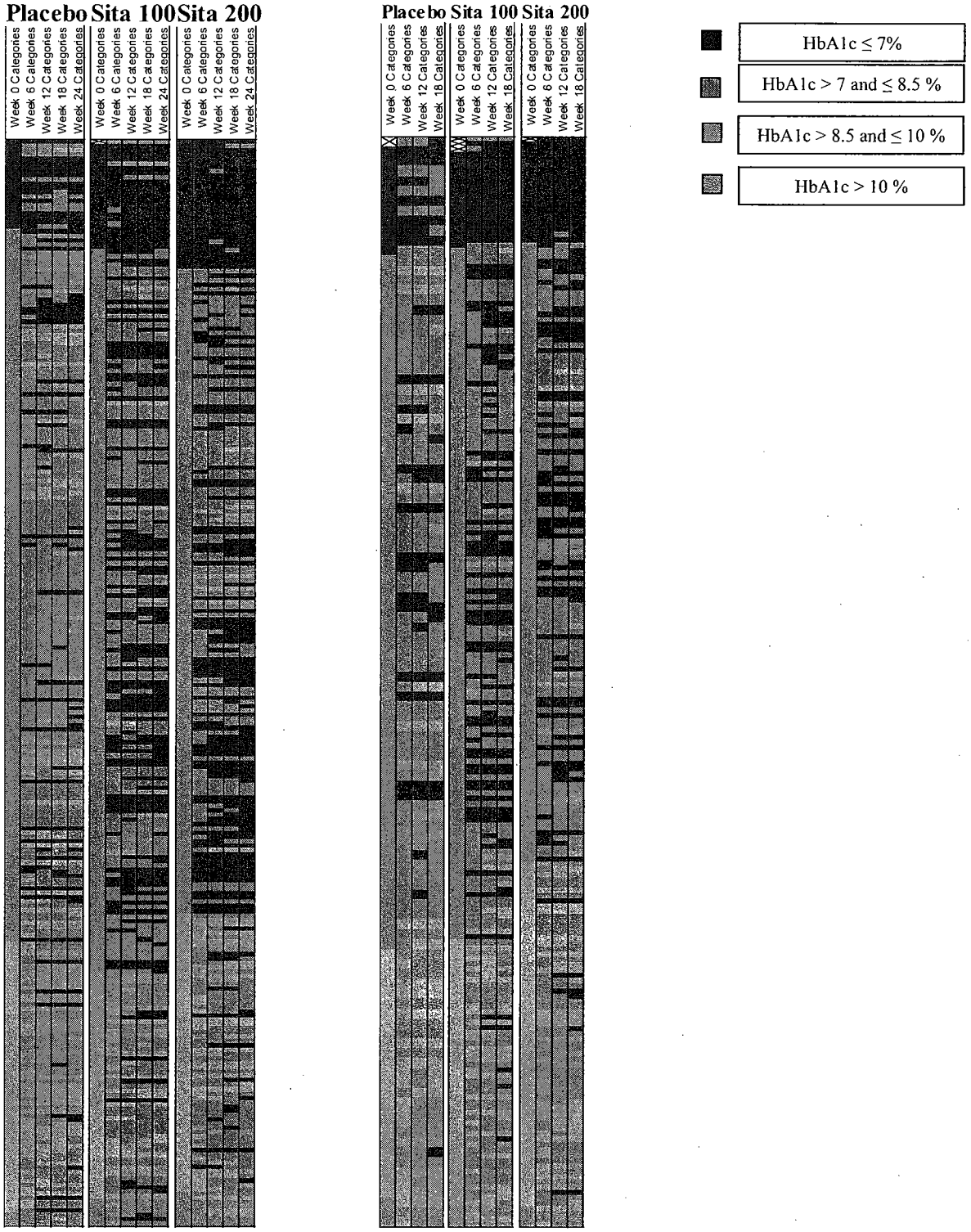
Figure 11. Changes in HbA1c categories, by subject, from baseline to study endpoint in Studies P021 and P023



In Figure 11, we note that for those subjects on placebo who had HbA1c greater than 8.5 % at baseline in each of the studies, few were able to reduce HbA1c to the other categories (to

between 7 and 8.5% or to < 7%). The majority of subjects randomized to either dose of sitagliptin in these studies with baseline HbA1c in the categories > 8.5 % were able to reduce their HbA1c to a more improved category within 6 weeks of treatment.

Proportion of subjects reaching ADA goal of HbA1c < 7 % at Study Endpoint for Studies P021 and P023

The applicant designated this analysis as a tertiary (or "other") endpoint. However, this reviewer considers the proportion of subjects reaching a pre-determined threshold of HbA1c as exploration of the primary efficacy endpoint. Therefore the data are presented here (Table 32).

Table 32. Proportion of subjects reaching HbA1c < 7 % at Study Endpoint in Studies P021 and P023

Treatment	N	n(%) < 7%	Difference in Proportion from Placebo (95 % CI)
P021 (Study Endpoint = Week 24)			
Sitagliptin 100 mg	229	93 (40.6)	23.8* (15.8, 31.9)
Sitagliptin 200 mg	238	108 (45.4)	28.6* (20.5, 36.7)
Placebo	244	41 (16.8)	-
P023 (Study Endpoint = Week 18)			
Sitagliptin 100 mg	193	69 (35.8)	20.2* (9.8, 30.6)
Sitagliptin 200 mg	199	57 (28.6)	13.1* (3.0, 23.2)
Placebo	103	16 (15.5)	-
* p <0.001; from logistic regression model, adjusting for baseline HbA1c and prior anti-diabetic medication status			

Adapted from the applicant's Table 2.7.3:12, in reference 2.7.3. Summary of Clinical Efficacy

The number of subjects reaching the ADA target of HbA1c < 7% was substantially greater in the sitagliptin groups, compared to placebo. In accordance with the data describing the absolute changes in HbA1c, the effect of sitagliptin 200 mg was slightly greater than 100 mg in Study P021 and was slightly smaller than the 100 mg group in Study P023.

6.1.4.3.4 Durability of sitagliptin effect from Phase 2 studies data

As T2DM is a chronic and often progressive condition, it is important to demonstrate durability of effect with any pharmacotherapy. In addition, secondary failure to anti-diabetic agents is a common feature of T2DM. The secondary failure occurs with all classes of anti-diabetic agents and is probably related to worsening of the pathogeneses of T2DM: insulin resistance and beta cell failure.

In order to evaluate the effect of sitagliptin on HbA1c beyond the 24 weeks of placebo-control study, the applicant compared HbA1c in the pooled groups that had received a total daily dose of sitagliptin of 100 mg (224 subjects in Studies P010 and P014 randomized to either 50 mg bid or to 100 mg qd in the 12 week base studies and who continued to be

treated with 100 mg qd during the 40-week extension) to 77 subjects randomized to glipizide in Study P010 (Figure 12).

Figure 12. Mean change in HbA1c in the base studies P010 and P014 and in their extension studies among subjects receiving a total daily dose of 100 mg of sitagliptin versus glipizide

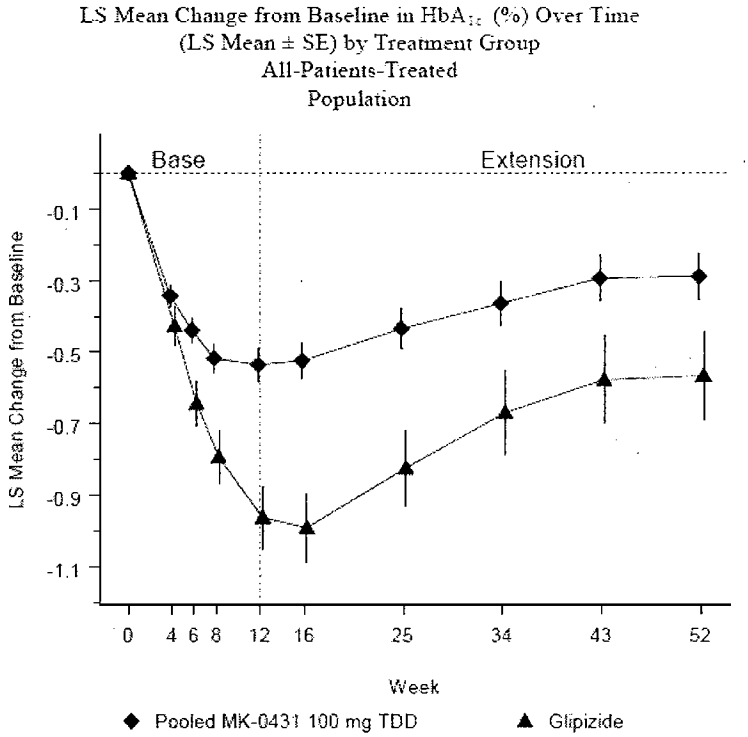


Figure 4 copied from the applicant's Original Submission, reference R23 Memo to Gertz B, Bain R, Amatruda J from Lunceford J, Stein P: Integrated Summary of Efficacy Results, 2005. The pooled sitagliptin group has 224 subjects and the glipizide group has 77 subjects.

The HbA1c lowering effect of glipizide was more evident than that of 100 mg of sitagliptin along the 52 weeks of these studies. Nevertheless, the figure demonstrates that the effect of sitagliptin persisted in the extension studies.
The applicant observes that the trend to return towards the baseline HbA1c between weeks 25 and 52 (the "slope" of LS Means) was higher for glipizide than for sitagliptin, which suggests a faster loss of treatment effect with the sulfonylurea treatment.

Table 33. "Coefficient of durability (COD)" of the sitagliptin effect of 100 mg compared to glipizide in Studies P010 and P014 and their extensions

Treatment	COD (% per Week)	SE	95% CI
Pooled Sitagliptin 100 mg TDD†	0.006	0.001	(0.003, 0.008)
Glipizide	0.010	0.003	(0.004, 0.016)

† The Pooled Sitagliptin 100 mg TDD group includes the Sitagliptin 50 mg b.i.d./100 mg qd treatment group from Protocol 010 and the Sitagliptin 50 mg b.i.d./100 mg qd and the Sitagliptin 100 mg q.d./100 mg qd treatment groups from Protocol 014.
TDD=Total Daily Dose; SE=Standard Error; CI=Confidence Interval.

Adapted from the applicant's Table 2.7.3:48, reference 2.7.3. Summary of Clinical Efficacy

Whether this is a benefit to patients is both speculative and unclear; one can equally speculate that having one year with improved glycemic control due to glipizide is a better choice overall than a faster loss of the benefit. The slope of LS Means of HbA1c also appear to become horizontal between weeks 43 and 52, which places into question the choice of interval calculated for the demonstration of the "coefficient of durability", the term coined by the applicant to note that sitagliptin effect tends to persist more than glipizide.
Regardless of the speculation in interpreting the data collected, it is important to conclude that there is evidence of durability of the treatment effect beyond 24 weeks in a substantial number of subjects.

6.1.4.3.5 Durability of sitagliptin effect on HbA1c reduction in Phase 3 studies

The applicant submitted 1-year efficacy data with the 4-month Safety Update Report for Study P021 (use of sitagliptin in monotherapy) and P020 (use of sitagliptin in combination with metformin).

Study P021
Study Design and Subject Disposition and Baseline characteristics
In Phase A of Study P021, subjects were randomized 1:1:1 to sitagliptin 100mg, 200 mg or placebo. At week 24, those subjects treated with either dose of sitagliptin who met eligibility to participate in the 80-week extension study (Phase B) remained treated with the dose they had been assigned originally. Subjects randomized to placebo in Phase A were re-randomized 1:1 to either sitagliptin 100 mg or sitagliptin 200 mg groups during Phase B. The groups are designated here as sitagliptin 100 mg, sitagliptin 200 mg, placebo / sitagliptin 100 mg or placebo / sitagliptin 200 mg.
The ITT population consisted of subjects with HbA1c at baseline of Phase A and at least one measurement during Phase B. Imputation of missing data was conducted through LOCF. Subject disposition is shown in Table 34.

Table 34. Accounting for subjects in Study P021 Phase B

	Number (%)				
	Sitagliptin 100 mg	Sitagliptin 200 mg	Placebo / sitagliptin 100 mg	Placebo / sitagliptin 200 mg	Total
Total Randomized	238	250	130	123	741
Entered Phase B (% of randomized)	190 (79.8)	198 (79.2)	82 (63.1)	84 (68.3)	554 (74.8)
Included in ITT*	188 (98.9)	194 (98)	81 (98.8)	83 (98.8)	546 (98.6)
Included in Completers*	150 (78.9)	135 (68.2)	65 (79.3)	62 (73.8)	412 (74.4)

* Except where noted, percentages are calculated relative to the number of subjects entering Phase B
Adapted from Table 6-2, reference r0027 in Amendment 0011 (4-month Safety Update Report)

Subjects who entered Phase B exhibited generally better baseline glycemic control, shorter mean duration of diabetes, lower prevalence of metabolic syndrome, lower baseline body

weight, and were less likely to have been taking anti-diabetic agents at screening relative to those who did not continue into Phase B. These characteristics likely reflect, in part, a higher propensity for patients with poorer glycemic control to require glycemic rescue due to progressively stricter glycemic rescue criteria implemented during Phase A of the study (Please refer to Section 6.1.3.1. General Overview of study design, for criteria for glycemic rescue therapy). For subjects entering Phase B, baseline demographic and anthropometric characteristics were generally balanced across the treatment groups as were variables describing disease history and baseline glycemic control.

Results

Table 35 shows data on the efficacy endpoints in Study P021, namely HbA1c, Fasting plasma glucose and 2-hour post-meal glucose in each of the groups. Data are shown as LS means of baseline and week 54 values (± SD) in the ITT population, as well as the least square means (± SE) and the proportion of the treatment effect observed for the endpoint in week 24 that is maintained at week 54.

Table 35. Changes from baseline to week 54 in HbA1c fasting and post-meal glucose in Study P021

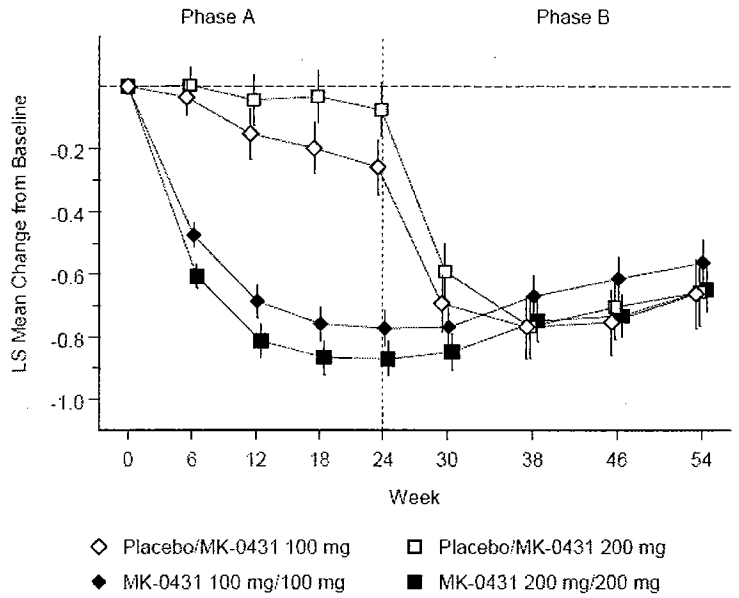
Endpoint		Sitagliptin 100	Sitagliptin 200	PBO / Sita 100	PBO / Sita 200
HbA1c (%)					
	N	188	194	81	83
	Baseline	7.9 (0.8)	8.0 (0.9)	7.9 (0.7)	7.8 (0.7)
	Week 54	7.3 (1.0)	7.3 (1.2)	7.2 (1.0)	7.2 (1.0)
	LS Mean change (SE)	-0.56 (0.1)	-0.65 (0.1)	-0.66 (0.1)	-0.66 (0.1)
	% week 24 effect maintained at week 54	73	75		
Fasting Plasma Glucose (mg/dL)					
	N	190	193	81	83
	Baseline	162 (34)	168 (43)	164 (34)	163 (38)
	Week 54	154 (38)	154 (44)	150 (51)	147 (39)
	LS Mean change (SE)	-9 (3)	-14 (3)	-14 (51)	-16 (5)
	% week 24 effect maintained at week 54	58	63		
2-hour post-meal glucose (mg/dL)					
	N	142	128	59	56
	Baseline	241 (68)	246 (71)	250 (58)	238 (69)
	Week 54	199 (55)	183 (62)	191 (75)	185 (76)
	LS Mean change (SE)	-43 (5)	-61 (5)	-54 (8)	-56 (8)
	% week 24 effect maintained at week 54	76	85		

Adapted from the applicant's Study report r0027, submitted 5/4/06 with the 4-Month Safety Update Report

In the sitagliptin 100 mg group, 77 of 188 subjects (41%) had HbA1c < 7 % at week 54, and in the sitagliptin 200 mg group, 90 of 194 subjects (46%) had HbA1c < 7%.
Regarding the effect in the subjects switched from placebo to either dose of sitagliptin, it is interesting to note that the magnitude of HbA1c lowering from week 24 to week 54 is consistent with that seen in the active treatment groups in Phase A and that the effect was seen within the initial 6 weeks after the switch to sitagliptin.
The completers population excluded approximately 25% of patients from the ITT cohort (who did not reach Week 54). Among completers treated with sitagliptin 100 mg or 200 mg

daily, the mean changes from baseline at Week 54 were -0.72% and -0.92% for maintenance of 87% and 93% of the Week 24 effects, respectively.

Figure 13. LS Mean change from baseline in HbA1c (%) over time by treatment group (LS Mean ± SE) in the ITT population



Copied from the applicant's Figure 8-1, in reference r0027

For each dose of sitagliptin, the placebo/sitagliptin treatment arms showed efficacy at Week 54 that was generally similar in magnitude to that of the original sitagliptin groups for both HbA_{1c} and FPG in the ITT and completers analysis populations. However, at the time of the Week 24 switch from placebo to sitagliptin, the placebo subjects entering Phase B had demonstrated decreases from baseline that were greater for those switching to sitagliptin 100 mg than those switching to sitagliptin 200 mg. In general, for HbA_{1c}, FPG, and 2-hour post-meal glucose, there was a trend towards greater durability with the 200 mg dose—a trend more marked in the completers population than the ITT population.

6.1.4.4 Secondary efficacy endpoints

6.1.4.4.1 Change in fructosamine

Although the applicant has not designated fructosamine as a secondary endpoint in either of the Phase 3 monotherapy studies, fructosamine measures integrated glycemic control in a way similar to the HbA1c. The main difference between fructosamine and HbA1c is the more rapid turnover of the former, thus assessing the average glycemic control over a period of 2- 3 weeks, instead of several months.

Table 36. Serum fructosamine (micromol/L) changes in Study P021

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	231	321 (60)	298 (58)	-23 (3)	-24 (3)	(-29, -18)	<0.001
Sitagliptin 200 mg	240	329 (62)	303 (56)	-26 (3)	-25 (3)	(-30, -19)	<0.001
Placebo	242	325 (59)	331 (69)	6 (3)	6 (3)	(1, 11)	0.028
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error							

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-29** (-37, -22)	<0.001
Sitagliptin 200 mg vs. Placebo	-31 (-38, -24)	<0.001
Sitagliptin 200 mg vs. Sitagliptin 100 mg	-1 (-9, 6)	0.689

Adapted from the applicant's Table 11-5, Reference P021v1

Table 37. Serum fructosamine (micromol/L) changes in Study P023

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	190	322 (56)	298 (56)	-24 (3)	-25 (3)	(-31, -19)	<0.001
Sitagliptin 200 mg	189	325 (53)	310 (58)	-16 (3)	-16 (3)	(-22, -10)	<0.001
Placebo	95	324 (58)	323 (62)	-1 (4)	-2 (5)	(-11, 7)	0.662
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error							

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-23** (-34, -12)	<0.001
Sitagliptin 200 mg vs. Placebo	-14 (-25, -3)	<0.001
Sitagliptin 200 mg vs. Sitagliptin 100 mg	9 (0, 18)	0.046

Adapted from Table 11-3, Reference P023v1

It is evident from the data presented in these 2 tables that sitagliptin at either 100 mg or 200 mg lowers the mean serum fructosamine by the study endpoint (week 18 in P023 and week 24 in P021), compared to placebo. It is interesting to note that, unlike the data on HbA1c, there is less of a distinction between the 2 studies regarding the dose proportionality in the response of this parameter. This corroborates the applicant's conclusion that there is no greater improvement in glycemic control to be expected with the use of the higher dose of sitagliptin (200 mg) compared to the lower dose (100 mg).

6.1.4.4.2 Fasting Plasma Glucose

Fasting plasma glucose has been considered an important parameter of glycemic control and also correlates with chronic diabetic morbidities.
Statistically and clinically significant mean changes in fasting plasma glucose in the sitagliptin groups were observed in both studies. The magnitude of the sitagliptin effect according to the dose (100 mg vs. 200 mg daily) parallels that of both HbA1c and fructosamine, with greater placebo-adjusted effect of the 200 mg in study P021 compared

to the 100 mg dose group and a smaller effect of the 200 mg dose group in Study P023, compared to the 100 mg dose group (Table 38).

Table 38. Changes in fasting plasma glucose (mg/dL) in Studies P021 and P023

		Mean (SD)		Change from Baseline			
Treatment	N	Baseline	Study Endpoint	Mean (SE)	LS Mean (SE)	95 % CI for LS Mean	LS Mean Difference from Placebo (95% CI)
Study P021 (Study Endpoint at week 24)							
Sitagliptin 100 mg	234	170 (43)	159 (45)	-11 (3)	-12† (3)	(-17, -7)	**-17** † (-24, -10)
Sitagliptin 200 mg	244	174 (46)	157 (47)	-17 (3)	-17 † (3)	(-21, -12)	-21 † (-28, -14)
Placebo	247	176 (41)	180 (56)	4 (3)	5 (3)	(0, 10)	-
Study P023 (Study Endpoint at Week 18)							
Sitagliptin 100 mg	201	180 (43)	168 (53)	-12 (3)	-13 † (3)	(-19, -6)	**-20** † (-31, -9)
Sitagliptin 200 mg	202	183 (45)	174 (57)	-10 (3)	-10* (3)	(-16. -3)	-17* (-28, -6)
Placebo	107	184 (48)	191 (60)	7 (5)	7 (5)	(-2, 16)	-
† p<0.001, * p<0.05; LS= Least Squares; SD = Standard Deviation; SE = Standard Error							

Adapted from the applicant's Table 2.7.3:15 in reference 2.7.3. Summary of Clinical Efficacy

Figure 14 shows means of fasting plasma glucose at each study visit and includes plasma glucose data obtained after initiation of glycemic rescue therapy. Thus the figure differs from the corresponding figure submitted by the applicant, plotting the change from baseline only and excluding data obtained after initiation of glycemic rescue therapy (Figure 15).

Figure 14. Mean changes in fasting plasma glucose in Study P021 by study visit

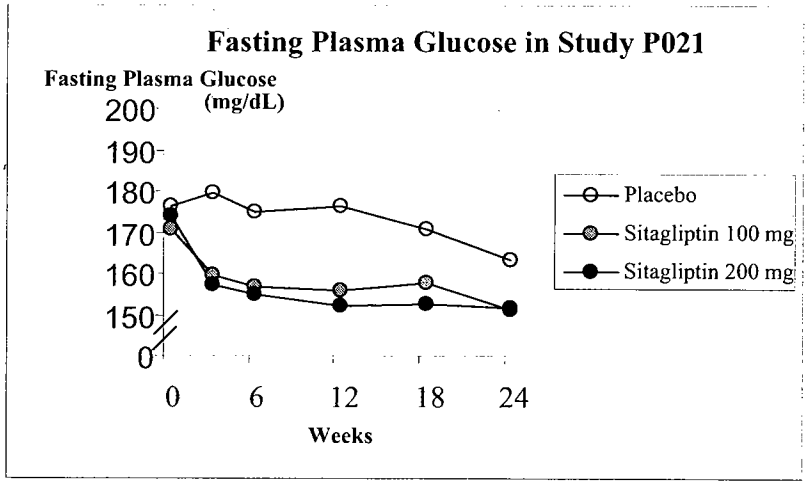
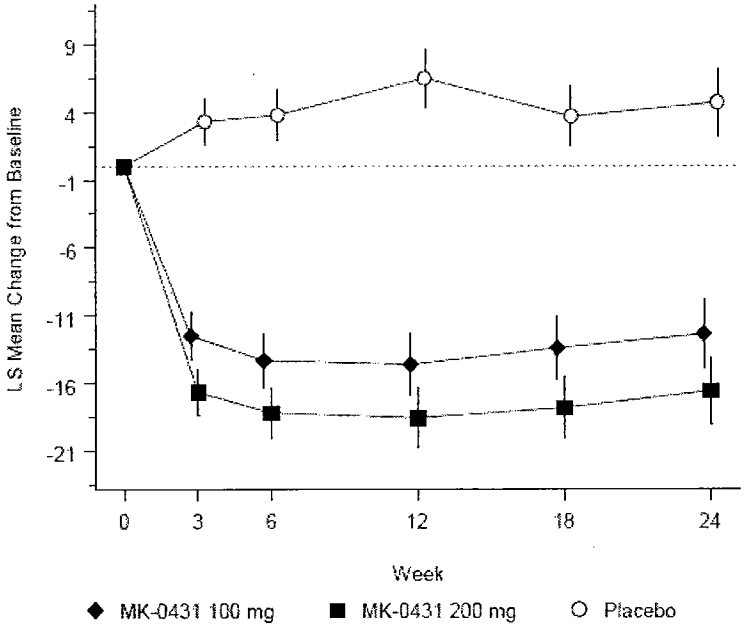


Figure 15. Change from baseline in fasting plasma glucose (mg/dL) in Study P021 by study visit, with missing data imputed by LOCF



Copied from the applicant's Figure 11-2, reference P021V1

The same sitagliptin effect on fasting plasma glucose was observed in Study P023 (Figure 16 and Figure 17).

Figure 16. Mean changes in fasting plasma glucose in Study P023 by study visit

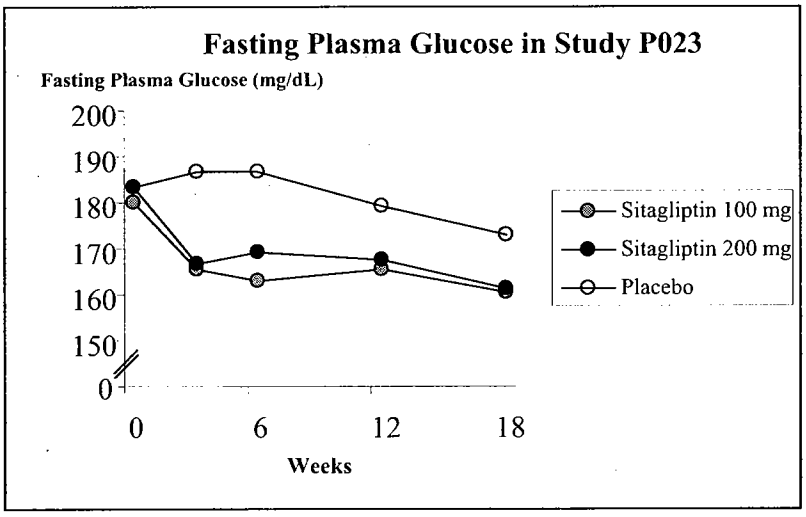
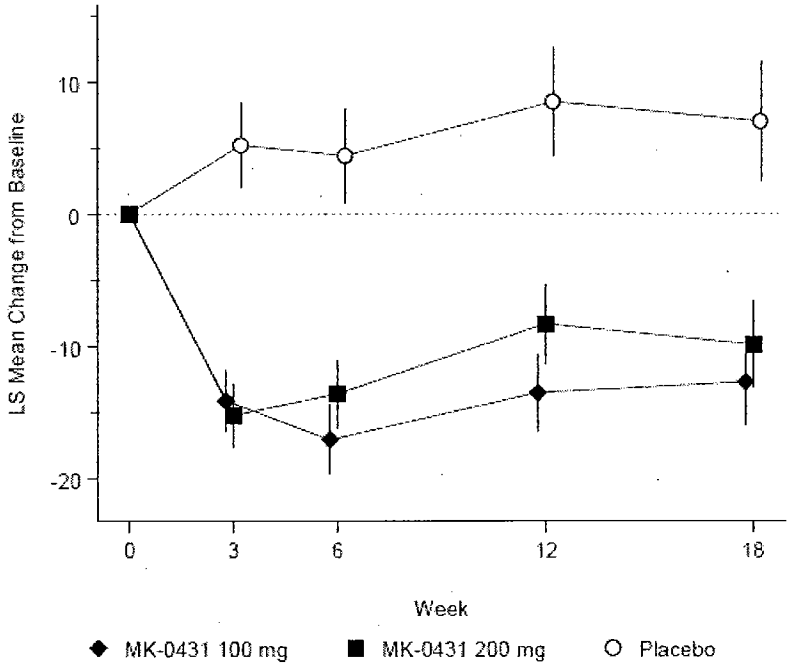


Figure 17. Change from baseline in fasting plasma glucose (mg/dL) in Study P023 by study visit, with missing data imputed by LOCF



Copied from the applicant's Figure 11-2, reference P023V1

Sitagliptin at 100 mg qd or 200 mg qd reduced fasting plasma glucose from baseline to the end of study period in the ITT population in both studies. Most of the glucose lowering occurred during the first 3 to 6 weeks after initiation of treatment. There was no difference in the magnitude of glucose lowering between the 2 doses of sitagliptin tested.

6.1.4.4.3 2-hour Post-meal glucose

Study P021

This secondary endpoint was evaluated as a protocol-mandated assessment only in Study P021 (Table 39). Study P023 included assessments of the more detailed 9-point MTT from a self-selected subset of study subjects, from which we can extract the 2-hour glucose values and include in this section.

Table 39. Changes from baseline in the 2-hour post-meal glucose (mg/dL) in Study P021

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	201	257 (72)	211 (73)	-46 (5)	-49 (5)	(-58, -40)	<0.001
Sitagliptin 200 mg	205	264 (80)	208 (73)	-56 (5)	-56 (4)	(-65, -48)	<0.001
Placebo	204	271 (73.2)	266 (91)	-5 (5)	-2 (4)	(-11, 7)	0.628

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-46** (-59, -31)	<0.001
Sitagliptin 200 mg vs. Placebo	-54 (-67, -42)	<0.001
Sitagliptin 200 mg vs. Sitagliptin 100 mg	-7 (-20, 5)	0.249

Adapted from Table 11-3, Reference P021v1

A rapid comparison between the mean changes in the 2-hour post-meal glucose and the fasting plasma glucose shows that either dose of sitagliptin was more effective in suppressing the plasma glucose rise in response to the carbohydrate-rich standardized meal than the fasting glucose. Suppression of the rise in post-meal glucose is the main mechanism an incretin mimetic or enhancer uses to improve glycemic control. This is accomplished by suppression of glucagon release, stimulation of insulin release and slower rate of gastric emptying.

Incremental glucose (glucose assessed at 2 hours post-meal minus glucose at time zero) is a measure of the sitagliptin effect on the post-prandial rise in glucose, independent of the absolute level of fasting glucose. It integrates the indirect effects of GLP1 on meal-related insulin and glucagon secretion rates and on the rate of gastric emptying. Changes in the 2-hour post-meal incremental glucose from baseline to week 24 in Study P021 are shown in Table 40.

Table 40. Changes in incremental 2-hour post-meal glucose (mg/dL) from baseline to week 24 in Study P021

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	201	90 (49)	55 (44)	-35 (4)	-37 (3)	(-43, -31)	<0.001
Sitagliptin 200 mg	205	94 (57)	55 (47)	-40 (4)	-39 (3)	(-45, -33)	<0.001
Placebo	204	96 (48)	89 (53)	-7 (3)	-5 (3)	(-11, 1)	0.083

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	-32 (-40, -24)	<0.001
Sitagliptin 200 mg vs. Placebo	-34 (-42, -26)	<0.001
Sitagliptin 200 mg vs. Sitagliptin 100 mg	-2 (-10, 6)	0.603

Adapted from the applicant's Table 11-4, reference P021v1

In addition to the incremental glucose level, the area under the glycemic curve is an index of glycemic response to the standardized meal, and the effect of sitagliptin treatment for 24 weeks in Study P021 is shown in Table 41.

Table 41. Changes in the area under the incremental glycemic curve (mg *h/dL) from baseline to week 24 in Study P021

Treatment	N	Mean (SD)		Change From Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	198	142 (57)	102 (50)	-40 (4)	-41 (3)	(-47, -34)	<0.001
Sitagliptin 200 mg	202	145 (59)	93 (53)	-52 (4)	-51 (3)	-58, -44)	<0.001
Placebo	201	144 (57)	137 (60)	-7 (4)	-7 (3)	(-13, 0)	0.042

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-34** (-43, -25)	<0.001
Sitagliptin 200 mg vs. Placebo	**-44** (-54, -35)	<0.001
Sitagliptin 200 mg vs. Sitagliptin 100 mg	**-10** (-20, -0.9)	0.032

Adapted from the applicant's Table 14-14, reference P021v1

Study P023

Unlike the endpoint data from study P021, 2-hour post-meal plasma glucose data in Study P023 were obtained from a self-selected subset of the study population: those subjects who volunteered to participate in the 9-point, 3-hour MTT. A comparison performed by the applicant on the demographic and baseline characteristics of this self-selected subset against the entire study population revealed that the characteristics of the subset to be comparable to the larger group. As seen in Table 42, Table 43, and Table 44, the post-prandial glucose lowering effect of sitagliptin was comparable to the effect observed in Study P021.

Table 42. Changes in 2-hour post-meal glucose (mg/dL) in Study P023

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	62	263 (77)	225 (80)	-38 (9)	-41 (8)	(-58, -25)	<0.001
Sitagliptin 200 mg	61	279 (75)	229 (79)	-50 (8)	-48 (8)	(-64, -31)	<0.001
Placebo	27	264 (67)	272 (88)	8 (13)	5 (12)	(-20, 30)	0.697

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-46.3** (-75.4, -17.3)	0.002
Sitagliptin 200 mg vs. Placebo	**-52.7** (-82.0, -23.4)	<0.001
Sitagliptin 200 mg vs. Sitagliptin 100 mg	**-6.4** (-29.3, 16.6)	0.584

Adapted from the applicant's Table 11-10, reference P023v1

Table 43. Changes in incremental glucose (mg/dL) from baseline to week 18 in Study P023

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	62	88 (45)	56 (47)	-32 (6)	-33 (5)	(-44, -22)	<0.001
Sitagliptin 200 mg	61	91 (45)	56 (53)	-34 (6)	-34 (5)	(-45, -23)	<0.001
Placebo	27	87 (55)	80 (47)	-7 (10)	-8 (8)	(-24, 8)	0.326

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-25** (-44, -6)	0.011
Sitagliptin 200 mg vs. Placebo	**-26** (-45, -7)	0.008
Sitagliptin 200 mg vs. Sitagliptin 100 mg	**-1** (-16, 14)	0.864

Adapted from the applicant's Table 11-11, reference P023v1

Table 44. Changes in incremental glucose AUC (mg *h/dL) from baseline to week 18 in Study P023

Treatment	N	Mean (SD)		Change From Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	63	218 (83)	153 (81)	-65 (10)	-68 (9)	(-86, -51)	<0.001
Sitagliptin 200 mg	61	227 (84)	158 (82)	-69 (10)	-68 (9)	(-86, -50)	<0.001
Placebo	27	227 (92)	209 (97)	-18 (15)	-18 (14)	(-44, 9)	0.196

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-51** (-82, -20)	0.002
Sitagliptin 200 mg vs. Placebo	**-50** (-82, -19)	0.002
Sitagliptin 200 mg vs. Sitagliptin 100 mg	**1** (-24, 25)	0.964

Adapted from the applicant's Table 14-13, reference P023 v1

6.1.4.5 Tertiary endpoints

6.1.4.5.1 Indices of beta cell function and insulin sensitivity

From the indices of beta cell function calculated and shown in Table 45, the only significant changes were the change in the proinsulin to insulin ratio and in the HOMA-beta, markers of improved beta cell function. While one would expect that improvements in beta cell function would bring about favorable changes in insulin sensitivity, the studies were unable to demonstrate this effect. The reason may be that most subjects had only moderately elevated glycemia at baseline, perhaps not associated with much glucotoxicity.

Table 45. Changes in indices of beta cell function and insulin sensitivity from baseline to week 18 or week 24 in Studies P023 and P021

		Study P023			Study P021		
Parameter	Treatment	Mean change from baseline (SE)	Difference in LS Means vs. placebo (95% CI)	p-Value	Mean change from baseline (SE)	Difference in LS Means vs. placebo (95% CI)	p-Value
Fasting serum insulin (µIU/mL)							
	Sitagliptin 100 mg	0.7 (0.6)	-04 (-3.3, 2.4)	0.759	1.1 (0.9)	1.5 (-0.7, 3.6)	0.184
	Sitagliptin 200 mg	0.5 (0.9)	-0.6 (-3.4, 2.2)	0.674	0.7 (0.8)	1.1 (-1.1, 3.2)	0.337
	Placebo	1.1 (1.3)			-0.4 (0.8)		
Fasting serum proinsulin (pmol/L)							
	Sitagliptin 100 mg	-2.6 (2)	-5.7 (-12.2, 0.8)	0.084	0.3 (1.8)	-0.9 (-6.0, 4.2)	0.732
	Sitagliptin 200 mg	-2.0 (1.6)	-4.9 (-11.4, 1.6)	0.138	0.5 (1.7)	-0.9 (-6.0, 4.2)	0.740
	Placebo	2.0 (3.7)			1.1 (2.0)		
Proinsulin to insulin ratio							
	Sitagliptin 100 mg	-0.05 (0.02)	-0.12 (-0.22, -0.01)	0.03	-0.10 (0.06)	-0.07 (-0.11, -0.02)	0.003
	Sitagliptin 200 mg	-0.02 (0.02)	-0.09 (-0.20, 0.02)	0.10	-0.10 (0.03)	-0.10 (-0.14, -0.05)	<0.001
	Placebo	0.07 (0.04)			0 (0.01)		
HOMA-Beta							
	Sitagliptin 100 mg	12.1 (2.2)	11.2 (0.3, 22.0)	0.045	13.3 (3.0)	12.9 (3.9, 21.9)	0.005
	Sitagliptin 200 mg	13.0 (4.0)	12.0 (1.2, 22.9)	0.03	13.2 (3.1)	12.8 (3.9, 21.7)	0.005
	Placebo	1.1 (3.5)			0.5 (3.6)		
HOMA-IR							
	Sitagliptin 100 mg	0 (0.3)	-1.3 (-3.0, 0.4)	0.128	0.2 (0.6)	0 (-1.3, 1.4)	0.950
	Sitagliptin 200 mg	-0.1 (0.5)	-1.2 (-2.9, 0.5)	0.153	0 (0.5)	-0.2 (-1.5, 1.1)	0.782
	Placebo	1.1 (0.9)			1.1 (0.9)		
QUICKI							
	Sitagliptin 100 mg	0 (0)	0 (0, 0.01)	0.599	0 (0)	0 (0, 0)	0.978
	Sitagliptin 200 mg	0 (0)	(0, 0.02)	0.203	0 (0)	0 (0, 0)	0.461
	Placebo	0 (0)			0 (0)		

Adapted from the applicant's Table 2.7.3: 38, reference 2.7.3. Summary of Clinical Efficacy

6.1.4.5.2 Post-meal insulin and C-peptide

No significant changes from baseline were seen in mean 2-hour post-meal insulin and C-peptide levels at week 24 across the treatment groups. When analyzing the changes in area under the curve (AUC) of post-meal insulin and C-peptide, on the other hand, both sitagliptin groups had statistically higher increases from baseline to week 24 compared to placebo: insulin AUC remained unchanged from baseline to week 24 in the sitagliptin groups while it decreased in the placebo group; mean C-peptide AUC increased in both sitagliptin groups while it remained unchanged in the placebo group (data not shown).

6.1.4.5.3 Changes in Appetite

Subjects filled a Global Appetite / Satiety Questionnaire at baseline and week 18 or week 24. No trends of change from baseline to study endpoint were seen between sitagliptin and placebo, and between the sitagliptin 100 mg and the 200 mg dose groups.
It is important to note that sitagliptin had a neutral effect on body weight during the Phase 3 monotherapy studies.

6.1.4.5.4 Insulin sensitivity and beta cell function endpoints assessed by the 9-point MTT

In Study P021 all randomized subjects had meal tolerance testing consisting of blood

sampling at pre-meal, 60 and 120 minutes. A subset of these randomized subjects , and a subset of subjects in Study P023, also volunteered for the 9-point MTT, which consisted of blood sampling at the following timepoints relative to the start of the meal: - 10, 0, 10, 20, 30, 60, 90, 120 and 180 minutes. The parameters investigated were:

- Insulin sensitivity, calculated as the composite index ISI: 10,000/sqrt[FPG X FPI]
- Pancreatic beta cell response, assessed through 5 calculated indices based on C-peptide minimal model:
  - Static beta-cell sensitivity to glucose (Fs)
  - Dynamic beta-cell sensitivity to glucose (Fd)
  - Basal beta-cell sensitivity to glucose (Fb)
  - Overall beta-cell sensitivity index (F)
  - Delay between static phase secretion and glucose concentration (T)
  - Disposition indices: evaluates the relationship between insulin sensitivity and each of the parameters of beta cell function
- Insulinogenic index: ratio of change in insulin at 30 minutes to change in glucose at 30 minutes, as a non-model assessment of early insulin secretion.

These analyses of the 9-point MTT revealed:

1) A trend towards improvement in insulin sensitivity, using a standard, validated index, was observed, but did not reach statistical significance.
2) Substantial improvements in parameters describing the beta-cell insulin secretion response during fasting and post-meal conditions were observed, including improvements in beta-cell function in the basal state and stimulated state and improvement in a parameter that describes overall beta-cell function.
3) Consistent and substantial improvements in the disposition indices, including disposition indices assessing static and overall beta-cell function, were observed; improvement in the disposition index assessing dynamic beta-cell function in the combination with metformin study.
4) No statistically significant changes in T (delay between static phase secretion and glucose concentration) were observed. Numerical increases observed in some studies did not correlate with changes in glycemic control and, hence, are unlikely to be clinically important.
5) Strong correlations between the improvement in beta-cell function and improvements in glycemic control suggesting that the improvements in beta-cell function contribute to the improvement in glycemic control observed with sitagliptin.

6.1.4.5.5 Changes in plasma glucagon in P023

A slightly smaller increase in 2-hour post-meal glucagon levels (pg/mL) was observed for the sitagliptin groups compared to placebo (mean [SE] of 19 [7] for sitagliptin 100 mg; 6 [6] for sitagliptin 200 mg and 28 [15] for placebo); the same conclusion applies to the total and incremental post-meal glucagon AUC. These results are based on small number of subjects (less than 10 per group) that had samples for glucagon collected, but are consistent with the expected mechanism of action of GLP-1 on attenuation of glucagon secretion post-meal.

6.1.4.5.6 Proportion of subjects requiring glycemic rescue therapy and time to rescue

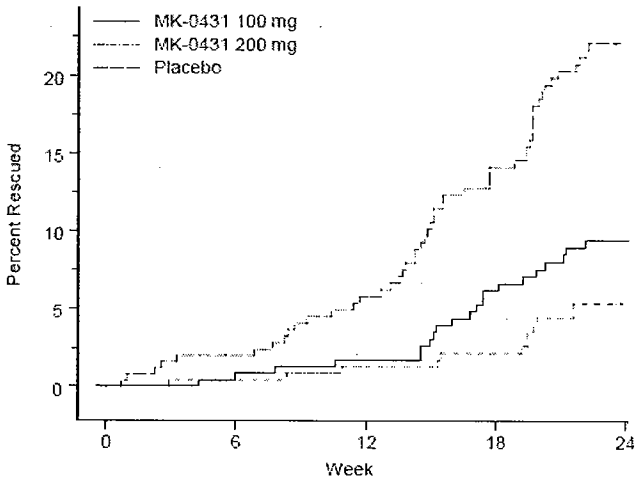
In both studies, more subjects randomized to placebo had to receive glycemic rescue therapy than either sitagliptin group (Table 46 and Table 47). In addition, subjects receiving placebo had to be rescued earlier than those in either sitagliptin treatment (Figure 18 and Figure 19).

Table 46. Proportion of subjects requiring glycemic rescue therapy in Study P021

Treatment	N	n (%)	Kaplan Meyer Estimate at week 18	
			%	95 % CI
Sitagliptin 100	238	21 (9)	9.4	(6.1, 13.7)
Sitagliptin 200	250	12 (5)	5.4	(2.9, 8.9)
Placebo	253	52 (21)	22.1	(17.0, 27.7)
Comparison with placebo		Kaplan-Meyer Difference at week 24 % (95% CI)		p-value
Sitagliptin 100 vs. placebo		**-12.7** (-19.3, -6.1)		<0.001
Sitagliptin 200 vs. placebo		**-16.7** (-22.9, -10.6)		<0.001

Adapted from applicant's Table 11-19, reference P021v1

Figure 18. Time to glycemic rescue therapy in Study P021



Patients at Risk					
MK-0431 100 mg	238	232	223	209	155
MK-0431 200 mg	250	238	225	215	170
Placebo	253	239	221	198	141

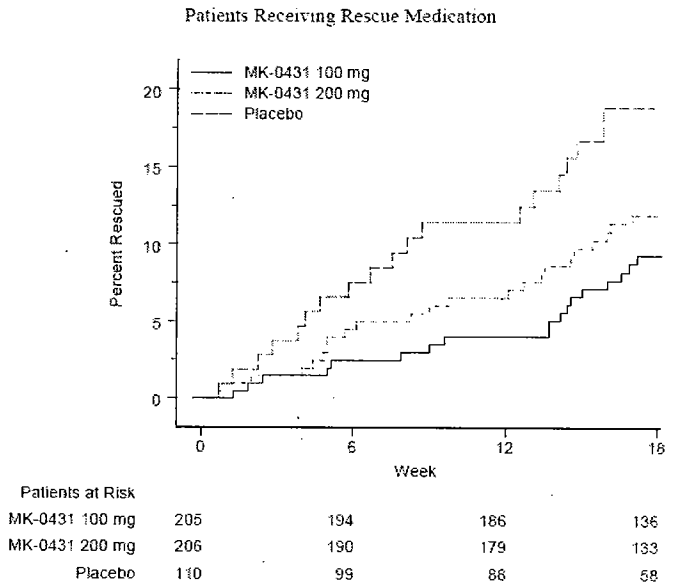
Copied from the applicant's Figure 11-10, reference P021v1

Table 47. Proportion of subjects requiring glycemic rescue therapy in Study P023

Treatment	N	n (%)	Kaplan Meyer Estimate at week 18	
			%	95 % CI
Sitagliptin 100	205	18 (9)	9.3	(5.7, 13.9)
Sitagliptin 200	206	24 (12)	11.9	(7.8, 16.9)
Placebo	110	19 (17)	18.9	(11.9, 27.1)
Comparison with placebo		Kaplan-Meyer Difference at week 24 % (95% CI)		p-value
Sitagliptin 100 vs. placebo		**-9.6** (-18.3, -0.9)		0.013
Sitagliptin 200 vs. placebo		**-7.0** (-15.9, 2.0)		0.095

Adapted from the applicant's Table 11-20, reference P023v1

Figure 19. Time to glycemic rescue therapy in Study P023



Copied from the applicant's Figure 11-6, reference P023v1

6.1.4.5.7 Lipid panel changes in both Studies P021 and P023

No significant changes in lipids were observed within and between treatment groups in LDL-C, HDL-C, Non-HDL-C, Triglycerides, or Triglycerides to HDL-C ratio.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Studies P021 and P023 clearly demonstrated consistent improvement in glycemic

control in subjects receiving sitagliptin as the sole anti-diabetic agent. The effect on the various glycemic indices (HbA1c, fructosamine, plasma glucose or proportion of subjects reaching the American Diabetes Association target of HbA1c < 7%) was not proportional to the dose employed. The improvement in mean fasting as well as post-meal glucose was evident by week 3 and the beneficial effect on HbA1c was seen as early as Week 6. The effect of sitagliptin on these variables of glycemic control was more pronounced in the suppression of post-prandial glucose rises, consistent with the known effects of GLP1 on glucose-dependent insulin secretion and a lesser increase in plasma glucagon, with less hepatic glucose output.

The effects on body weight and appetite were neutral, in contrast to the substantial nausea and weight loss achieved with exenatide or the weight gain observed with insulin or insulin secretagogues.

The effect of sitagliptin on the reduction in HbA1c was seen across the demographic subsets. The effect was clearly more robust in subjects who had poorer glycemic control at baseline, and tended to be stronger among those with better beta cell function and shorter duration of T2DM.

Durability of the treatment effect to 1 year has been shown in Study P021 and through the extensions of studies P010 and P014 as compared to other anti-diabetic agents.

Study P028 was not intended to provide evidence of the efficacy of sitagliptin treatment in diabetic subjects with chronic renal insufficiency, but was intended to be rather a study to investigate the safety of this treatment in that population. Analysis of the changes in HbA1c in Study P028 demonstrates a substantial improvement in glycemic control by week 12, as compared to placebo.

6.2 Indication: Use of sitagliptin in combination with other oral agents

6.2.1 Methods

The development program for sitagliptin treatment in combination with other oral agents included one Phase 2 Study investigating the effect of sitagliptin in combination with metformin (Study P015) and 2 Phase 3 studies, one in combination with metformin (Study P020) and the other in combination with pioglitazone (Study P019). Although more studies designed to explore the effects of sitagliptin in combination with other therapeutic classes of anti-hyperglycemic products would be desirable (such as sulfonylureas, meglitinides and insulin itself), it is understandable that the applicant elected to study the glycemic effect of sitagliptin (primarily an insulin secretagogue) in combination with insulin sensitizers.

This section will present the data for each study separately. Regarding the combination of sitagliptin and metformin, the more detailed description will be dedicated to the Phase 3 study, with data from the Phase 2 study provided briefly for support of the Phase 3 findings.

Study P020 has both a "Phase A" component and a "Phase B" component. Phase A is the double-blind, placebo-controlled, 24-week trial of sitagliptin or placebo added on to the

treatment of subjects already on metformin. Phase B is the extension of that study, an 80-week trial in which subjects randomized to placebo during Phase A were switched to glipizide and subjects originally randomized to sitagliptin were continued on the same treatment. Study P019 lasted 24 weeks, having no extension to investigate the combined sitagliptin-pioglitazone for periods longer than 24 weeks.

6.2.2 General Discussion of Endpoints

The primary efficacy endpoint is a mean change in HbA1c from baseline to week 24 in both studies in the intent-to-treat population. The intent-to-treat population consisted of all randomized subjects with a baseline measurement, consumption of at least one dose of double blind medication and at least one post-randomization measurement. Measurements obtained after initiation of glycemic rescue therapy were considered missing data for the purpose of efficacy analyses. All missing data were imputed by LOCF.
The secondary endpoints in Study P020 were the mean change in fasting plasma glucose from baseline to week 24 and the mean change in the 2-hour post-meal glucose from baseline to week 24.
The secondary endpoints in Study P019 were the mean change in fasting plasma glucose from baseline to week 24 and the proportion of subjects requiring glycemic rescue therapy. As sensitivity analyses, these endpoints will be tested in the completers populations (all subjects with baseline and week 24 measurements) as well.

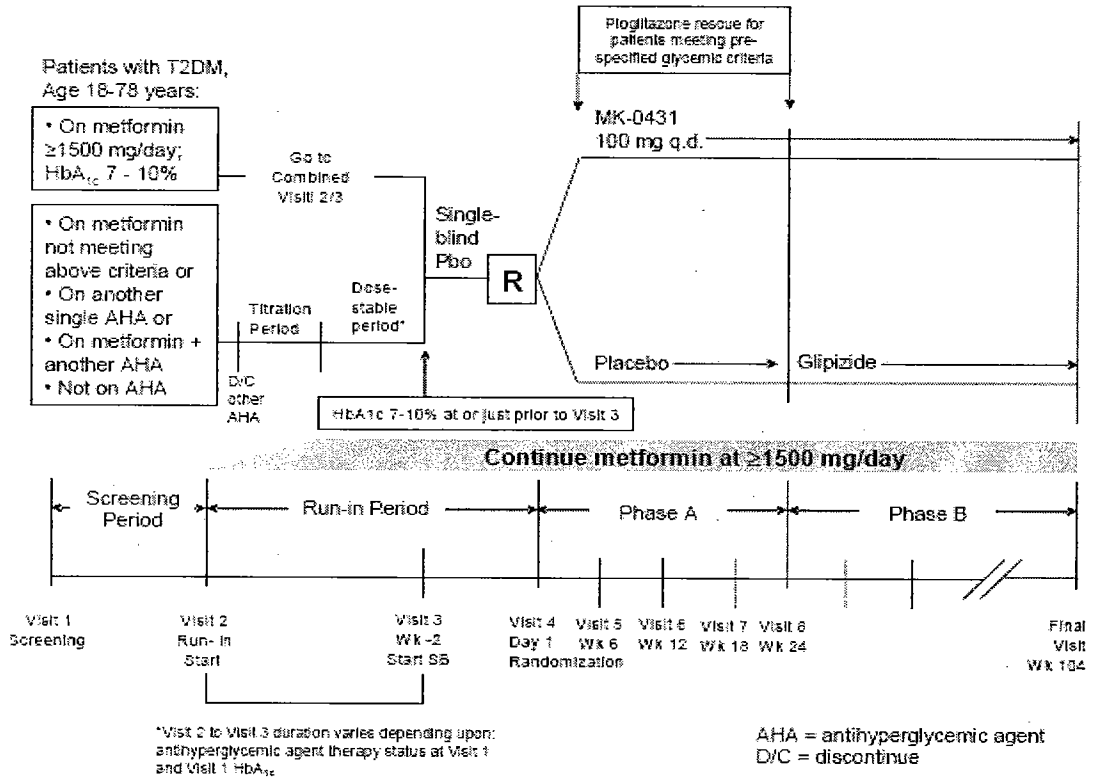
6.2.3 Study Design

6.2.3.1 General overview of study design

Study P020

Study P020 was a multinational, randomized, parallel-group study with a single-blind placebo run-in period followed by a placebo-controlled, double-blind treatment period. Seven-hundred one (701) patients with T2DM who had inadequate glycemic control with diet and exercise and on metformin at a dose of at least 1500 mg/day were randomized in a 2:1 ratio to receive either sitagliptin 100 mg daily or placebo, respectively. The duration of the study was up to 123 weeks (with 17 visits) for each subject. This 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/stabilization 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 24-week, placebo-controlled, double-blind treatment period (referred to as "Phase A"). After completion of Phase A, subjects entered an 80-week double-blind treatment period ("Phase B") at the start of which subjects on placebo were switched to treatment with glipizide (5 mg qd that could be up-titrated to 15 mg qd) and subjects on sitagliptin 100 mg were continued on this treatment (please refer to Figure 20). Only the 100 mg dose of sitagliptin was selected for testing, and this dose was determined from the Phase 2 studies P010 and P014 as the dose that would yield maximum glycemic benefit.

Figure 20. Study Design of Phase A of Study P020



Copied from the applicant's Figure9-1, reference P020v1

If a subject was not on an anti-diabetic agent and had HbA1c ≥ 8 % he/she would have a metformin dose-stabilization period of 10 weeks prior to Visit 3, the single-blind, placebo run-in period. If on metformin ≥ 1500 mg qd for at least 10 weeks, and HbA1c was ≥ 7 % and ≤ 10 %, the subjects could go directly to the combined Visit 2/3. If the subject had been on metformin ≥ 1500 mg qd for at least 10 weeks, but HbA1c was > 10 %, the subject could try to improve glycemia in a period of up to 6 weeks prior to eligibility. If a subject had been on monotherapy (including metformin at a dose < 1500 mg qd) and HbA1c ≥ 7%, then he/she would undergo a metformin stabilization period of up to 6 weeks (8 Weeks for PPAR agonists) prior to Visit 3. If the subject was on a combination therapy (metformin and sulfonylurea or metformin and PPAR agonist) and HbA1c ≥ 7 % and ≤ 10 %, the subject would have a 6 week or 8 week metformin-stabilization period when discontinuing the other agent. If the subject was on a similar combination therapy with HbA1c ≥ 6 % and < 7 %, then the metformin stabilization period would last between 6 to 10 weeks (at least 8 weeks for a PPAR) to wash out the therapeutic effects of the other anti-diabetic agent. While the minimum daily dose of metformin was 1500 mg, the maximum was either 2500 mg or 3000 mg, depending on the labeled dosage in each particular country where the study took place. If a subject continued to be under poor glycemic control during the trial beyond protocol-specified thresholds of fasting plasma glucose (see below), rescue therapy with pioglitazone was to be instituted, thus allowing the subject to remain in the study and

continue to provide data on safety and tolerability of sitagliptin.
Criteria for rescue therapy with pioglitazone (all with FPG with value repeated and confirmed after reinforcement of diet/exercise counseling)

- FPG > 270 mg/dL after **Visit 4/Day 1** through **Visit 5/Week 6**,
- FPG > 240 mg/dL after **Visit 5/Week 6** through **Visit 6/Week 12**,
- FPG > 200 mg/dL after **Visit 6/Week 12** up to (but not including) **Visit 8/Week 24.**

Study P019

The main difference in design between this study and Study P020 (described above) is the longer period necessary to achieve glycemic stabilization with the use of pioglitazone (for those subjects who were not on stable doses of pioglitazone at visit 2). The other difference is that the randomization ratio for this study was 1:1, rather than 2:1 favoring active treatment, as in Study P020.
Since both doses of pioglitazone result in effective decrease in plasma glucose, both 30 and 45 mg were accepted as part of combination therapy. These subjects could not have their pioglitazone dose increased after Visit 2, and if glycemic rescue therapy was necessary after randomization, it was to be accomplished with use of metformin. In order to be eligible, subjects who were not on stable doses of pioglitazone at the time of screening were required to have a minimum of 20 mg /dL decrease in their fasting plasma glucose before randomization, to demonstrate that they can respond to a PPAR agonist.

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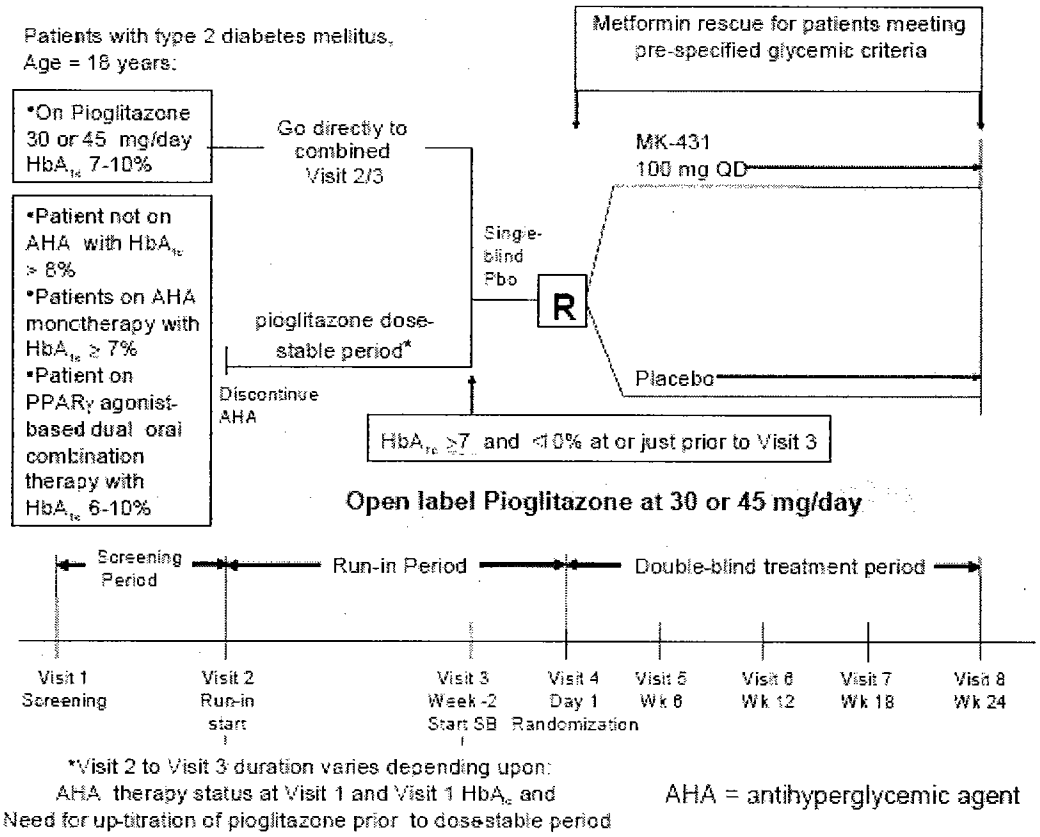
Figure 21. Study Design for Study P019



Copied from the applicant's Figure 9-1, reference P019

6.2.3.2 Subject eligibility

<u>Study P020</u>

Subjects were eligible if they met the following criteria:

- Age ≥ 18 and ≤ 78 years of age, BMI between 20 and 43 kg/m^2
- HbA1c ≥ 7 % and ≤ 10 % on metformin with a dose ≥ 1500 mg qd for at least 10 weeks by Visit 3 OR any one of the following conditions if the investigator believes that the subject will meet HbA1c inclusion criteria (between 7 and 10 %, inclusive) after the metformin stabilization period:
- Subject on metformin monotherapy with dose ≥ 1500 mg and HbA1c > 10%
- Subject on metformin monotherapy with dose < 1500 mg or monotherapy with other AHA and screening HbA1c ≥ 7%
- Subject on metformin in combination with another anti-diabetic agent and has screening HbA1c ≥ 6 % and ≤ 10 %
- Subject not on a anti-diabetic agent and has screening HbA1c > 8 %
- ≥ 75 % compliance with placebo treatment during the placebo run-in at Visit 4 (randomization)

- None of the following: history of Type 1 diabetes or screening C-peptide ≤ 0.8 ng/mL, insulin requirement within the prior 8 weeks, on weight loss program or medications while not on a maintenance phase, female subjects pregnant, lactating, or not on active contraception; any subject with uncontrolled thyroid function, viral hepatitis or liver dysfunction, kidney insufficiency or significant albuminuria, CPK > 2XULN or triglycerides > 600 mg/dL, acute coronary syndrome or coronary intervention within the past 6 months, presence of HIV, hematological disorder including anemia, neoplastic disease

Study P019

Nearly identical eligibility criteria compared to those of Study P020, except for:

- Requirement of having demonstrated a glycemic response of ≥ 20 mg/dL from Visit 2 to Visit 3 for the subjects that had been on therapy with anti-diabetic agents other than pioglitazone or that were not receiving any drug treatment at the time of screening
- History of cardiovascular disease, or excessive weight gain / edema with the use of pioglitazone prior to randomization.

Eligibility criteria for both studies are adequate and appropriately balance the need for comprehensive assessment of the intended population in a Phase 3 study with the ethical need to avoid prolonged exposure to severe hyperglycemia in a placebo arm.

6.2.3.3 Randomization

Study P020

Eligible subjects were randomized to sitagliptin 100 mg qd or placebo in a 2:1 ratio. There was no stratification for this study.

Study P019

Eligible subjects were randomized to sitagliptin 100 mg qd or placebo in a 1:1 ratio. There was no stratification for this study.

6.2.3.4 Study Endpoints and Analyses

Primary endpoint

The primary endpoint is the same in both studies P019 and P020: the change in mean HbA1c from baseline to week 24. The comparison between the effect in the sitagliptin 100 mg group and the placebo group was conducted with an analysis of covariance using the least square means of both treatment groups. The ANCOVA model included terms for treatment, prior anti-diabetic agent status (not on anti-diabetic agent, on monotherapy oral anti-diabetic agent or on metformin based oral combination therapy), and baseline HbA1c as a covariate.

Secondary endpoints

Secondary endpoints in Study P020 were change from baseline to week 24 in fasting plasma glucose and change from baseline in 2-hour post-meal glucose. The only secondary endpoint for Study P019 was the change from baseline in fasting plasma glucose at week 24 compared between the 2 treatment groups. The same statistical procedure was used in both studies to analyze the secondary endpoint of mean changes in fasting plasma glucose between the groups, and for the 2-hour post-meal glucose in Study P020. Study P019 did not require 2-hour glucose assessments, and therefore this was not an efficacy endpoint in the study.

Exploratory endpoints

Study P019
Change from baseline in
- fasting pro-insulin
- fasting insulin
- pro-insulin / insulin ratio
- HOMA- beta
- HOMA-IR
- QUICKI
- Proportion of subjects meeting HbA1c goal of < 7 %
- Time to metformin rescue

Study P020
In addition to the exploratory endpoints listed for Study P019, the following endpoints were selected for Study P020 and analyzed as a change from baseline to week 24:
- C-peptide
- 2-hour post-meal insulin
- 2-hour post meal C-peptide
- 2-hour incremental post-meal glucose
- Total and incremental (above the fasting level) AUC for glucose, C-peptide, insulin, and insulin glucose ratio
- Time to pioglitazone rescue
- Changes in lipids and their fractions

An analysis of the proportion of individuals meeting HbA1c goals (< 7.0% as primary; < 6.5%, < 7.5% as secondary) at Week 24 was conducted using a logistic regression model to compare sitagliptin 100 mg against placebo.
A time-to-rescue analysis was performed using the Kaplan-Meier estimate and the logrank test. The proportion of patients rescued in each treatment group was also summarized.

6.2.4 Efficacy Findings

6.2.4.1 Subject disposition

Study P020

A total of 1464 subjects were screened and 763 were excluded, mostly because they did not meet HbA1c criteria for entry or because they had elevated serum creatinine or decreased creatinine clearance. The remaining 701 subjects were randomized at 99 sites worldwide.

Table 48. Disposition of subjects in Study P020

	Number (%)		
	Sitagliptin 100 mg	Placebo	Total
Total Randomized	464	237	701
Included in the ITT† Analysis	453 (97.6)	224 (94.5)	677 (96.6)
Included in the Completers Analysis	399 (86.0)	171 (72.2)	570 (81.3)
Excluded from the ITT† Analysis	11 (2.4)	13 (5.5)	24 (3.4)
No Baseline Data	1 (0.2)	2 (0.8)	3 (0.4)
No On-treatment Data	10 (2.2)	11 (4.6)	21 (3.0)
Excluded from the Completers Analysis‡	54 (11.6)	53 (22.4)	107 (15.3)
Rescued Prior to Week 24§	18 (3.9)	28 (11.8)	46 (6.6)
No Data at Week 24‖	36 (7.8)	25 (10.5)	61 (8.7)

†ITT: Intent-to-treat Population.
‡The completers population is a subset of the ITT population including all patients with Week 24 data.
§Efficacy data obtained on a patient after initiation of rescue therapy are treated as missing.
‖ For patients not on rescue medication.

Adapted from applicant's Table 10-3, reference P020v1

Study P019

Study investigators screened 928 subjects and excluded 575 subjects. The most common reason to exclude screened subjects by far (50.1%) was related to failure to meet HbA1c criteria for eligibility. Each of the other reasons affected less than 5 % of the screen failures. The remaining 353 subjects were randomized at 69 sites worldwide.

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Table 49. Disposition of subjects in Study P019

	Number (%)		
	Sitagliptin 100 mg	Placebo	Total
Total Randomized	175	178	353
Included in the ITT† Analysis	163 (93.1)	174 (97.8)	337 (95.5)
Included in the Completers Analysis	131 (74.9)	136 (76.4)	267 (75.6)
Excluded from the ITT† Analysis	12 (6.9)	4 (2.2)	16 (4.5)
No Baseline Data	1 (0.6)	0 (0.0)	1 (0.3)
No On-treatment Data	11 (6.3)	4 (2.2)	15 (4.2)
Excluded from the Completers Analysis‡	32 (18.3)	38 (21.3)	70 (19.8)
Rescued Prior to Week 24§	11 (6.3)	23 (12.9)	34 (9.6)
No Data at Week 24‖	21 (12.0)	15 (8.4)	36 (10.2)

† ITT: Intent-to-treat population.
‡ The completers population is a subset of the ITT population including all patients with Week 24 data.
§ Efficacy data obtained on a patient after initiation of rescue therapy are treated as missing.
‖ For patients not on rescue medication.

Adapted from applicant's Table 10-3, reference P019

Both studies exceeded the protocol-specified target, due to the difficulty in predicting the proportion of subjects who would be found eligible after the placebo run-in period and the applicant's policy not to drop eligible subjects from the run-in period after having met the pre-specified sample size.

In addition to being substantially smaller in size compared to P020, Study P019 did not continue into an extension beyond week 24. Few subjects in each study were excluded from the intent-to-treat analysis, because they either had no baseline data or no data after randomization. Exclusion of such subjects from the analyses in the intent-to-treat population is reasonable, and still permits proper interpretation of study findings.

6.2.4.2 Baseline and demographic characteristics

Study P020

Baseline characteristics and demographics relevant to this patient population were similar between the two treatment groups, thus allowing adequate interpretation of the study findings (Table 50 and Table 51). It is important to note, however, that both treatment groups had a substantially smaller proportion of African Americans compared to the proportion of African American patients with T2DM in the US population.

Table 50. Demographic characteristics in subjects participating in Study P020

Age					
Treatment	N	Mean (SD)	Range		
Sitagliptin 100 mg	464	54.4 (10.4)	19 - 78		
Placebo	237	54.7 (9.7)	26 - 76		
All	701	54.5 (10.2)	19 - 78		
Baseline Body Weight (kg)					
Sitagliptin 100 mg	464	86.7 (17.8)	49 – 161.5		
Placebo	237	89.6 (17.5)	53 - 146.7		
Baseline BMI (kg/m^2)					
Sitagliptin 100 mg	464	30.9 (5.3)	19.6 – 43.9		
Placebo	237	31.5 (4.9)	20.8 – 43.6		
Gender					
	Male	Female	Total		
	N (%)	N (%)			
Sitagliptin 100 mg	259 (55.8)	205 (44.2)	464		
Placebo	141 (59.5)	96 (40.5)	237		
All	400 (57.1)	301 (42.9)	701		
Race					
	White	Black	Hispanic	Asian	Other
	N (%)	N (%)	N (%)	N (%)	N (%)
Sitagliptin 100 mg	293 (63.1)	31 (6.7)	72 (15.5)	49 (10.6)	19 (4.1)
Placebo	159 (67.1)	14 (5.9)	28 (11.8)	26 (11.0)	10 (4.2)

Adapted from the applicant's Table 10-4 Reference P020v1

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Table 51. Baseline characteristics in subjects participating in Study P020

Study P020			
Baseline HbA1c (%)			
Treatment	**N**	**Mean**	**SD**
Sitagliptin 100 mg	463	8.0	0.8
Placebo	235	8.0	0.8
All	698	8.0	0.8
Baseline FPG (mg/dL)			
Sitagliptin 100 mg	464	170	41
Placebo	236	174	42
All	700	172	41
Baseline Fasting Insulin (μIU/mL)			
Sitagliptin 100 mg	464	12.3	10.1
Placebo	236	12.4	7.6
All	700	12.3	9.4
Duration of Type 2 Diabetes Mellitus (years)			
Sitagliptin 100 mg	462	6.0	5.0
Placebo	237	6.6	5.5
All	699	6.2	5.2
Use of Anti-Hyperglycemic Medication at Screening			
	Present	Absent	Total
Sitagliptin 100 mg	437 (94.2 %)	27 (5.8%)	464
Placebo	223 (94.1)	14 (5.9)	237
All	660 (94.2%)	41 (5.8%)	701
Prevalence of Metabolic Syndrome†			
	Present	Absent	Total
Treatment	N (%)	N (%)	N
Sitagliptin 100 mg	282 (60.8)	182 (39.2)	464
Placebo	149 (62.9)	88 (37.1)	237
All	431 (61.5)	270 (38.5)	701
Distribution of HbA1c at Baseline			
Number (%) of Subjects with Baseline HbA1c			
Treatment	<8%	≥8 and <9%	≥9%
Sitagliptin 100 mg	253 (54.6)	146 (31.5)	64 (13.8)
Placebo	128 (54.5)	71 (30.2)	36 (15.3)
All	381 (54.6)	217 (31.1)	100 (14.3

Adapted from the applicant's Table 10-5, reference P020v1

Study P019

The treatment groups were balanced for relevant baseline and demographic characteristics, thus allowing adequate interpretation of the study findings (Table 52 and Table 53).

Table 52. Demographic characteristics in subjects participating in Study P019

Age					
Treatment	N	Mean (SD)	Range		
Sitagliptin 100 mg	175	55.6 (10.4)	31 - 80		
Placebo	178	56.9 (11.1)	24 - 87		
All	353	56.2 (10.8)	24 - 87		
Baseline Body Weight (kg)					
Sitagliptin 100 mg	175	90.9 (17.0)	50.5 – 133.5		
Placebo	178	86.4 (17.4)	50.0 – 135.2		
Baseline BMI (kg/m^2)					
Sitagliptin 100 mg	175	32.0 (5.2)	20.1 – 44.2		
Placebo	178	31.0 (5.0)	20.9 – 43.8		
Gender					
	Male	Female	Total		
	N (%)	N (%)			
Sitagliptin 100 mg	93 (53.1)	82 (46.9)	175		
Placebo	103 (57.9)	75 (42.1)	178		
All	196 (55.5)	157 (44.5)	353		
Race					
	White	Black	Hispanic	Asian	Other
	N (%)	N (%)	N (%)	N (%)	N (%)
Sitagliptin 100 mg	127 (72.6)	11 (6.3)	21 (12.0)	10 (5.7)	6 (3.4)
Placebo	129 (72.5)	12 (6.7)	22 (12.4)	5 (2.8)	10 (5.6)

Adapted from the applicant's Table 10-4, reference P019.

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Table 53. Baseline characteristics in subjects participating in Study P019

Study P019			
Baseline HbA1c (%)			
Treatment	**N**	**Mean**	**SD**
Sitagliptin 100 mg	174	8.1	0.8
Placebo	178	8.0	0.8
All	352	8.0	0.8
Baseline FPG (mg/dL)			
Sitagliptin 100 mg	174	168	39
Placebo	178	165	40
All	352	167	39
Baseline Fasting Insulin (μIU/mL)			
Sitagliptin 100 mg	169	9.7	5.7
Placebo	174	9.1	5.5
All	343	9.4	5.6
Duration of Type 2 Diabetes Mellitus (years)			
Sitagliptin 100 mg	175	6.1	5.4
Placebo	178	6.1	5.7
All	353	6.1	5.6
Use of Anti-Hyperglycemic Medication at Screening			
	Present	Absent	Total
Sitagliptin 100 mg	161 (92%)	14 (8%)	175
Placebo	157 (88.7%)	20 (11.3%)	177
All	318 (90.3%)	34 (9.7%)	352
Prevalence of Metabolic Syndrome†			
	Present	Absent	Total
Treatment	N (%)	N (%)	N
Sitagliptin 100 mg	92 (52.6)	83 (47.4)	175
Placebo	90 (50.6)	88 (49.4)	178
All	182 (51.6)	171 (48.4)	353
Distribution of HbA1c at Baseline			
Number (%) of Subjects with Baseline HbA1c			
Treatment	<8%	≥8 and <9%	≥9%
Sitagliptin 100 mg	88 (50.6)	56 (32.2)	30 (17.2)
Placebo	97 (54.5)	53 (29.8)	28 (15.7)
All	185 (52.6)	109 (31.0)	58 (16.5)

Adapted from the applicant's Table 10-5, reference P019.

6.2.4.3 Primary efficacy endpoint: Change in HbA1c

6.2.4.3.1 Main analyses

Study P020

Study P020 showed substantial reduction of mean HbA1c by sitagliptin treatment at week 24, compared to placebo. The primary data analysis was based on the ITT population, with missing data or data following pioglitazone glycemic rescue therapy being imputed by

LOCF. The difference between groups in LS means, with the 95 % CI, is -0.65 % (-0.8, -0.5) ($p < 0.001$). The same conclusion can be drawn from the analysis of the completers in both groups (Table 54 and Table 55, respectively).
Most of the reduction in mean HbA1c occurred in the first 12 weeks of the study, with HbA1c remaining relatively constant from week 12 to week 24. The placebo-adjusted difference in mean HbA1c was smaller among the completers population, because of the removal from the analysis of a larger proportion of subjects randomized to placebo who had to receive pioglitazone rescue due to poor glycemic control (Table 71).

Table 54. Change of HbA1c from baseline to week 24 in Study P020 (ITT population)

		Mean (SD)		Change from baseline			
					LS Mean	95% CI for LS	p-Value
Treatment	N	Baseline	Week 24	Mean (SE)	(SE)	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 P021v1

Table 55. Change in HbA1c from baseline to week 24 in Study P020 (Completers population)

		Mean (SD)		Change from baseline			
					LS Mean	95% CI for LS	p-Value
Treatment	N	Baseline	Week 24	Mean (SE)	(SE)	Mean	
Sitagliptin 100 mg	399	7.9 (0.8)	7.1 (0.8)	-0.8 (0)	-0.8 (0)	(-0.9, -0.7)	< 0.001
Placebo	171	7.9 (0.8)	7.7 (0.9)	-0.3 (0.1)	-0.3 (0.1)	(-0.4, -0.1)	< 0.001
Between Treatment Difference		Difference in LS means (95 % CI)					p-Value
Sitagliptin 100 mg vs. Placebo		**-0.55** (-0.7, -0.4)					< 0.001
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.							

Adapted from the applicant's Table 14-8, reference P021

Study P019

Study P019 also showed a significant reduction in mean HbA1c among subjects treated with sitagliptin 100 mg compared to placebo (placebo-adjusted LS mean HbA1c was -0.7 %). Most of the reduction in serum HbA1c occurred by week 12, although there was some continued improvement in mean glycemic control until week 24, compared to placebo. The point estimate of the treatment effect appears more attenuated in the analysis of completers, because of the larger proportion of subjects in the placebo group who required metformin rescue therapy.

Table 56. Change in HbA1c from Baseline to week 24 in Study P019 (ITT Population)

Treatment	N	Mean (SD)		Change From Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	163	8.0 (0.8)	7.2 (0.9)	-0.9 (0)	-0.8 (0.1)	(-1.0, -0.7)	<0.001
Placebo	174	8.0 (0.8)	7.8 (1.1)	-0.2 (0.1)	-0.2 (0.1)	(-0.3, 0)	0.017

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-0.70** (-0.8, -0.5)	<0.001

Adapted from the applicant's Table 11-1, reference P019

Table 57. Change in HbA1c from Baseline to week 24 in Study P019 (Completers Population)

Treatment	N	Mean (SD)		Change From Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	131	7.9 (0.7)	7.0 (0.8)	-1.0 (0.1)	-0.9 (0.1)	(-1.0, -0.8)	<0.001
Placebo	136	7.9 (0.8)	7.6 (0.9)	-0.3 (0.1)	-0.3 (0.1)	(-0.4, -0.2)	<0.001

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-0.63** (-0.8, -0.5)	<0.001

Adapted from the applicant's Table 14-6, reference P019

6.2.4.3.2 Individual changes in HbA1c categories over time in Studies P019 and P020

Figure 22 shows the changes in HbA1c (HbA1c data being divided in 4 color-coded categories) occurring in each subject from baseline to week 24, with subjects sorted in ascending order according to their baseline HbA1c. Missing data were imputed by LOCF, according to the statistical analytical plan described in each of these study protocols.

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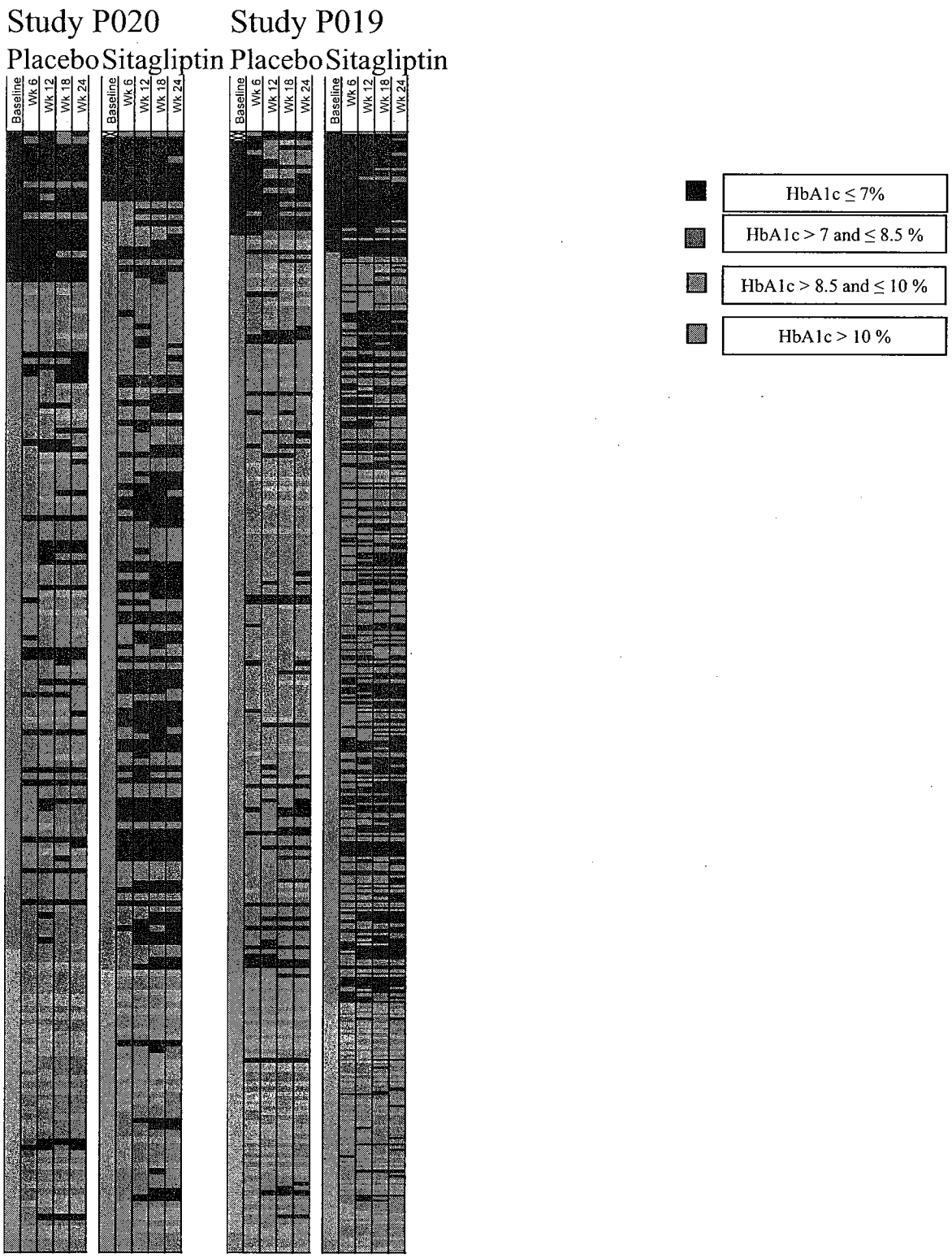
Figure 22. Changes in HbA1c categories, by subject, from baseline to week 24 in Studies P019 and P020



Similar to the conclusions from Figure 11, a plot of individual changes in HbA1c categories of studies assessing sitagliptin use as monotherapy, the plot in Figure 22 demonstrates that more subjects improved their glycemic control in the sitagliptin groups, compared to placebo. This reduction in HbA1c during sitagliptin treatment is particularly evident in those subjects that had higher HbA1c at baseline, compared to placebo.

6.2.4.3.3 Exploratory analyses

Inclusion of data after glycemic rescue therapy

Plots demonstrating the effect of sitagliptin on mean levels of HbA1c are shown in Figure 23 and Figure 24, for studies P020 and P019, respectively. These figures include the HbA1c data recorded in all ITT subjects, regardless of glycemic rescue therapy.

Figure 23. Changes in mean HbA1c (%) (± SE) by study visit in Study P020

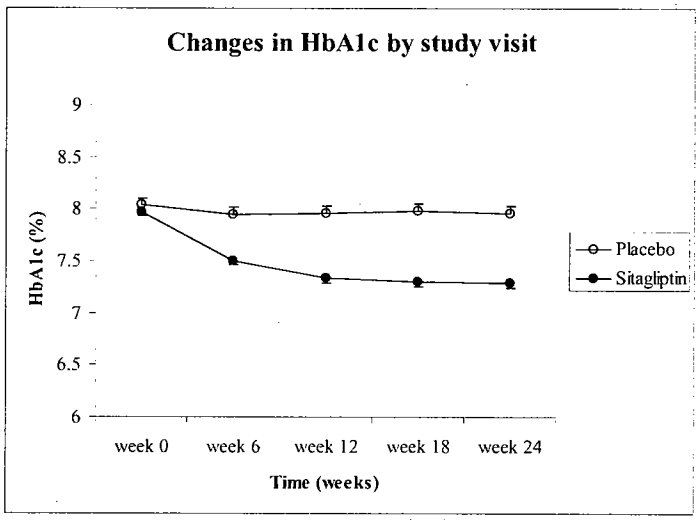
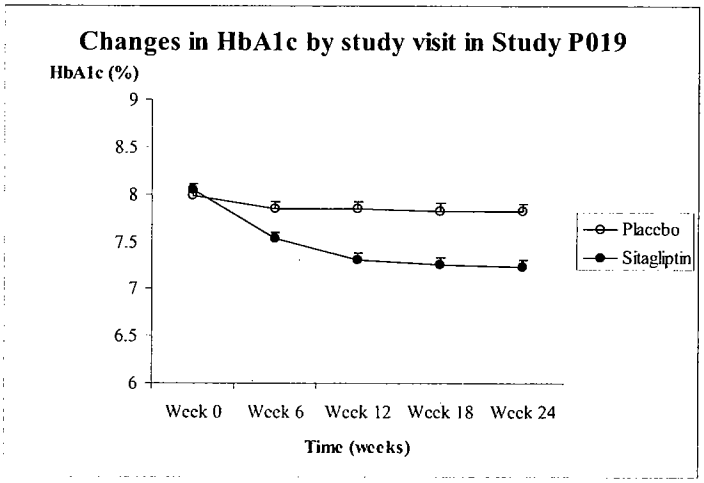


Figure 24. Changes in mean HbA1c (%) (± SE) by study visit in Study P019



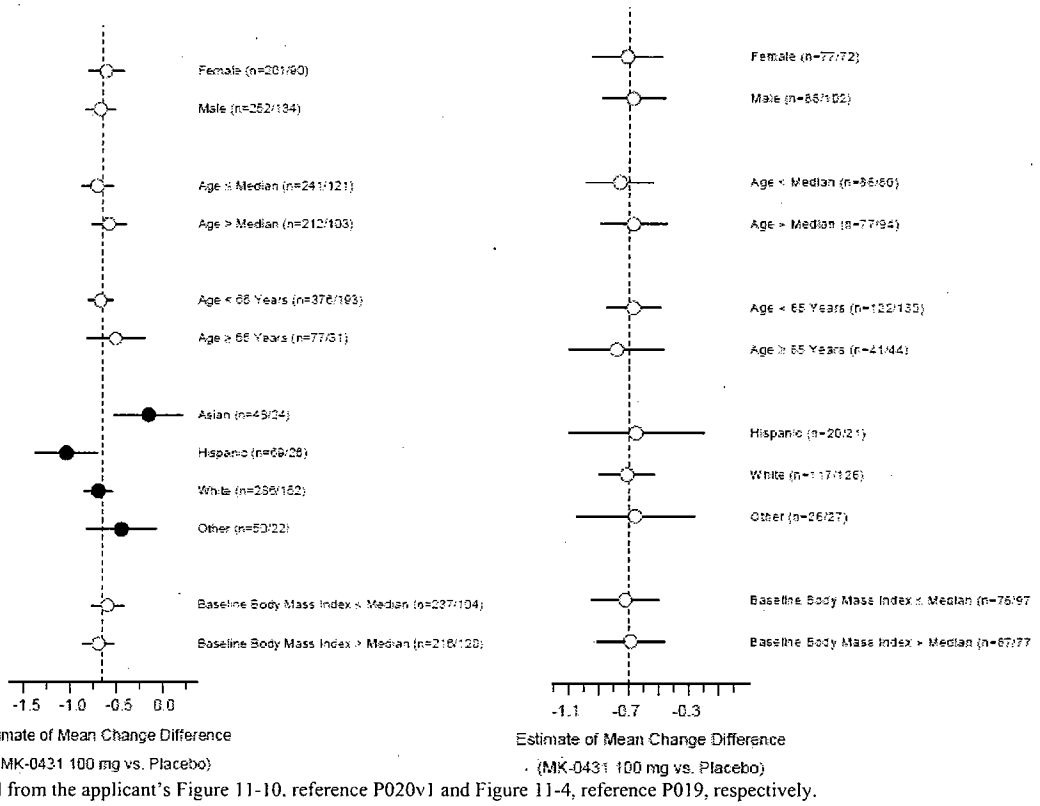
Inclusion of HbA1c data following glycemic rescue therapy does not change the overall conclusion that sitagliptin therapy results in a significant improvement in glycemic control,

as compared to placebo.

<u>HbA1c changes in demographic subgroups of the ITT population based on baseline and demographic characteristics</u>

The effect of sitagliptin on the changes in HbA1c were also analyzed in subgroups based on demographic or baseline characteristics as shown in Figure 25 and Figure 26.

Figure 25. Analyses of changes in HbA1c based on demographic characteristics in Studies PO20 and P019, respectively



Copied from the applicant's Figure 11-10, reference P020v1 and Figure 11-4, reference P019, respectively.

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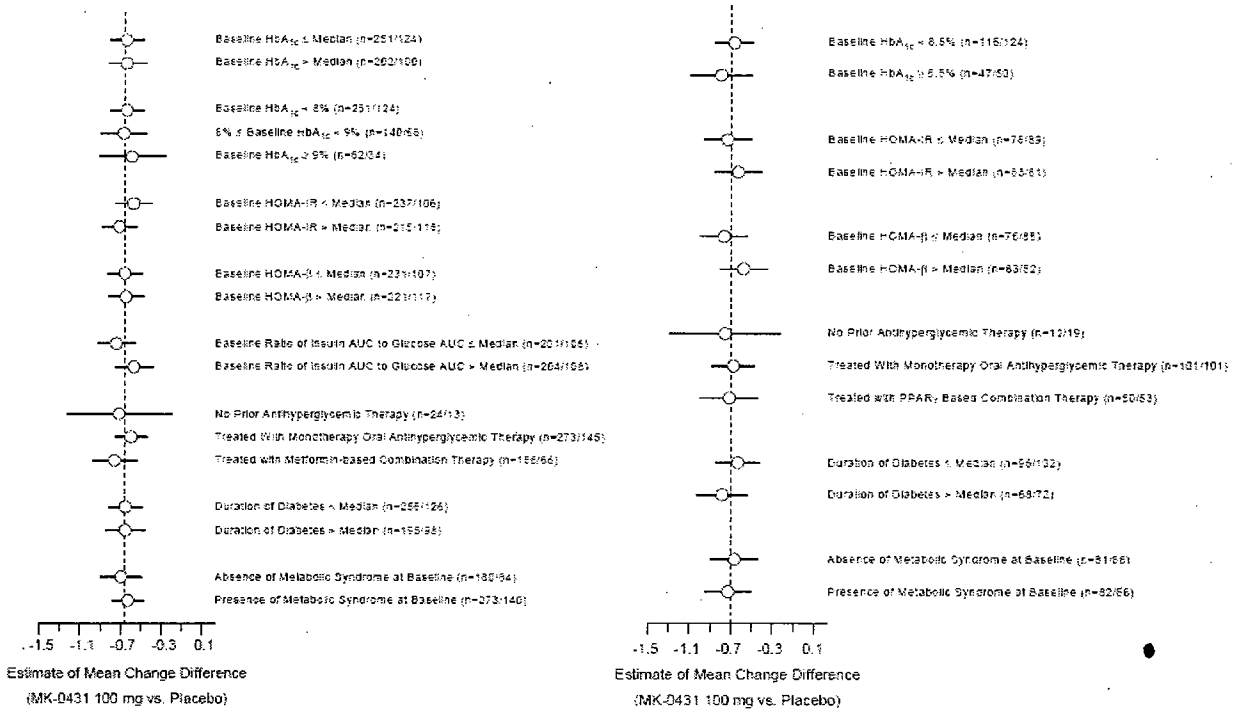
Figure 26. Analyses of changes in HbA1c based on baseline characteristics in Studies P020 and P019, respectively



Copied from the applicant's Figure 11-11, reference P020v1 and Figure 11-5, reference P019, respectively.

There were no relevant differences in the magnitude of sitagliptin effect on HbA1c reduction in the subsets analyzed, as compared to the mean point estimate observed fro the entire treatment group.

<u>Proportion of subjects reaching the ADA goal of HbA1c < 7 %</u>

The proportion of subjects reaching the ADA's goal of HbA1c < 7 % was not an exploratory endpoint in Study P020, but the applicant has provided these data in the application. This reviewer views this as an arbitrary, although clinical important cutoff in the range of glycemic control and thus included these data as exploratory analyses of the primary endpoint (Table 58).

Table 58. Proportion of subjects achieving the ADA goal of HbA1c < 7 % in Study P020

Treatment	N	n (%) < 7%	Difference in Proportion (%) From Placebo (95% CI†)
Sitagliptin 100 mg	453	213 (47.0)	**28.7**‡ (21.5, 35.9)
Placebo	224	41 (18.3)	-

† Confidence Interval computed using the Wilson score method.
‡ p<0.001: from the logistic regression model, adjusting for baseline HbA1c, and prior anti-hyperglycemic medication status

Adapted from the applicant's Table 2.7.3: 21

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The proportion of subjects reaching the ADA's goal of HbA1c < 7% and the proportion of subjects requiring glycemic rescue therapy were deemed tertiary endpoints in Study P019 by the applicant, but this reviewer interprets these data as exploratory analyses of the primary endpoint (Table 59).

Table 59. Proportion of subjects achieving the ADA goal of HbA1c < 7 % in Study P019

Treatment	N	N (%)
Sitagliptin	163	74 (45.4)
Placebo	174	40 (23.0)
Comparison with placebo	Difference in Proportion (%) (95 %CI)	p-value
Sitagliptin vs. placebo	**22.4** (12.3, 32.5)	<0.001

Adapted from the applicant's Table 11-9, reference P019

6.2.4.3.4 Durability of sitagliptin effect in combination with metformin in Study P020

Summary of study design, subject disposition and baseline characteristics

Study P020 was a study investigating effects of sitagliptin in combination with maximal or near maximal doses of metformin. Similar to P021, it contained a Phase A, double-blind, placebo-controlled, randomized, 24-week study and a Phase B 80-week extension. During Phase A 701 subjects were randomized 2:1 to sitagliptin 100 mg or placebo, respectively. During Phase B, subjects treated with placebo during Phase A were switched to treatment with glipizide. The groups are designated here as sitagliptin 100 mg, or placebo / glipizide. Endpoints that were carried from Phase A to Phase B were HbA1c and fasting plasma glucose (subject disposition into Phase B shown in Table 60).

Table 60. Disposition of subjects in Phase B of Study P020

	Number (%)		
	Sitagliptin 100 mg	Placebo / glipizide	Total
Total Randomized	464	237	701
Entered Phase B (% of randomized)	391 (84.3)	164 (69.2)	555 (79.2)
Included in ITT*	387 (99.0)	157 (95.7)	544 (98.0)
Included in Completers*	334 (85.4)	141 (86.0)	475 (85.6)
* Except where noted, percentages are calculated relative to the number of subjects entering Phase B			

Adapted from the applicant's Table 6-2, reference r0026, in the 4-month Safety Update Report

Relative to subjects not entering Phase B, subjects who entered Phase B generally had lower baseline HbA_{1c} (7.9% for subjects entering Phase B vs. 8.4% for subjects not entering Phase B) and FPG values (165 mg/dL for subjects entering Phase B vs. 198 mg/dL for subjects not entering Phase B), a lower prevalence of metabolic syndrome, and lower body weight. A larger proportion of subjects entering Phase B had been on an anti-diabetic agent monotherapy compared to those not continuing into Phase B. For subjects entering Phase B, baseline demographic and anthropometric characteristics were generally balanced across the treatment groups as were variables describing disease history and baseline glycemic control (e.g., disease duration, prior use of anti-diabetic agent, HbA_{1c} and FPG).

Results

Table 61 shows 54-week data on the efficacy endpoints in Study P020, namely HbA1c and fasting plasma glucose, in each of the groups. Data are shown as LS means of baseline and week 54 values (± SD) in the ITT population, as well as the least square means (± SE) and the proportion (%) of the treatment effect observed for the endpoint in week 24 that is maintained at week 54.

Table 61. Changes from baseline to week 54 in HbA1c and fasting plasma glucose In Study P020 (Phase A and Phase B)

Endpoint		Sitagliptin 100	PBO /Glipizide
HbA1c (%)			
	N	387	157
	Baseline	7.9 (0.8)	7.9 (0.7)
	Week 54	7.1 (0.9)	6.9 (0.7)
	LS Mean change (SE)	-0.7 (0.1)	-0.9 (0.1)
	% week 24 effect maintained at week 54	87	
Fasting Plasma Glucose (mg/dL)			
	N	190	83
	Baseline	166 (38)	161 (34)
	Week 54	151 (38)	146 (35)
	LS Mean change (SE)	-12 (3)	-14 (3)
	% week 24 effect maintained at week 54	57	

Most of the treatment effect achieved with sitagliptin by week 24 was maintained at week 54, demonstrating durability of the effect on glycemic control.
The placebo / glipizide group had a mean HbA1c reduction of -0.3% at week 24 (end of Phase A, when subjects in that group were switched from placebo to glipizide), so that the additional mean reduction with glipizide treatment (5 to 20 mg daily, titrated as needed) over the remaining 30 weeks of the study was -0.6%.
Among 387 subjects in the sitagliptin group, 198 (55 %) had HbA1c < 7 % at week 54, and of the 157 subjects in the placebo / glipizide group, 96 (61 %) had HbA1c < 7% in the ITT population analyzed.
Similar to the findings in the extensions to Studies P010 and P014 (a 1-year comparison of the effect on HbA1c between sitagliptin 100 mg and glipizide – see Figure 12), the glipizide effect was greater than that of sitagliptin, but shows a nadir at week 46 with a trend of loss of some of the effect by week 54 (Figure 27).
For the Week 54 completers population, which excluded approximately 13% of subjects in the ITT cohort who did not reach Week 54, the LS mean changes from baseline at Week 54 were -0.82 % and -0.97% for the sitagliptin 100 mg and placebo / glipizide groups, respectively.

Figure 27. LS Mean change from baseline in HbA1c (%) over time by treatment group (LS Mean ± SE)

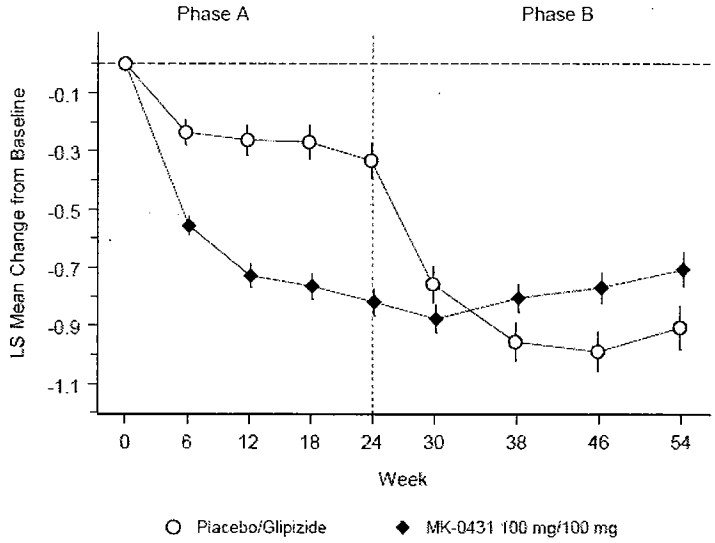


Figure 8-1, copied from reference r0026 from the 4-month Safety Update Report

6.2.4.4 Secondary efficacy endpoints: Change in fasting plasma glucose and 2-hour post-meal glucose

6.2.4.4.1 Fasting plasma glucose

Study P020

Mean fasting plasma glucose decreased over the 24 weeks of Study P020 (Table 62), with a placebo-adjusted difference in LS means of 25 mg/dL (95 % CI of -31, -20) (p <0.001). Most of the reduction in fasting plasma glucose in the sitagliptin-treated subjects occurred within the first 6 weeks of therapy. A slight attenuation of this treatment effect was seen in the analysis of completers, due to the larger proportion of subjects in the placebo group who needed glycemic rescue therapy.

Table 62. Changes in Fasting Plasma Glucose (mg/dL) in Study P020

Treatment	N	Mean (SD)		Change From Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	454	170 (41)	151 (40)	-19 (2)	-17 (2)	(-22, -12)	<0.001
Placebo	226	174 (42)	179 (51)	5 (3)	8 (3)	(3, 14)	0.003

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-25** (-31, -20)	<0.001

Adapted from the applicant's Table 11-2, Reference P020

Study P019

The fasting plasma glucose decreased in the sitagliptin group by a placebo-subtracted 18 mg/dL (difference in LS Means between groups, p<0.001). Most of the glucose level decrease occurred within the first 6 weeks of the study. No decrease in mean glucose was seen in the placebo group, suggesting that the pre-randomization period was adequate to ensure stability of the pioglitazone effect. The placebo-subtracted change in fasting plasma glucose in the Completers analysis was smaller compared to the analysis in the ITT population.

Table 63. Changes in Fasting Plasma Glucose (mg/dL) in Study P019

Treatment	N	Mean (SD)		Change From Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	163	168 (40)	150 (37)	-18 (3)	-17 (3)	(-22, -11)	<0.001
Placebo	174	166 (40)	166 (44)	0 (3)	1 (3)	-4, 6)	0.716

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-18** (-24, -11)	<0.001

Adapted from the applicant's Table 11-2, Reference P019

6.2.4.4.2 2-hour post-meal glucose

Study P020

Table 64 shows changes from baseline to week 24 in the plasma glucose levels 2 hours after the standardized meal in Study P020.

Table 64. Changes from baseline to week 24 in mean 2-hour post-meal plasma glucose (mg/dL)

Treatment	N	Mean (SD)		Change From Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	454	274 (74)	214 (61)	-61 (3)	-62 (4)	(-70, -54)	<0.001
Placebo	226	272 (67)	263 (75)	-9 (5)	-11 (5)	(-22, -1)	0.03

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-51** (-60, -41)	<0.001

Adapted from the applicant's Table 11-3, reference P020v1.

The comparison between least-square means of changes from baseline in plasma glucose levels between groups suggests an important effect of sitagliptin on limiting the rise of glucose in response to meals. This endpoint, however, could be reflecting mostly a lower fasting glucose level, which rises proportionally after a meal. A comparison between the differences in LS means of fasting plasma glucose and 2-hour post-meal glucose (25 mg/dL vs. 51 mg/dL, respectively) shows a greater effect on the post-prandial plasma glucose than on fasting plasma glucose. This effect can be explained by the numerous actions of GLP-1 on insulin and glucagon secretions and the slower emptying of the stomach from increased levels of GLP-1. Other ways to explore the sitagliptin effect on the post-prandial excursion of glucose were to look at the rise of glucose (2-hour post meal glucose minus the fasting glucose), regardless of the baseline glucose value, termed here and in the applicant's study

report as glucose increment and at the area under the post-fasting glycemic curve following the test meal.

Plasma Glucose Increment 2 hours after a standard meal

Incremental glucose is calculated as the plasma glucose level at 120 minutes following the standard meal minus the baseline plasma glucose. A substantial reduction in the mean response of glucose to the standard meal was noted in the sitagliptin treatment compared to placebo (Table 65).

Table 65. Change from baseline to week 24 in the post-meal plasma glucose increment (mg/dL)

Treatment	N	Mean (SD)		Change From Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	386	106 (51)	64 (44)	-42 (3)	-43 (3)	(-49, -37)	<0.001
Placebo	182	102 (44)	88 (52)	-14 (4)	-18 (4)	(-25, -10)	<0.001

Between Treatment Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	**-25** (-32, -18)	<0.001

Adapted from the applicant's Table 11-4, reference P020v1.

In addition, the areas under the curve of total 2-hour glucose and incremental 2-hour glucose at week 24 were smaller for the sitagliptin group compared to placebo, indicating an effect of sitagliptin treatment on the post-prandial glucose (Table 66).

Table 66. Changes in Glucose Total and Incremental AUC (mg*h/dL) from baseline to week 24 in Study P020

Treatment	N	Mean (SD)		Change From Baseline				
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value	Difference in LS Means (95% CI)
Total AUC								
Sitagliptin 100 mg	377	494 (113)	404 (97)	-90 (5)	-91 (6)	(-104, -77)	<0.001	**-82** (-32, -18)
Placebo	179	498 (102)	487 (120)	-11 (8)	-10 (8)	(-26, -6)	0.232	-
Incremental AUC								
Sitagliptin 100 mg	377	158 (60)	106 (52)	-53 (3)	-53 (4)	(-60, -46)	<0.001	**-31** (-39, -22)
Placebo	179	157 (53)	136 (61)	-21 (4)	-22 (5)	(-31, -13)	<0.001	-

Adapted from the applicant's Tables 11-13 and 14-11, reference P020v1

Results of Study P015: 24-Hour Weighted Mean Glucose (WMG)

In Study P015, the endpoint examined was 24-hour WMG based upon collection of 7 blood samples pre- and post-meals and overnight.
The WMG was calculated as the area under the 24-hour glucose curve (AUC [0-24 hr]) divided by 24; the 24-hour glucose profile was formed by 7 plasma glucose measurements collected at the site.
This study was designed as a 2-period crossover study, with subjects with T2DM taking metformin at stable doses ≥ 1500 mg qd randomized to receive either placebo then

sitagliptin 100 mg / day (as 50 mg bid) or sitagliptin 100 mg / day then placebo. The sequence was then reverse during Period 2.
Each therapy was given during 4-week treatment periods and 24-hour WMG was measured at the end of each 4-week treatment period.
Analysis based upon data from the 2 periods combined showed a statistically significant between-treatment difference in 24-hour WMG of -17.2 mg//dL (p<0.001).
A carry-over effect was observed in this study in the sitagliptin 100 mg / placebo sequence and, as a result, the focus of the efficacy analyses for Study P015 was directed to data from the first 4-week treatment period (Period 1).
If considering only Period 1 as a randomized, placebo-controlled, parallel group 4-week study only, the changes in 24-h WMG are as shown in Table 67 and in Figure 28.

Table 67. Analysis of effect of sitagliptin combined with metformin on 24-Hour Weighted Mean Glucose (mg/dL) at week 4 in Study P015

Treatment	N	Mean	Between-Subject SD	Median	LS Mean	95% CI for LS Mean	LS Mean Difference From Placebo (95% CI)
Sitagliptin 100 mg	13	125	14	117	125	(113, 137)	**-33** † (-50, -16)
Placebo	13	158	26	156	158	(146, 170)	
† p<0.001. CI = Confidence Interval; LS = Least Squared; SD = Standard Deviation.							

Adapted from the applicant's Table 7-1, reference P015.

Figure 28. Profile Plot of 24-Hour Glucose (Mean) after 4-Weeks of Treatment in Study P015

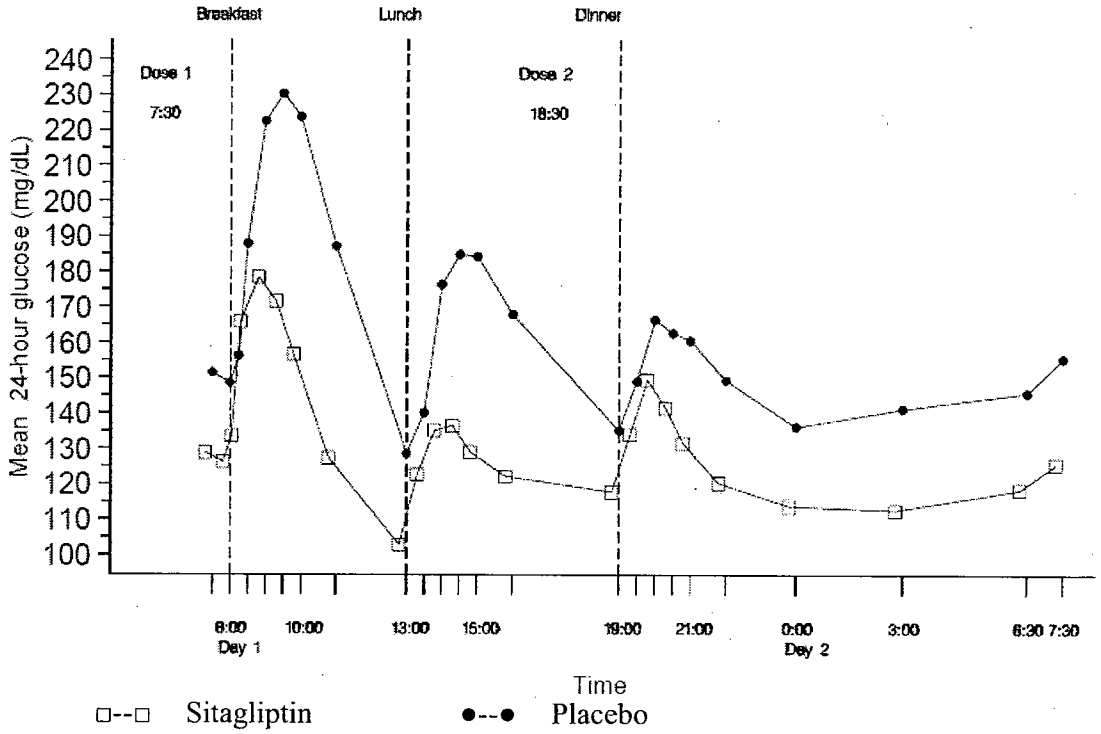
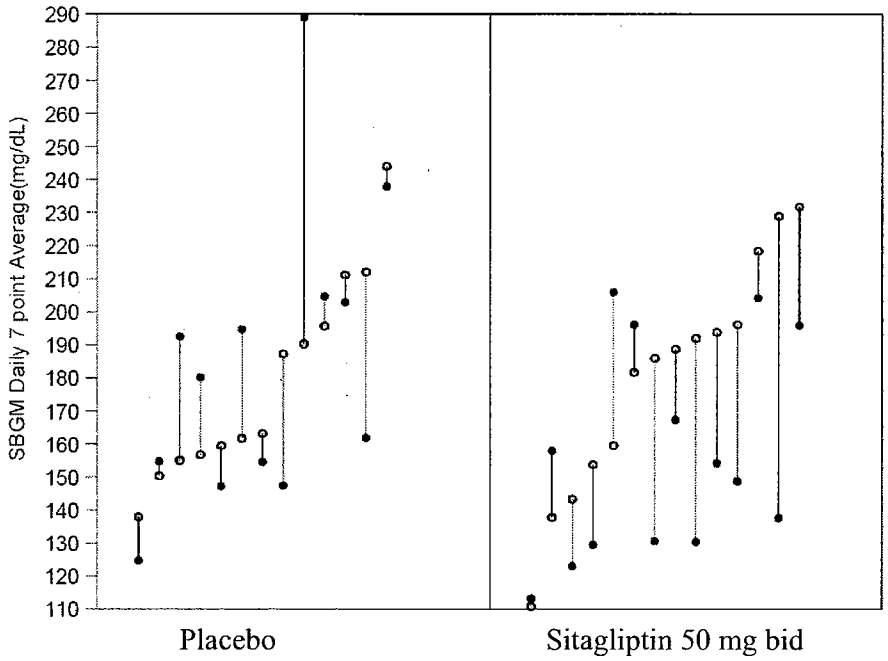


Table 67 and Figure 28 show a significant effect of sitagliptin on fasting plasma glucose

after 1 month of treatment, but an even stronger effect on the excursions of plasma glucose after meals.
Similar conclusions can be reached when looking at the plot of individual changes in the mean value of 7 daily self-assessments of capillary glucose at baseline and at week 4 (Figure 29).

Figure 29. Self blood glucose monitoring daily 7-point average values (mg/dL) at baseline and after 4 Weeks of Treatment (using Period 1 data only)



Adapted from the applicant's Figure S-4, reference P015

Study P019

2-hour post-meal glucose

The 2-hour post-meal plasma glucose level was not an endpoint in Study P019, since a standardized meal test was not a protocol-guided procedure for all subjects in the study. The number of subjects that volunteered for the 9-point 2-hour meal tolerance test in Study P019 and the results of these studies are not included in the study report.

6.2.4.5 Exploratory efficacy endpoints

The exploratory efficacy endpoints for Study P020 and Study P019 related to assessments of beta cell function in the fasting state and in response to the 9-point MTT, and the changes from baseline to week 24 in those endpoints. Insulin secretion in the fasting state was inferred by HOMA-beta and after a meal by increases in insulin levels and insulin/glucose AUC, and beta cell function was also assessed by changes in the ratio of proinsulin to insulin. Insulin sensitivity index (QUICKI) and HOMA-IR were also calculated (Table 68 and Table 69).

Table 68. Parameters of beta cell function and insulin sensitivity calculated from the 9-point MTT in Study P020

Parameter	Treatment	Mean change from baseline (SE)	Difference in LS Means (95% CI)	p-Value
Fasting serum insulin (μIU/mL)				
	Sitagliptin	1.5 (0.5)	1.5 (0.1, 2.9)	0.038
	Placebo	0 (0.4)		
Fasting serum proinsulin (pmol/L)				
	Sitagliptin	0.5 (1.3)	-1.9 (-6.1, 2.4)	0.392
	Placebo	2.3 (1.7)		
Proinsulin to insulin ratio				
	Sitagliptin	-0.03 (0.01)	-0.04 (-0.08, -0.01)	0.007
	Placebo	0 (0.02)		
HOMA Beta				
	Sitagliptin	18.9 (2.5)	16.1 (8.3, 23.8)	<0.001
	Placebo	2.5 (2.3)		
HOMA IR				
	Sitagliptin	0.1 (0.2)	0 (-0.7, 0.7)	0.978
	Placebo	0.1 (0.2)		
QUICKI				
	Sitagliptin	0.0 (0.)	0 (0, 0.0)	0.019
	Placebo	-0.1 (0.2)		
Post-meal insulin (μIU/mL)				
	Sitagliptin	0.6 (1.7)	6.0 (0.4, 11.6)	0.037
	Placebo	-5.2 (2.6)		

Adapted from the applicant's Tables 11-5, 11-6, 11-7, 11-8, 11-9, 11-10, and 11-11, reference P020v1.

Table 69. Parameters of beta cell function and insulin sensitivity calculated from the 9-point MTT in Study P019

Parameter	Treatment	Mean change from baseline (SE)	Difference in LS Means (95% CI)	p-Value
Fasting serum insulin (μIU/mL)				
	Sitagliptin	0.8 (0.5)	0 (-1.1, 1.1)	0.963
	Placebo	0.8 (0.3)		
Fasting serum proinsulin (pmol/L)				
	Sitagliptin	-1.6 (1.2)	-4.7 (-8.3, -1.2)	0.009
	Placebo	2.9 (1.3)		
Proinsulin to insulin ratio				
	Sitagliptin	-0.07 (0.02)	-0.07 (-0.11, -0.04)	< 0.001
	Placebo	0.01 (0.02)		
HOMA-Beta				
	Sitagliptin	11.8 (2.2)		
	Placebo	5.7 (2.4)	5.7 (-0.7, 12.1)	0.08
HOMA-IR				
	Sitagliptin	-0.1 (0.2)	-0.3 (-0.8, 0.3)	0.315
	Placebo	0.3 (0.2)		
QUICKI				
	Sitagliptin	0 (0)	0 (0, 0)	0.207
	Placebo	0 (0)		

Adapted from the applicant's Tables 11-3, 11-4, 11-5, 11-6, 11-7, and 11-8, reference P019.

The only parameter clearly affected by the treatment with sitagliptin in both studies is one related to beta cell function, namely the proinsulin to insulin ratio. The studies of sitagliptin in monotherapy (P021 and P023) assessing beta cell function and insulin sensitivity

showed similar findings.

Proportion of subjects requiring glycemic rescue therapy

Study P019
This is another proposed exploratory endpoint in Study P019. The analysis corroborates the findings of the same endpoint in the monotherapy studies of sitagliptin (Table 70).

Table 70. Proportion of subjects requiring glycemic rescue therapy

Treatment	N	n (%)	Kaplan Meyer Estimate at week 24	
			%	95 % CI
Sitagliptin	175	12 (7)	7.8	(4.2, 12.7)
Placebo	178	25 (14)	15.0	(10.2, 20.9)
Comparison with placebo		Kaplan-Meyer Difference at week 24 % (95% CI)		p-value
Sitagliptin vs. placebo		**-7.2** (-14.1, -0.3)		0.042

Adapted from the applicant's Table 11-11, reference p019

Study P020
Proportion of subjects requiring glycemic rescue therapy was not a study endpoint. To be consistent with data from other studies, these data are shown for Study P020 as well.

Table 71. Proportion of subjects requiring glycemic rescue therapy in Study P020

Treatment	N	n (%)	Kaplan Meyer Estimate at week 24	
			%	95 % CI
Sitagliptin	464	21 (4.5)	4.8	(3.1, 7.1)
Placebo	237	32 (13.5)	14.8	(10.4, 19.8)
Comparison with placebo		Kaplan-Meyer Difference at week 24 % (95% CI)		p-value
Sitagliptin vs. placebo		**-10** (-15.1, -4.8)		< 0.001

Adapted from the applicant's table 11-19, reference P020v1.

Lipid panel

There were no differences in changes from baseline to week 24 in the lipids examined: total cholesterol, LDL-cholesterol, HDL-cholesterol, non-HDL cholesterol, and triglycerides.

6.2.5 Clinical Microbiology

Not applicable.

6.2.6 Efficacy Conclusions

Treatment with sitagliptin improves glycemic control in patients who do not achieve adequate glycemic control despite the use of maximally or near-maximally effective doses of either metformin or pioglitazone. Addition of sitagliptin to these therapies also results in lowering fasting plasma glucose and to an even greater extent, in lowering the post-prandial rise in plasma glucose. No important differences were found when comparing the

effect of sitagliptin across subgroups based on either demographic categories or based on categories of factors present at baseline that can affect the study endpoint, when compared to the entire group's point estimate. The effect on HbA1c appears to be durable to one year, at least based on results from study P020 in combination with metformin.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The overall exposure to sitagliptin in the 34 clinical studies that are part of this development program is 3276 subjects, with a cumulative exposure of 1339 subject-years. The applicant has defined 2 large groups for their integrated analysis of the safety of sitagliptin: the Pooled Phase 3 Population and the Long-Term Safety Population.
The Pooled Phase 3 Population includes 1538 subjects treated with sitagliptin at doses of 100 mg daily or 200 mg daily, as compared to the 778 subjects treated with placebo in these studies. The Pooled Phase 3 Population includes subjects participating in Studies P019, P020, P021 and P023 who received at least one dose of double-blind study medication.
The Long-Term Safety Population consists of all subjects treated with sitagliptin at a dose of 100 mg daily for at least 1 year in Phase 2 and subjects randomized to sitagliptin at a dose of 100 mg or 200 mg daily in Phase 3 studies, including extensions of originally controlled studies. The Phase 2 studies P010 and P014 were dose-ranging trials of sitagliptin. In the randomized, controlled Phase A of these studies, subjects received sitagliptin doses from 5 mg bid to 50 mg bid (in Study P010) and from 25 mg qd to 100 mg qd or 50 mg bid (in Study P014) for 12 weeks. Subjects entered the extension studies (Phase B) while receiving sitagliptin doses to which they had been initially randomized in Phase A. After the applicant's review of the effects of different sitagliptin doses in Studies P010 and P014, the applicant decided to switch the treatment dose of all subjects receiving any dose of sitagliptin to 100 mg daily (this is referred to as "dose collapse"). Dose collapse occurred to all subjects originally randomized to sitagliptin, at or around week 25 after randomization in Phase A. For details, please refer to the description of these studies in Section 10 of this review document.
Table 72 shows the overall database in Phase 2 and Phase 3 studies. The Table does not include Study P028 among the individual Phase 3 studies listed. That study was conducted in 65 subjects with chronic renal insufficiency and the applicant felt that the safety profile in that population is different than of general diabetic population. The safety of sitagliptin in that study is therefore reviewed separately from the pooled studies.
This reviewer agrees with the proposed strategy for integrated analyses, as the pooled data are more likely to demonstrate patterns of adverse events (AEs) that cannot be readily recognized during the review of single studies. The Pooled Phase 3 Population provide more robust data to support the safety of sitagliptin, because of the large number of

participating subjects and the controlled design of the studies. The disadvantage of using the Pooled Phase 3 Population is that the safety data were only collected for up to 24 weeks, for a drug that, if approved, will be used indefinitely. The Long-Term Safety Population therefore complements the safety data derived from the analysis of the Pooled Phase 3 Population. Certain AEs are more likely to be identified with longer exposure, such as trend to increase cardiovascular disease or the appearance of skin necrosis noted with use of sitagliptin in monkey toxicology studies. One disadvantage of the Long-Term Safety Population is that there may have been a bias (readily identifiable or not) in the selection of those subjects electing to participate in extension studies (for example, less AEs or issues related to tolerability, or more compliant than the average subject in the Pooled Phase 3 Population). In addition, the number of subjects in the Long-Term Safety Population is substantially reduced compared to the Pooled Phase 3 Population, and there is overlap between the two. Another disadvantage in considering the Pooled Long-Term Safety Population is the absence of a concurrent control group with similar duration of exposure and safety monitoring.

Table 72. Subjects in the Phase 2 and Phase 3 studies of sitagliptin by total daily dose

	Dose of Sitagliptin				Non-exposed or placebo
	<100 mg	100 mg	200 mg	Total	
	Phase 2 Studies				
Study	N	N†	N	N	N
P010, P010-10	170	402 ‡	N/A	572	168
P014	99	342	N/A	441	111
P015	N/A	28	N/A	28	N/A
RC431A201	N/A	75	N/A	75	76
Phase 2 totals	269	847	N/A	1116	355
	Phase 3 Studies				
Study					
P019	N/A	175	N/A	175	178
P020	N/A	464	N/A	464	237
P021	N/A	238	250	488	253
P023	N/A	205	206	411	110
Phase 3 totals	0	1082	456	1538	778
Phase 2 & 3 total	269	1929	456	2654	1133

† Includes all subjects exposed to 100 mg at any time during the study. (Note: subjects initially randomized to doses of sitagliptin <100 mg who subsequently received 100 mg after dose collapse are counted only once in this table, in the 100-mg group). Also includes 80 subjects who were randomized to placebo in study P010 who subsequently received sitagliptin during the extension study P010-10.

‡ One subject from the glipizide treatment group in PO10X1 was mistakenly dosed with sitagliptin 100 mg for 39 days. This patient is not included in the total Sitagliptin 100 mg exposed patients for P010.

Adapted from the applicant's table 2.7.4:1. reference Summary of Clinical Safety

The protocols for these studies include a stipulation of instituting additional anti-diabetic therapy to rescue subjects in the trials that continue to be under poor glycemic control after a protocol specified period of time ("glycemic rescue therapy"). The primary safety

analysis in the individual study reports and in the Pooled Phase 3 Population excludes non-serious adverse events and laboratory abnormalities that occurred to a subject after initiation of glycemic rescue therapy for the studies (Table 73). This approach avoids the potential of events associated with the rescue therapy to confound the sitagliptin analysis of safety. The safety analysis of SAEs and discontinuations due to AEs in the Pooled Phase 3 Population includes all data regardless of initiation of glycemic rescue therapy. The Pooled Long-Term Safety dataset has a larger proportion of subjects receiving glycemic rescue therapy, and its analysis included all AEs regardless of the use of rescue therapy. The applicant's stated goal of the Long-Term Safety analysis is not to define precisely the safety and tolerability profile of sitagliptin, but rather provide an assessment of safety in long-term exposure to this product. This review document will indicate whether the data include safety parameters observed after initiation of glycemic rescue therapy or not. More placebo-treated subjects met protocol-defined criteria for initiation of glycemic rescue therapy and at an early time compared to sitagliptin-treated subjects. Therefore, censoring of safety data after initiation of rescue therapy constitutes a conservative approach in the review of common AEs between the treatment groups in the Pooled Phase 3 Population.

Table 73. Exposure by sitagliptin dose or placebo in the Pooled Phase 3 Population

Weeks on therapy								Range of days on drug	Mean number of days on drug
Sitagliptin	< 2	≥ 2 to <6	≥ 6 to < 12	≥ 12 to <16	≥ 16 to < 22	≥ 22	Total		
Excluding Data After Initiation of Glycemic Rescue therapy									
100 mg	19	25	40	30	243	725	1082	1 – 216	147
200 mg	4	22	29	17	179	205	456	1 - 189	134
Any dose	23	47	68	46	424	930	1538	1 - 216	143
Placebo	14	33	52	42	148	489	778	1 - 190	141
Including Data After Initiation of Glycemic Rescue Therapy									
100 mg	17	22	31	22	234	756	1082	1 - 216	149
200 mg	4	18	23	13	188	210	456	1 - 189	136
Any dose	21	40	53	34	424	966	1538	1 - 216	146
Placebo	14	21	33	21	137	552	778	1 - 190	148
Although some patients may have taken 2 or more different doses, they have been counted only one time each, on the "Any Dose" row									

Adapted from the applicant's Table 2.7.4:4

The Pooled Long-Term Safety Population consists of subjects exposed to sitagliptin for more than 1 year in Phase 2 studies P010 and P014, and Phase 3 studies P020 and P021 and their extensions. Study P019 did not continue beyond the initial 24 weeks of the original protocol and study P023 had an extension to week 36 only.

For the Pooled Phase 2 studies, a subject who had received sitagliptin at doses less than 100 mg daily in Studies P010 and P014 had to have at least 1 year of exposure to sitagliptin at a dose of 100 mg daily after the "dose collapse" in order to be part of the Long-Term Safety Population. From the Phase 3 studies, subjects were included in the Sitagliptin 100 mg or 200 mg exposed groups if they received treatment with this dose for at least 1 year. Sitagliptin 100 mg treatment groups were available from P020 and P021, while a Sitagliptin 200 mg treatment group was available from Study P021 only. Non-sitagliptin exposed subjects came from P020 only: subjects randomized to placebo in Phase A and then switched to treatment with glipizide upon entry to Phase B of the study (at Week 24).

Subjects in P021 who were randomized to the placebo group were switched to treatment with sitagliptin (100 mg or 200 mg in a 1: 1 ratio) upon entry to Phase B of this study (at Week 24), and hence did not meet criteria (i.e., at least 1 year of exposure) for the Pooled Long-Term Safety Population.

The modified ITT analysis (designated by the applicant as "All Patients as Treated" population) comprises all subjects who received at least 1 dose of double-blind study therapy and, for analyses based on laboratory assessments, subjects who had at least 1 post-baseline laboratory test result.

The Pooled Long-Term Safety Population, while providing valuable safety data on exposure to sitagliptin, is an arbitrarily selected subset (Table 74). The inception cohort is composed of all subjects who were either randomized or had their dose collapsed to 100 mg prior to a specified date (for Phase 2: October 16, 2004 and for Phase 3: October 18, 2004). The inception cohort consists of subjects would have met criteria for participation in the Long-Term Safety Population. Of these, 46.5 % were included in the Long-Term Safety Population. Among subjects who did not participate, only 42 of 989 sitagliptin-treated subjects (4.2%) and 28 of 322 non-exposed subjects (8.7%) were discontinued due to clinical or laboratory adverse events. (Please refer to Section 7.1.3 in this review).

Table 74. Proportion of the total study populations included in the Pooled Long-Term Safety Population

	# eligible to contribute	# in any DB treatment	# contributing to Sita 100 mg	# contributing to Sita 200 mg	# contributing to placebo/glipizide (P020) or glipizide (P010)	# contributing to Placebo/ metformin (P014)
Phase 2 studies						
P010 and extensions	476	215	154	NA	61	NA
P014 and extensions	424	173	124	NA	NA	49
Ph. 2 total	900	388	278	NA	61	49
Phase 3 studies						
P020	267	153	109	NA	44	NA
PO21	144	69	42	27	NA	NA
Phase 3 total	411	222	151	27	44	NA
Ph2 and Ph 3 total	1311	610	429	27	105	49

Adapted from the applicant's Table 3 in the Statistical Report P010C1.

Table 75 shows the exposure to sitagliptin according to the dose used in the Pooled Long-Term Safety Population

Table 75. Exposure by sitagliptin dose in the Pooled Long-Term Safety Population

	< 180 days	≥180 to < 360 days	≥ 360 to < 540 days	≥ 540 to <720 days	≥ 720 days	Total	Range of days on drug	Mean # days on drug
Phase 2 cohort								
Sita Any dose *	0	4	97	164	13	278	329-766	552
5 mg	27	0	0	0	0	27	1-60	6.6
10 mg	8	17	2	0	0	27	87-370	227
12.5 mg	19	0	0	0	0	19	1-26	4
25	30	16	3	0	0	49	1-365	132
50 mg	111	23	3	0	0	137	1 – 374	61
100 mg	0	26	152	99	1	278	269-738	474
Comparator								
Any dose **	0	3	44	58	5	110	345-752	543
Glipizide 5 - 30 mg	76	10	21	30	1	138		
Metformin 850 – 3400 mg	53	11	34	4	0	102		
Placebo	49	0	0	0	0	49	70 – 119	85.3
Phase 3 cohort								
Sita Any dose	0	8	170	0	0	178	349-434	378
100 mg	3	7	144	0	0	154	1 – 433	371
200 mg	9	1	26	0	0	36	1 – 388	280
Comparator								
Any dose &	3	8	33	0	0	44	165-436	351
Glipizide 5 – 30 mg	73	14	0	0	0	87		
Placebo	42	2	0	0	0	44	139-190	170
Combined Sita exposure in Ph 2 and Phase 3 cohorts								
100 mg		11	241	164	13	429	329-766	491
200 mg		1	26	0	0	27	349-388	373
Non-exposed		5	84	60	5	154	343-752	497

* Although some subjects may have taken ≥ 2 different dosages, they have been counted only once each on the "Sita Any Dose" row.
** For subjects in the placebo /metformin treatment group, the numbers in the "Any Dose" row represent the combined exposure for the placebo and metformin double blind medication.
& For subjects in the placebo / glipizide treatment group, the numbers in the "Any dose" row represent the combined exposure for the placebo and glipizide double-blind treatment medication.
Adapted from the applicant's Tables 18 – 22 in the Statistical Report P010C1.

7.1.1 Deaths

As of October 18, 2005 (the reporting cutoff date for the Worldwide Adverse Experience System for this application), a total of 12 deaths have occurred during the clinical development of sitagliptin (Table 76). Of these, three occurred prior to randomization in the Phase 3 studies, being definitely unrelated to sitagliptin. Of the remaining nine deaths, four deaths occurred during the double blind treatment periods in the Phase 2 studies, and five deaths occurred during the double blind treatment periods of the Phase 3 studies.

Table 76. Death listings in the Phase 2 and Phase 3 studies with the cutoff date of October 18, 2005

Protocol	Therapy	Subject ID #	Gender	Age at entry	Relative day of death	Cause of death	Relevant Med. Hx
Phase 2							
P010	Glipizide 5 – 20 mg	2074	Male	62	315	Acute myocardial infarction	Hypercholesterolemia, obesity, HTN, Family Hx CAD
P010	Sitagliptin 12.5 bid	2211	Male	62	180	Closed head injury	Alcohol-related traumatic injury
P010	Sitagliptin 100 qd	3882	Male	45	510	Acute myocardial infarction	Hx peripheral vascular disease, current smoker
P010	Sitagliptin 100 qd	3515	Male	48	449	Acute myocardial infarction	Hx CAD, prior inferior MI, hypercholesterolemia
Phase 3							
P020	Sitagliptin 100 qd	33240	Male	62	295	Stroke	Hx CAD and HTN, current smoker
P021	Pre-random (run in)	BN86001	Male	64	Pre-random	Acute myocardial infarction	Hx MI, Hx CAD
P023	Pre-random (run-in)	BN48006	Female	58	Pre-random	Myocardial infarction	Hyperlipidemia
P028	Pre-random (run-in)	BN43009	Female	71	Pre-random	Sudden death	HTN, hypercholesterolemia, chronic renal insufficiency
P028	Sitagliptin 25 qd	40510	Male	71	96	Acute myocardial infarction	Hx ESRD, Hx MI, PVD, HTN, worsening CAD
P028	Sitagliptin 25 qd	40464	Male	74	70	Sudden death	Hx ESRD, ischemic cardiomyopathy, PE, PVD, HTN, pulmonary HTN
P028	Sitagliptin 50 qd	40030	Male	72	191	Pancreatic cancer with liver metastases	
Ongoing study							
P024	Glipizide 5 qd	42185	Male	49	45	Myocardial infarction	Hx CAD, obesity, dyslipidemia, current smoker

Out of the 12 deaths, 10 were caused by complications of cardiovascular morbidity, being seven with myocardial infarctions, two with sudden death and one with stroke. These deaths occurred in subjects with history of multiple risk factors for cardiovascular disease. An analysis of the role of sitagliptin in these common events in diabetics with multiple other risk factors requires a comparison of the proportion of deaths among the treatment groups. Three of the 7 myocardial infarction deaths occurred in subjects treated with sitagliptin, while two occurred prior to randomization and another two occurred in subjects randomized to glipizide treatment. One subject on sitagliptin had sudden death while the other event of sudden death occurred in a subject prior to randomization. Finally the single subject who died of a cerebrovascular accident was being treated with sitagliptin. Using the total exposure numbers from Table 72, five subjects treated with sitagliptin out of 2654 subjects exposed to this drug died of combined cardiovascular complications (0.19 %), while five subjects not exposed to sitagliptin out of 1133 died of combined cardiovascular complications (0.44 %). As a consequence of too few events, one cannot conclude that sitagliptin treatment raises risk of cardiovascular mortality.

Of the two non-cardiovascular deaths, one was a result of a closed head injury related to alcohol intake in a subject treated with sitagliptin 12.5 mg bid. The other death was a consequence of metastatic pancreatic cancer in a subject treated with sitagliptin 50 mg qd for 6 months. No available information about the timing of the diagnosis with respect to initiation of sitagliptin treatment was available. In both cases, the likelihood that the deaths were due to sitagliptin treatment appears remote.

7.1.1.1 Brief narratives of Deaths

Only deaths occurring after randomization are summarized in this section.

AN 2074, a 63 year-old male with T2DM, hyperopia, hypercholesterolemia, dry skin, foot deformity, fungal infection of nail, tinea pedis, sensory abnormality of lower extremities, sinus congestion, sinus bradycardia, abrasion NOS, lower limb deformity, positive Romberg's, joint crepitation, injury and obesity, was on glipizide in the base study and was continued on glipizide in the first extension on Day 85. There were no concomitant medications. On Day 315 the patient was pronounced deceased by a coroner. The coroner's report stated that based on the patient's history of diabetes, obesity, family history of heart disease, and the position of the body, it was concluded that the cause of death was related to natural causes, probable acute myocardial infarction. No action was taken with regard to blinded study therapy prior to the death. Last dose of glipizide was taken on Day 315. The reporting investigator felt that acute myocardial infarction was probably not related to glipizide.

AN 2211, a 62 year-old male with T2DM, allergic rhinitis, and diabetic neuropathy, was on placebo in the base study and was reassigned to sitagliptin 12.5 mg bid in the first extension on Day 71. Concomitant therapies included multivitamins and thiamine. On Day 163 the subject left work, had several alcoholic beverages, and was involved in a bike accident. There was no automobile involved in the accident. The subject was found lying down, unresponsive and was transported to the hospital by an ambulance. The subject's blood alcohol level was 319 mg/ dL (0.319 %) upon admission. CT scan revealed a diagnosis of expanding subdural hematoma, extensive subarachnoid and subdural hemorrhage with accompanying occipital bone fracture. The subject also had intervals of increasing edema and effacement of cortical sulci and basal cisterns. The subject was intubated, sedated and taken to surgery for craniotomy. The principal procedure was the elevation of skull fracture fragments. Other procedures were as follows: excision/ destruction of lesion/ tissue of brain, incision of brain, ventriculostomy, ventricular shunt to the abdominal cavity and organs, removal of ventricular shunt, interruption of the vena cava (placement of a prophylactic inferior vena cava filter), insertion of endotracheal tube, continuous mechanical ventilation for less than 96 consecutive hours, and transfusion of packed cells and transfusion of serum. The subject's last dose of study drug was on Day 161, two days prior to the accident. The subject was in a coma until Day 180 when he died. The investigator determined that the closed head injury was definitely not related to study therapy. In addition, there is no evidence of hypoglycemic symptoms or documented hypoglycemia for this subject during the study.

AN 3882, a 46 year old male from Malaysia, started on sitagliptin 100 mg qd under Study P010 on March 19, 2004 and had been on this extension of P010 since April 7, 2005. He died of acute myocardial infarction on This information was taken from the Worldwide Adverse Experience System, since no narrative exists in the study report.

AN 3515, a 49 year old male from Norway, started on sitagliptin 100 mg qd under Study P010 June 10, 2004 and had been on this extension (P010-20) since September 9, 2004. In addition to sitagliptin, he was being treated with xylometazoline and atorvastatin. He died of acute myocardial infarction on This information was taken from the Worldwide Adverse Experience System, since no narrative exists in the study report.

AN 33240, a 62 year old male from the United States, started on sitagliptin 100 mg qd under Study P020 on June 2, 2005 and died of acute ischemic stroke on [redacted] He was also being treated with amlodipine besylate and benazepril combination, ibuprofen, metformin and vitamins (unspecified). This information was taken from the Worldwide Adverse Experience System, since no narrative exists in the study report.

AN 40464, randomized to sitagliptin 25 mg qd, had sudden death on Day 70. This subject was a 74 year old Hispanic male with long-standing diabetes and end stage renal disease on hemodialysis. This subject had a complicated and extensive medical history including peripheral vascular disease, ischemic cardiomyopathy, pulmonary edema, chronic bronchitis, and pulmonary hypertension requiring oxygen. This adverse experience of sudden death was considered by the investigator as probably not drug-related.

AN 40510, a 71 year old male on hemodialysis treated with Sitagliptin 25 mg qd, with a complex medical history (including coronary artery disease, stable angina, myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and anemia) who developed a non-serious adverse experience of worsening coronary artery disease on Day 83 during Phase A of the study. He subsequently died due to a serious adverse experience of myocardial infarction during study Phase B (on Day 96).

AN 40030, a 73 year old male from the Russian Federation, treated with sitagliptin 50 mg qd under Study P028, died of liver metastasis from a pancreatic carcinoma on [redacted] He started on sitagliptin on March 24, 2005. In addition, he was taking enalapril maleate since September 2003. This information was taken from the Worldwide Adverse Experience System, since no narrative exists in the study report.

AN 42185, a 49 year old male from New Zealand, treated with glipizide under Study P024 (a comparison between sitagliptin and glipizide in improving glycemic control in patients not adequately controlled with metformin), died of a myocardial infarction on [redacted] . He started glipizide on January 5, 2005. In addition to the glipizide, he was treated with simvastatin, metformin, aspirin and acetaminophen.

7.1.2 Other Serious Adverse Events

In the applicant's analyses, SAEs were counted in the summary tables if the event occurred while on study medication or up to 14 days after the last dose of study medication. All SAEs are accounted for in this section of the review, not only the ones that were observed and recorded in the Pooled Phase 3 Population or the Long-Term Safety Population.

Study P015, a Phase 2 study of sitagliptin / metformin combination, did not report any SAEs.
Table 77 shows the number of subjects who experienced non-fatal SAEs during the Phase 2 and Phase 3 studies, including the 40-week extensions to Studies P010 and P014. The table

excludes SAEs that occurred prior to randomization.
This reviewer conducted an analysis of SAEs that occurred in 4 specific categories: infections, benign and malignant neoplastic events, cardiovascular events, and psychiatric events. The reasons for combining these selected SAEs into the four categories are:
Infections and neoplastic events: DPP4 is identical to CD26, a cell surface protein in lymphocytes thought to modulate function. Although there was no evidence of immune deficiency in mice studies investigating sitagliptin (unlike non-selective DPP IV inhibitors), and there is no evidence of increased numbers of infections in CD26 knock out mice, it is still important to assess whether subjects treated with sitagliptin are more prone to infections or to more severe infections. The same argument can be used to analyze neoplastic SAEs. The latter tend to occur more often in the setting of T-cell immunosuppression.
Cardiovascular events: these events are expected to occur with high prevalence in diabetic populations, and only a thorough analysis of rate of events in combined studies would be able to demonstrate whether sitagliptin causes an increase in these events.
Psychiatric events: Sitagliptin binds to serotonin receptors with a K_i of 2-5 μM, but is devoid of agonist activity; it is not known if sitagliptin reduces activation of 5HT2 and 2A receptors by endogenous serotonin. The applicant has reported a higher incidence of depression in patients receiving 100 mg sitagliptin vs. placebo (13 pts. vs. 0 pts, respectively) in the Long-Term Safety Population; a prior history of depression, insomnia, or anxiety was established in only 5/13 patients.

As seen in Table 77, there were no increases in rates of infections among subjects treated with sitagliptin in two of the Phase 2 studies and their 40-week extensions, as well as in the four Phase 3 studies. The same is noted when analyzing for cardiovascular events or psychiatric events. There was a small increase in the rate of neoplasias among sitagliptin-treated subjects. The 17 events of neoplasia in subjects treated with sitagliptin included a variety of neoplasms, some occurring within several months of starting therapy, while others occurring after more than 1 year of exposure. The predominant neoplastic sites were prostate, colorectal and skin.

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Table 77. Number and proportion of SAEs grouped in specific categories, by study and by treatment in Phase 2 and Phase 3 trials

		Placebo			Glipizide			Sitagliptin			Metformin		
	Study	N	# Subjects in Group	%	N	# Subjects in Group	%	N	# Subjects in Group	%	N	# Subjects in Group	%
Infections	P010	1	125	0.8	2	123	1.6	0	492	0	NA	NA	
	P010x	NA	NA		0	79	0	4	430	0.9	NA	NA	
	P014	0	111	0	NA	NA		0	444	0	NA	NA	
	P014x	NA	NA		NA	NA		2	275	0.7	0	63	0
	P019	0	178	0	NA	NA		1	175	0.6	NA	NA	
	P020	0	237	0	NA	NA		5	464	1.1	NA	NA	
	P021	2	253	0.8	NA	NA		4	488	0.8	NA	NA	
	P023	1	110	0.9	NA	NA		0	411	0	NA	NA	
Cardio-vascular	P010	0	125	0	2	123	1.6	4	492	0.8	NA	NA	
	P010x	NA	NA		3	79	3.8	7	430	1.6	NA	NA	
	P014	0	111	0	NA	NA		3	444	0.7	NA	NA	
	P014x	NA	NA		NA	NA		4	275	1.5	0	63	0
	P019	0	178	0	NA	NA		0	175	0	NA	NA	
	P020	0	237	0	1	NA		2	464	0.4	NA	NA	
	P021	3	253	1.2	NA	NA		3	488	0.6	NA	NA	
	P023	0	110	0	NA	NA		3	411	0.7	NA	NA	
Neoplastic	P010	0	125	0	0	123	0	1	492	0.2		NA	
	P010x	NA	NA		2	79	2.5	3	430	0.7		NA	
	P014	1	111	0.9	NA	NA		1	444	0.2	NA	NA	
	P014x	NA	NA		NA	NA		2	275	0.7	1	63	1.6
	P019	0	178	0	0	NA		1	175	0.6	NA	NA	
	P020	0	237	0	1	NA		3	464	0.6	NA	NA	
	P021	1	253	0.4	NA	NA		4	488	0.8	NA	NA	
	P023	1	110	0.9	NA	NA		2	411	0.5	NA	NA	
Psychiatric	P010	0	125	0	1	123	0.8	0	492	0	NA	NA	
	P010x	NA	NA		0	79	0	0	430	0	NA	NA	
	P014	0	111	0	NA	NA		1	444	0.2	NA	NA	
	P014x	NA	NA		NA	NA		0	275	0	NA	63	0
	P019	0	178	0	NA	NA		1	175	0.6	NA	NA	
	P020	0	237	0	0	NA		0	464	0	NA	NA	
	P021	0	253	0	NA	NA		1	488	0.2	NA	NA	
	P023	0	110	0	NA	NA		0	411	0	NA	NA	

A pre-clinical toxicology study in dogs revealed slight skeletal muscle degeneration after exposure to sitagliptin at a dose of 50 mg / kg / day, which represents a 26-fold exposure by AUC compared to the dose of 100 mg daily in the clinical studies. Myopathy became an event of clinical interest in the Phase 2 studies, and was subject to immediate reporting. There were no SAEs related to myopathy; only one placebo-treated subject was admitted to

the hospital with the primary complaint of generalized weakness and diaphoresis. Similarly, no laboratory findings that would qualify as SAEs (such as significant elevations of creatine phosphokinase) were noted among subjects treated with sitagliptin. Another signal of interest that arose in the pre-clinical toxicology studies in dogs exposed to sitagliptin at a dose of 50 mg / kg/ day was neurotoxicity characterized by decreased activity, ataxia, tremor, tilting of the head and abnormal respiration, symptoms that were reversible within 3 hours after dosing. No such neurologic SAEs were identified in the analyses of safety in Phase 2 and Phase 3 clinical studies.

Table 78 shows the number and types of SAEs observed in subjects that participated in the four Phase 3 studies (P019, P020, P021 and P023) categorized by System Organ Class (SOC).

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Table 78. Number (%) of subjects with non-fatal SAEs by treatment group and by SOC in the Pooled Phase 3 Population, including data after initiation of glycemic rescue therapy

	Sita 100 mg (N =1082)		Sita 200 mg (N =456)		Placebo (N = 778)	
	n	(%)	n	(%)	n	(%)
Injury, Poisoning And Procedural Complications	**4**	**0.4**	**2**	**0.4**	**5**	**0.6**
Gun Shot Wound	0	0	0	0	1	(0.1)
Head Injury	0	0	0	0	1	0.1
Lower Limb Fracture	0	0	0	0	1	0.1
Lung Injury	1	0.1	0	0	0	0
Overdose	1	0.1	0	0	0	0
Polytraumatism	1	0.1	1	0.2	0	0
Radial Nerve Injury	0	0	1	0.2	0	0
Skin Laceration	1	0.1	0	0	0	0
Tendon Rupture	0	0	0	0	1	0.1
Traumatic Fracture	0	0	0	0	1	0.1
Investigations	**1**	**0.1**	**0**	**0**	**0**	**0**
Hepatic Enzyme Increased	1	0.1	0	0	0	0
Metabolism And Nutrition Disorders	**0**	**0**	**0**	**0**	**1**	**0.1**
Hyperglycemia	0	0	0	0	1	0.1
Musculoskeletal And Connective Tissue Disorders	**0**	**0**	**1**	**0.2**	**1**	**0.1**
Intervertebral Disc Protrusion	0	0	1	0.2	1	0.1
Neoplasms Benign, Malignant And Unspecified (Incl. Cysts And Polyps)	**8**	**0.7**	**4**	**0.9**	**4**	**0.5**
B-Cell Lymphoma	1	0.1	0	0	0	0
Basal Cell Carcinoma	0	0	1	0.2	1	0.1
Bladder Cancer	1	0.1	0	0	0	0
Breast Cancer	1	0.1	0	0	0	0
Colon Cancer	1	0.1	0	0	0	0
Lung Neoplasm Malignant	0	0	0	0	1	0.1
Non-Small Cell Lung Cancer	1	0.1	0	0	0	0
Pancreatic Carcinoma	1	0.1	0	0	0	0
Prostate Cancer	1	0.1	0	0	0	0
Rectal Cancer	0	0	1	0.2	0	0
Renal Cell Carcinoma Stage Unspecified	0	0	1	0.2	0	0
Squamous Cell Carcinoma	1	0.1	1	0.2	0	0
Thyroid Adenoma	0	0	0	0	1	0.1
Thyroid Neoplasm	0	0	0	0	1	0.1
Nervous System Disorders	**3**	**0.3**	**1**	**0.2**	**3**	**0.4**
Cerebrovascular Accident	1	0.1	0	0	0	0
Dizziness	0	0	0	0	1	0.1
Hemorrhagic Stroke	1	0.1	0	0	0	0
Lacunar Infarction	0	0	0	0	1	0.1
Syncope	1	0.1	0	0	0	0
Transient Ischemic Attack	0	0	1	0.1	1	0.1
Pregnancy, Puerperium And Perinatal Conditions	**0**	**0**	**0**	**0**	**1**	**0.1**
Abortion Spontaneous	0	0	0	0	1	0.1
Psychiatric Disorders	**2**	**0.2**	**0**	**0**	**0**	**0**
Depression	1	0.1	0	0	0	0
Intentional Self-Injury	1	0.1	0	0	0	0
Suicide Attempt	1	0.1	0	0	0	0
Renal And Urinary Disorders	**2**	**0.2**	**1**	**0.2**	**1**	**0.1**
Hematuria	1	0.1	0	0	0	0
Nephrolithiasis	0	0	1	0.2	1	0.1
Renal Colic	1	0.1	0	0	0	0
Reproductive System And Breast Disorders	**1**	**0.1**	**1**	**0.2**	**0**	**0**
Benign Prostatic Hyperplasia	1	0.1	0	0	0	0
Vaginal Cyst	0	0	1	0.2	0	0
Respiratory, Thoracic And Mediastinal Disorders	**1**	**0.1**	**1**	**0.2**	**1**	**0.1**
Pleural Effusion	0	0	1	0.2	0	0
Pulmonary Embolism	1	0.1	0	0	0	0
Respiratory Failure	0	0	0	0	1	0.1

Table 78 (Continued)

	Sita 100 mg (N =1082)		Sita 200 mg (N =456)		Placebo (N = 778)	
	n	(%)	n	(%)	n	(%)
Skin And Subcutaneous Tissue Disorders	**1**	**0.1**	**0**	**0**	**0**	**0**
Angioneurotic Edema	1	0.1	0	0	0	0
Vascular Disorders	**1**	**0.1**	**0**	**0**	**1**	**0.1**
Atherosclerosis Obliterans	0	0	0	0	1	0.1
Leriche Syndrome	1	0.1	0	0	0	0
Although a subject may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same subject may appear in different categories.						

From the applicant's Table 2.7.4:49

No specific pattern emerges from this Table, and the few SAEs with more than one subject in any System Organ Class do not show specificity of the AE within the class (for example, among those with neoplasia, there was no predominant type of neoplasia or tissue from which the neoplasia originated) or any dose-related findings.

Table 79 shows the SAEs observed in the Pooled Long-Term Population. The proportion of subjects in the Pooled Long-Term Population receiving glycemic rescue therapy increased over time, as the target glycemia became stricter. The SAEs observed in these subjects after initiation of glycemic rescue therapy are included in the table. Some of the SAEs listed in the Pooled Phase 3 Population (Table 78) are the same as ones listed in Table 79, if the subject who experienced the SAE continued to receive sitagliptin after the Phase A (18 or 24 weeks) of these studies for one year or longer.

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Table 79. SAEs by treatment groups and by SOC in the Pooled Long-Term Safety Population (including data after initiation of glycemic rescue therapy)

	Sita 100 mg (N =429)		Sita 200 mg (N =27)		Non-Exposed (N = 154)	
	n	(%)	n	(%)	n	(%)
Subjects with ≥ 1 SAE	33	7.7	1	3.7	15	9.7
Cardiac Disorders	**5**	**1.2**	**0**	**0**	**4**	**2.6**
Acute Myocardial Infarction	1	0.2	0	0	0	0
Angina Unstable	1	0.2	0	0	0	0
Atrioventricular block	1	0.2	0	0	0	0
Coronary Artery Disease	1	0.2	0	0	1	0.6
Coronary Artery Insufficiency	0	0	0	0	1	0.6
Coronary Artery Stenosis	0	0	0	0	1	0.6
Myocardial Infarction	1	0.2	0	0	0	0
Palpitations	0	0	0	0	1	0.6
Ear and Labyrinth Disorders	**1**	**0.2**	**0**	**0**	**0**	**0**
Vertigo	1	0.2	0	0	0	0
Gastrointestinal Disorders	**3**	**0.7**	**0**	**0**	**0**	**0**
Abdominal pain	1	0.2	0	0	0	0
Duodenal Ulcer Hemorrhage	1	0.2	0	0	0	0
Food Poisoning	1	0.2	0	0	0	0
General Disorders and Administration Site Conditions	**1**	**0.2**	**0**	**0**	**2**	**1.3**
Chest pain	1	0.2	0	0	2	1.3
Hepatobiliary Disorders	**1**	**0.2**	**1**	**3.7**	**0**	**0**
Biliary colic	1	0.2	0	0	0	0
Cholangitis	1	0.2	0	0	0	0
Cholecystitis Acute	0	0	1	3.7	0	0
Infections and Infestations	**6**	**1.4**	**0**	**0**	**2**	**1.3**
Cellulitis	1	0.2	0	0	0	0
Gastroenteritis	1	0.2	0	0	0	0
Helicobacter gastritis	0	0	0	0	1	0.6
Oral Infection	1	0.2	0	0	0	0
Otitis Media Chronic	1	0.2	0	0	0	0
Pneumonia	1	0.2	0	0	1	0.6
Urethritis	1	0.2	0	0	0	0
Injury, Poisoning and Procedural Complications	**4**	**0.9**	**0**	**0**	**6**	**3.9**
Accidental Overdose	1	0.2	0	0	0	0
Drug Toxicity	0	0	0	0	1	0.6
Head Injury	0	0	0	0	1	0.6
Lower limb fracture	1	0.2	0	0	0	0
Overdose	1	0.2	0	0	1	0.6
Polytraumatism	1	0.2	0	0	0	0
Radius fracture	0	0	0	0	1	0.6
Tendon Rupture	0	0	0	0	1	0.6
Traumatic Fracture	0	0	0	0	1	0.6
Metabolism and Nutrition Disorders	**1**	**0.2**	**0**	**0**	**0**	**0**
Hyperglycemia	1	0.2	0	0	0	0
Musculoskeletal and Connective Tissue Disorders	**4**	**0.9**	**0**	**0**	**1**	**0.6**
Ankylosing Spondylitis	0	0	0	0	1	0.6
Intervertebral Disc Degeneration	1	0.2	0	0	0	0
Osteoarthritis	3	0.7	0	0	0	0
Neoplasms Benign, Malignant And Unspecified (Incl. Cysts And Polyps)	**5**	**1.2**	**0**	**0**	**0**	**0**
Adrenal Adenoma	1	0.2	0	0	0	0
Basal Cell Carcinoma	2	0.5	0	0	0	0
Breast Cancer	1	0.2	0	0	0	0
Ovarian Adenoma	1	0.2	0	0	0	0

Table 79 (Continued)

	Sita 100 mg (N =429)		Sita 200 mg (N =27)		Non-Exposed (N = 154)	
	n	(%)	n	(%)	n	(%)
Subjects with ≥ 1 SAE	33	7.7	1	3.7	15	9.7
Nervous System Disorders	**0**	**0**	**0**	**0**	**1**	**0.6**
Sciatica	0	0	0	0	1	0.6
Psychiatric Disorders	**2**	**0.5**	**0**	**0**	**0**	**0**
Depression	2	0.5	0	0	0	0
Renal and Urinary Disorders	**3**	**0.7**	**0**	**0**	**0**	**0**
Nephrolithiasis	1	0.2	0	0	0	0
Renal Colic	1	0.2	0	0	0	0
Renal Failure Acute	1	0.2	0	0	0	0
Reproductive System and Breast Disorders	2	0.5	0	0	0	0
Pelvic Hematoma	1	0.2	0	0	0	0
Pelvic Peritoneal Adhesions	1	0.2	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**0**	**0**	**1**	**0.6**
Epistaxis	1	0.2	0	0	0	0
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**0**	**0**	**1**	**0.6**
Urticaria	0	0	0	0	1	0.6

Although a subject may have 2 or more clinical AEs, the subject is counted only once within a category. The same subject may appear in different categories

Adapted from the Applicant's Table 2.7.4:50, reference 2.7.4. Summary of Clinical Safety.

Again, as in the analysis of the Pooled Phase 3 Population, the SAEs observed in these subsets of subjects followed for more than one year do not show any specific pattern, with common conditions in diabetics occurring in the same proportions in subjects exposed to sitagliptin as in the non-exposed group. In addition, there is no increase in the numbers or proportions of SAEs in the cohort of subjects given 200 mg daily; however, it is notable that data at this dose are limited (n = 27) in this safety analysis.

Serious adverse events observed in Study P028 are shown in Table 80 below. This study was conducted in subjects with chronic renal insufficiency, and the overall safety profile for this patient population is substantially different from that of diabetic with preserved renal function.

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Table 80. Specific Serious Clinical Adverse Experiences by SOC by treatment group in study P028, including data after initiation of glycemic rescue therapy

	Sitagliptin		Placebo	
	(N = 65)		(N = 26)	
	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	9	13.8	1	3.8
Cardiac Disorders	**3**	**4.6**	**0**	**0**
Cardiac Failure	1	1.5	0	0
Cardiac Failure Congestive	1	1.5	0	0
Myocardial Infarction	1	1.5	0	0
Gastrointestinal Disorders	**1**	**1.5**	**0**	**0**
Gastroduodenitis	1	1.5	0	0
General Disorders And Administration Site Conditions	**1**	**1.5**	**0**	**0**
Sudden Death	1	1.5	0	0
Infections And Infestations	**3**	**4.6**	**1**	**3.8**
Gastroenteritis	1	1.5	0	0
Pneumonia	2	3.1	0	0
Staphylococcal Infection	0	0	1	3.8
Urinary Tract Infection	1	1.5	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**1**	**1.5**	**0**	**0**
Squamous Cell Carcinoma	1	1.5	0	0
Nervous System Disorders	**2**	**3.1**	**0**	**0**
Cerebrovascular Accident	1	1.5	0	0
Loss Of Consciousness	1	1.5	0	0

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Adapted from the applicant's Table 12-9, Reference P028V1

Except for the SAEs of staphylococcal infections, the incidence of SAEs was higher in the sitagliptin group versus placebo. However, given the small sample size and the nature of these SAEs which are very prevalent in the study population, the study is inadequate to definitely conclude about sitagliptin risks in SAEs in this population.
The subjects with SAEs in the cardiac and nervous system classes had extensive prior cardiac medical histories, as described here.

Subject AN 40458, a 75 year old Asian male with end stage renal disease on peritoneal dialysis, randomized to sitagliptin, accounts for two of the SAEs listed in Table 80: congestive heart failure and loss of consciousness. He was discontinued from the study due to a drug-related SAE of loss of consciousness. This subject had an extensive medical history of cardiac disease (including congestive heart failure) and had an adverse experience of peritonitis starting 2 days prior to randomization (treated with antibiotics until Day 23). The subject had a subsequent AE of congestive heart failure exacerbation (on Day 7) requiring hospitalization. After discharge from the hospital, on Study Day 9, the patient had an AE of loss of consciousness while taking a shower. The cause of this event was not known, but upon presentation to the hospital, the subject was considered hypotensive and assessed as dehydrated by the medical officer. Subsequent to this AE, the subject was restarted on study drug (for 1 day), without adverse effects. However, since the investigator considered the SAE of loss of consciousness to be possibly drug-related, the subject was discontinued.

Subject AN 40031, a 69 year old white male with a complex cardiovascular history (including hypertension, myocardial infarction, post-infarction cardiosclerosis, congestive heart failure, and angina pectoris) developed the AE of worsening cardiac failure on study Day 57. Additional medical history was significant for chronic obstructive pulmonary disease and active cigarette use. This AE was not considered drug-related; study medication was discontinued (Day 57) due to the requirement for treatment with a cardiac glycoside, which was a prohibited concomitant medication. The adverse experience of worsening congestive heart failure stopped on day 77.

Subject AN 40064, a 71 year old Hispanic female with longstanding diabetes (22 years), had a SAE of myocardial infarction. Prior cardiovascular history was significant for coronary artery disease (status post stent placement and 3 coronary artery bypass grafts), stroke, hypertension, and hypercholesterolemia. On Day 44, the subject developed the SAE of myocardial infarction, considered to be moderate in intensity probably not related to study drug. Study drug was interrupted for 6 days starting on Day 46. This subject continued on study drug in Phase B.

Subject AN 40492, a 58 year old black female was discontinued from the study due to the SAE of cerebrovascular accident (CVA). The subject had a long-standing history of diabetes (23 years), was on treatment with insulin, and had severe renal insufficiency with (creatinine clearance <30 mL/min). Medical history included congestive heart failure and hypertension. On Day 83, the subject experienced an acute CVA and was admitted to the hospital. She was subsequently discontinued on Day 84, having completed Phase A of the study. This event was considered probably not drug-related.

7.1.3 Dropouts and Other Significant Adverse Events

An appropriate method to review study discontinuations without relying on the applicant's tables of AE-related discontinuation is based on the analysis of the "inception cohort for the Pooled Long-Term Safety Population. The "inception cohort" consists of all subjects who were randomized or dose collapsed (the latter applicable to the Phase 2 studies) to sitagliptin 100 mg qd and would therefore be eligible to participate in the Pooled Long-Term Safety Population. The Long-Term Safety population is derived from the inception cohort (Table 81). Analysis of the reasons for not participating in the Long-Term Safety Population could provide signals for dropouts in this comprehensive population.
In addition, discontinuations related to AEs were reviewed thoroughly in each of the Phase 2 and Phase 3 studies and their extensions.

Table 81. Disposition of subjects in the inception cohort from which the Long-Term Safety Population derived (from studies P010, P014, P020 and P021)

Patient Disposition	P010 and P014		P020 and P021			Combined Totals		
	Sita 100 mg	Non-exposed	Sita 100 mg	Sita 200 mg	Non-exposed	Sita 100 mg	Sita 200 mg	Non-exposed
Randomized	N=1064	N=234	N=702	N=250	N=490	N=1766	N=250	N=724
Eligible	667	233	257	65	89	924	65	322
Included in Long-Term Cohort	278	110	151	27	44	429	27	154
Not included in Long-Term Cohort	389	123	106	38	45	495	38	168
Reason for Not Being Included								
Data Not Received by Cut-Off	111	0	33	3	10	144	3	10
Completed (did not extend)†	120	43	N/A	N/A	N/A	120	N/A	43
Completed not Continuing‡	N/A	N/A	13	5	10	13	5	10
Laboratory AE	N/A	N/A	1	0	0	1	0	0
Lack of efficacy	N/A	N/A	2	0	0	2	0	0
Patient discontinuing for other	N/A	N/A	9	3	9	9	3	9
Patient withdrew consent	N/A	N/A	1	1	0	1	1	0
Protocol deviation	N/A	N/A	0	1	1	0	1	1
Patient discontinuing	158	80	60	30	25	218	30	105
Clinical adverse experience	20	20	7	3	4	27	3	24
Laboratory adverse experience	6	1	5	0	3	11	0	4
Lack of efficacy	53	13	15	8	8	68	8	21
Lost to follow-up	14	5	6	2	2	20	2	7
Patient discontinuing for other	5	4	12	4	1	17	4	5
Patient moved	5	3	2	1	2	7	1	5
Patient withdrew consent	48	32	10	9	4	58	9	36
Protocol deviation	6	2	3	1	1	9	1	3
Site terminated	1	0	0	1	0	1	1	0
Protocol-specified discontinuation criteria	0	0	0	1	0	0	1	0

† "Completed" was used in Phase 2 only. Patients had a status of "completed" if they did not enter the extension study.
‡ "Completed not Continuing" was used in Phase 3 only. Patients had a status of "completed not continuing" if they completed Phase A but did not enter Phase B.

Adapted from the applicant's Table 2.7.4:6 Reference 2.7.4 Summary of Clinical Safety

Table 81 lists all reasons preventing subjects for qualifying to participate in the Pooled Long-Term Safety Population according to their treatment groups. Among subjects who completed Phase A but did not continue in Phase B (in the Phase 3 studies P020 and P021) and subjects discontinued form the Phase 2 studies, 47 are listed as discontinued for "other" reasons, either before or after completing the "base" studies: 33 subjects in the sitagliptin groups and 14 in the non-exposed group. For subjects in this category, the most common reason for discontinuation was initiation of glycemic rescue medication, recorded for 9 subjects in the sitagliptin exposed groups and 9 subjects in the non-exposed group (per protocol these patients were not allowed to proceed to Phase B of the study). The second most common reason among subjects in this category was meeting a protocol-specified discontinuation criterion (hyperglycemia criterion for 11 subjects in the sitagliptin groups, none in the non-exposed group; creatinine clearance criteria for 3 subjects in the sitagliptin groups, 1 subject in the non-exposed group). Other reasons for being in this category include lack of compliance, site termination, and death (two subjects in the inception cohort died, one from the Sitagliptin 100 mg group and one subject from the glipizide group).
The pattern of subjects from the inception cohort who elected not to continue study participation does not suggest a clear safety or tolerability issue related to sitagliptin use.

7.1.3.1 Overall profile of dropouts

The overall profile of dropouts is listed in the tables 11- 18 in the application, according to study.

Table 82. Reasons for subject discontinuation in Study P010

	PBO	Sitagliptin				Glipizide	Total
		5 mg bid	12.5 mg bid	25 mg bid	50 mg bid		
Total Number of Randomized Patients	125	125	123	123	124	123	743*
Discontinued prior to completion of study	17	18	7	15	12	23	92
Reason for discontinuation							
Clinical AE	1	1	3	1	2	7	15
Laboratory AE	0	1	0	0	1	0	2
Lack of Efficacy	9	7	2	8	1	2	29
Lost To Follow-Up	0	2	0	0	0	1	3
Patient Discontinued for Other	1	2	0	3	1	1	8
Patient Moved	0	0	0	0	0	2	2
Patient Withdrew Consent	5	4	2	2	6	9	28
Protocol Deviation	1	1	0	1	1	1	5

*Of these 743 subjects, 3 did not take a single dose of double blind therapy.

Table 83. Reasons for subject discontinuation in Study PO10 Extension

	PBO/ Sita	Sitagliptin				Glipizide	Total
		5 mg bid / 100 mg	12.5 mg bid / 100 mg	25 mg bid / 100 mg	50 mg bid/ 100 mg		
Entered extension study	80	85	82	92	91	79	430
Discontinued prior to completion of study	15	16	21	14	16	15	97
Reason for discontinuation							
Clinical AE	3	4	2	0	0	5	14
Laboratory AE	1	0	1	0	0	1	3
Lack of Efficacy	2	4	3	8	5	0	22
Patient Withdrew Consent	5	3	7	0	7	6	28
Other	4	5	8	6	4	3	30

Other includes the following: lost to follow up, discontinued for other reason, moved, protocol deviation, site terminated

In both Study P010 and its 40-week extension, the main reasons for discontinuation were perceived lack of efficacy and withdrawal of informed consent, accounting for approximately half of the total number of discontinuations of sitagliptin- or placebo-treated subjects. Clinical and laboratory AEs that led to discontinuation will be discussed in Sub section 7.1.1.3, below.

Table 84. Reasons for subject discontinuation in Study PO14

	Placebo	Sitagliptin				Total
		25 mg qd	50 mg qd	100 mg qd	50 mg bid	
Randomized subjects who took ≥ 1 dose of study drug	111	110	110	110	111	552
Patient Discontinued prior to completion of study	30	15	6	18	11	80
Reason for discontinuation						
Clinical AE	4	2	0	5	1	12
Laboratory AE	0	0	0	0	1	1
Lack of Efficacy	9	8	2	9	2	30
Lost To Follow-Up	3	0	0	0	3	6
Patient Discontinued for Other	1	0	0	0	0	1
Patient Moved	0	1	0	0	0	1
Patient Withdrew Consent	12	3	2	2	2	21
Protocol Deviation	1	1	2	2	2	8

Table 85. Reasons for subject discontinuation in Study PO14 Extension

	PBO/ Metformin	Sitagliptin				Total
		25 mg qd / 100 mg qd	50 mg qd / 100 mg qd	100 mg qd / 100 mg qd	50 mg bid/ 100 mg qd	
Entered extension study	63	70	69	65	71	338
Discontinued prior to completion of study	12	13	13	16	10	64
Reason for discontinuation						
Clinical AE	4	0	3	2	2	11
Lack of Efficacy	2	0	3	6	2	13
Patient Withdrew Consent	5	8	5	7	4	29
Other*	1	5	2	1	2	11

*Other includes the following reasons: lost to follow up, discontinued for other reason, moved, protocol deviation

In Study P014 and its extension, a pattern similar to that of Study P010 for reasons for discontinuation emerges, with nearly half of subjects discontinuing due to perceived lack of efficacy or withdrawing consent.

Table 86. Reasons for subject discontinuation in Study PO19

	Placebo	Sitagliptin 100 mg qd	Total
Randomized subjects who took ≥ 1 dose of study drug	178	175	353
Discontinued prior to completion of study	20	26	46
Reason for discontinuation			
Clinical AE	2	11	13
Lack of Efficacy	2	0	2
Lost To Follow-Up	1	3	4
Patient Discontinued for Other	5	4	9
Patient Moved	1	1	2
Patient Withdrew Consent	6	5	11
Protocol Deviation	3	2	5

Study P019 had no "Phase B" so all AEs listed that led to discontinuation occurred during the double-blind placebo controlled study. Approximately 28 % of the cases of early discontinuation were due to perceived lack of efficacy or withdrawal of informed consent. Another 28 % were due to AEs (half of these were due to edema, with similar proportions in the placebo and sitagliptin groups, in this study of the safety and efficacy of sitagliptin as add-on to pioglitazone).

Table 87. Reasons for subject discontinuation in Study PO20

	Placebo	Sitagliptin 100 mg qd	Total
Randomized subjects who took ≥ 1 dose of study drug	237	464	701
Discontinued prior to completion of Phase A	45	48	93
Reason for discontinuation			
Clinical AE	5	11	16
Laboratory AE	4	6	10
Lack of Efficacy	13	7	20
Lost To Follow-Up	5	4	9
Patient Discontinued for Other	4	6	10
Patient Moved	3	2	5
Patient Withdrew Consent	10	10	20
Protocol Deviation	1	2	3
Did not enter Phase B	28	23	51
Reason for not entering Ph. B			
Clinical AE	1	1	2
Laboratory AE	2	1	3
Lack of Efficacy	2	2	4
Patient discontinued for Other	24	18	42
Patient withdrew Consent	1	1	2

In Phase A of Study P020, 28 % of AEs were due to clinical or laboratory AEs (in similar proportions in the 2 treatment groups), while 43 % were due to a combination of perceived lack of efficacy and withdrawal of informed consent. During Phase B, the extension study comparing the long-term safety and efficacy of sitagliptin to glipizide, the majority of

discontinuations were caused by initiation of glycemic rescue therapy.

Table 88. Reasons for subject discontinuation in Study PO21

	Placebo	Sitagliptin 100 mg qd	Sitagliptin 200 mg qd	Total
Randomized subjects who took ≥ 1 dose of study drug	253	238	250	741
Discontinued prior to completion of Phase A	37	29	36	102
Reason for discontinuation				
Clinical AE	4	5	4	13
Laboratory AE	0	0	1	1
Lack of Efficacy	9	3	5	17
Lost To Follow-Up	2	5	4	11
Patient Discontinued for Other	5	2	3	10
Patient Moved	1	3	1	5
Patient Withdrew Consent	11	10	17	38
Protocol Deviation	4	1	2	7
Did not enter Phase B	49	19	16	84
Reason for not entering Ph. B				
Lack of Efficacy	8	3	1	12
Patient discontinued for Other	38	16	10	64
Patient withdrew Consent	1	0	2	3
Protocol Deviation	2	0	2	4

In Study P021, 54% of the subjects discontinuing participation prematurely did so due to withdrawal of informed consent or perceived lack of efficacy. Most subjects who did not enter Phase B were discontinued due to initiation of glycemic rescue therapy.

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Table 89. Reasons for subject discontinuation in Study PO23

	Placebo	Sitagliptin 100 mg qd	Sitagliptin 200 mg qd	Total
Randomized subjects who took ≥ 1 dose of study drug	110	205	206	521
Discontinued prior to completion of Phase A	19	17	22	58
Reason for discontinuation				
Clinical AE	4	1	0	5
Laboratory AE	0	0	2	2
Lack of Efficacy	6	0	4	10
Lost To Follow-Up	2	3	3	8
Patient Discontinued for Other	0	1	1	2
Patient Moved	1	1	1	3
Patient Withdrew Consent	3	6	7	16
Protocol Deviation	3	5	4	12
Did not enter Phase B	0	6	1	7
Reason for not entering Ph. B				
Clinical AE	0	3	1	4
Patient discontinued for Other	0	1	0	1
Patient withdrew Consent	0	2	0	2

Again in Study P023 nearly half of the subjects discontinued from the trial due to withdrawal of informed consent and perceived lack of efficacy, in equal proportions among the treatment groups. Most drop outs for clinical adverse experiences occurred in the placebo group.

7.1.3.2 Adverse events associated with dropouts

All AEs associated with study discontinuation are listed from Table 90 through Table 99, according to study. To avoid duplication in this review document, all laboratory AEs that led to subject discontinuations are listed under Section *7.1.7.3.3. Marked outliers and dropouts for laboratory abnormalities.*

Table 90. Non-fatal clinical AEs that led to discontinuation in Study P010

Subject	Gender	Race	Age	Therapy (mg/d)	Day of Onset	Adverse Experience	Day Dropped	Serious
Sita 5 mg bid								
2116	F	Hispanic	51	Sita 10	17	Amnesia	19	N
Sita 12.5 mg bid								
3394	M	white	44	Sita 25	15	Nervousness	16	N
3262	F	white	57	Sita 12.5	1	Dizziness	1	N
2654	F	multi	51	Sita 25	22	Headache	24	N
Sita 25 mg bid								
3319	F	white	52	Placebo	1	Dizziness	6	N
Sita 50 mg bid								
3360	F	white	45	Sita 50	1	Nausea	1	N
2189	M	white	53	Sita 100	41	Asthenia	58	N
Glipizide								
2005	F	white	41	Glipizide 5	2	Gastritis	14	N
3314	F	white	45	Glipizide 10	18	Depression	24	Y
2019	F	white	64	Glipizide 5	45	Hypoglycemia	45	N
2096	F	white	47	Glipizide 5	30	Hypoglycemia	40	N
2117	M	black	26	Glipizide 5	3	Hypoglycemia	14	N
2117	M	black	26	Glipizide 5	7	Hypoglycemia	14	N
3493	M	multi	60	Glipizide 10	17	Infection	39	Y
3548	F	white	44	Glipizide 10	78	Coronary disease	84	Y

Based on the applicant's Table 8-9, Reference P010

Three patients, all in the glipizide treatment group, had SAEs that led to discontinuation. None of these SAEs was considered by the investigator to be related to study drug.

Table 91. Non-fatal clinical AEs that led to discontinuation in Study P010 Extension, from beginning of extension to dose collapse

Subject	Gender	Race	Age	Therapy (mg/d)	Day of Onset	Adverse Experience	Day Dropped	Serious
Placebo / Sitagliptin								
2120	F	black	45	Sita 100	301	Hyperglycemia	317	N
3269	M	black	54	Sita 25	96	Neoplasm prostate	113	Y
Sitagliptin 5 mg bid / 100 mg qd								
3255	M	white	60	Sita 10	120	Musculoskeletal chest pain	120	N
3455	F	multi	58	Sita 10	179	Hydronephrosis	192	N
Sitagliptin 12.5 mg bid / 100 mg qd								
2623	F	Hispa	54	Sita 25	252	Coronary artery disease	252	Y
Sitagliptin 25 mg bid / 100 mg qd								
2056	F	white	40	Sita 50	260	Diarrhea	371	N
Glipizide								
3286	F	Polyn	48	Glipizide 5	219	Hypoglycemia	251	N
3898	F	Asian	59	Glipizide 20	162	Liver Cancer	231	Y
3883	F	multi	69	Glipizide 20	137	Cerebrovascular accident	137	Y

Based on the applicant's Table 8-14, Reference P010X1

Four subjects had non-fatal SAEs that led to discontinuation prior to dose collapse: subject 3269 in the placebo/ sitagliptin treatment group (prostate cancer); subject 2623 in the sitagliptin 12.5 mg bid / 100 mg qd treatment group (coronary artery disease); and 2 in the glipizide treatment group (liver cancer in subject 3898 and cerebrovascular accident in subject 3883).

Table 92. Non-fatal clinical AEs that led to discontinuation in Study P010, from dose collapse to the end of the extension study

Subject	Gender	Race	Age	Therapy	Day of Onset	Adverse Experience	Day Dropped	Serious
Pooled Sitagliptin								
3422	M	white	63	Sita 100 mg	292	Chronic myeloid leukemia	293	Y
3477	M	white	70	Sita 100 mg	294	Prostate cancer	323	Y
2199	M	white	59	Sita 100 mg	218	Myocardial infarction	221	Y
Glipizide								
3518	F	multi	31	Glipizide 10 mg	315	Abortion spontaneous	317	Y

Based on the applicant's Table 8-15, Reference P010X1

Subject 3518 had a spontaneous abortion while on Glipizide but after starting glycemic rescue therapy. Subject 3422 had hematological abnormalities prior to randomization (medical history of low platelet count) and was found to have Philadelphia chromosome positive CML.

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Study P014

Table 93. Non-fatal clinical AEs that led to discontinuation in Study P014

Subject	Gender	Race	Age	Therapy	Relative Day of Onset	Adverse Experience	Day Dropped	Serious
Placebo								
6282	M	white	57	Off Drug 1 day	40	small intestinal obstruction	39	Y
6473	M	white	62	Placebo	2	nausea	4	N
6461	F	white	39	Placebo	2	erythema multiforme	3	N
5119	F	white	37	Placebo	69	edema	70	N
Sitagliptin 25 mg qd								
5010	F	white	61	Sita 25 mg	25	hypoesthesia	36	N
6426	F	white	50	Sita 25 mg	3	chest pain	3	N
Sitagliptin 100 mg qd								
6904	F	black	40	Sita 100 mg	47	suicide attempt	47	Y
5037	F	white	57	Off Drug 1 day	50	ileus	49	Y
5060	M	white	49	Off Drug 3 days	33	chest wall pain	30	N
6430	M	white	55	Sita 100 mg	38	paresthesias	48	N
6525	F	white	51	Sita 100 mg	21	urticaria	37	N
Sitagliptin 50 mg bid								
6914	F	white	70	Off Drug 1 day	80	cholecystitis acute	79	Y

Based on the applicant's Table 8-8, Reference P014

Study P014 Extension

From the beginning of the extension study until dose collapse, 2 subjects in the sitagliptin 50 mg bid / 100 mg qd treatment group had SAEs that led to discontinuation: one subject with the AE of colon cancer and one subject with the AE of cerebrovascular accident. Neither SAE was considered drug related.

Table 94. Non-fatal clinical AEs that led to discontinuation in Study P014, from beginning of extension until dose collapse

Subject	Gender	Race	Age	Therapy (mg/d)	Study Day of Onset	Adverse Experience	Day Dropped	Serious
Placebo / Metformin								
6290	M	white	52	Metformin 1700	150	Diarrhea	167	N
6300	M	white	46	Metformin 850	122	Nausea	126	N
5039	M	white	63	Metformin 1700	201	Diarrhea	245	N
Sitagliptin 50 mg qd / 100 mg qd								
5148	M	white	56	Sita 50	222	Nausea	242	N
6366	M	white	63	Sita 50	97	Dermatitis allergic	98	N
6366	M	white	63	Sita 50	97	Viral infection	98	N
Sitagliptin 50 mg bid /100 mg qd								
5055	F	white	70	Sita 100	205	Colon cancer	255	Y
5126	M	white	60	Sita 50	215	Cerebrovascular accident	215	Y

Based on the applicant's Table 8-14, Reference P014X1

Subject 6366, in the sitagliptin 50 mg dose group, had an exanthema that was initially diagnosed as drug-related allergic dermatitis, but that diagnosis was subsequently revised to exanthema related to a viral infection, after the onset of headache and fever.

Table 95. Non-fatal clinical AEs that led to discontinuation in Study P014, from dose collapse to the end of the extension study

Subject	Gender	Race	Age	Therapy (mg/d)	Study Day of Onset	Adverse Experience	Day Dropped	Serious
Placebo / Metformin								
6349	M	white	64	Metformin 1700	296	Prostate cancer	301	Y
Pooled Sitagliptin Groups								
5124	F	white	51	Off Drug 1 day	304	Cardiac failure congestive	303	Y
5124	F	white	51	Off Drug 1 day	304	Myocardial infarction	303	Y
5124	F	white	51	Off Drug 1 day	304	Respiratory arrest	303	Y
6254	F	Hispa	59	Sita 100	312	Dyspepsia	333	N
6542	F	Hispa	74	Sita 100	162	Myalgia (Nl. CPK)	163	N
5628	F	black	61	Sita 100	304	Rash	368	N

Based on the applicant's Table 8-15, Reference P014X1

Study P019

Table 96. Non-fatal clinical AEs that led to discontinuation in Study P019

Subject	Gender	Race	Age	Therapy (mg/d)	Study Day of Onset	Adverse Experience	Day Dropped	Serious
Sitagliptin 100 mg qd								
36023	F	white	51	Sita 100	3	Vision blurred	8	Y
36035	F	White	71	Sita 100	15	Palpitation	84	N
36049	F	White	64	Sita 100	22	Arthralgia	68	N
36062	F	White	51	Sita 100	21	Edema	41	N
36493	F	White	52	Sita 100	33	Headache	32	N
36415	F	Multi	67	Sita 100	86	Angioneurotic edema	86	Y
36249	F	White	62	Sita 100	3	Edema Peripheral	5	N
36371	F	White	54	Sita 100	43	Edema Peripheral	57	N
36324	M	White	57	Sita 100	61	Hypersensitivity	63	Y
36481	F	White	47	Sita 100	41	Suicide attempt	43	Y
Placebo								
36250	F	white	60	Placebo	2	Edema Peripheral	13	N
36495	F	white	64	Placebo	57	Edema Peripheral	86	Y

Based on the applicant's Table 12-11, Reference P019

Since this study investigates the effects of sitagliptin in combination with pioglitazone, the 4 cases of discontinuation due to peripheral edema could be related to the PPAR agonist. One important AE that was considered by the investigator as drug related is angioneurotic edema. The subject presenting with this AE had no respiratory symptoms, but was hospitalized and treated with anti-histamines and corticosteroids. Upon further investigation, the subject was found to keep sheep at home and had used disinfectants to clean sheep feces prior to the onset of this AE. The other possible allergic event, termed hypersensitivity in subject 36324, has also questionable relation to sitagliptin, as the narrative description relates to a rash in hands and trunk one hour following pioglitazone intake, in a subject being treated for purulent cholecystitis.

Study P020

Table 97. Non-fatal clinical AEs that led to discontinuation in Study P020

Subject	Gender	Race	Age	Therapy (mg/d)	Study Day of Onset	Adverse Experience	Day Dropped	Serious
Sitagliptin 100 mg								
33012	F	Black	66	Sita 100	68	Polytraumatism	67	Y
33338	M	White	62	Sita 100	81	Pyelonephritis	87	Y
33016	F	Hispa	59	Sita 100	113	Alopecia areata	126	N
33283	M	White	69	Sita 100	130	Pneumonia	130	Y
33147	M	White	69	Sita 100	124	Pancreatic carcinoma	127	Y
33817	M	Asian	43	Sita 100	54	Rash	162	N
33587	M	White	64	Sita 100	62	Urticaria	160	N
33843	F	Polyn	65	Sita 100	50	B-cell lymphoma	145	Y
33523	M	White	62	Sita 100	4	Somnolence	11	N
33859	M	Asian	55	Sita 100	3	Nausea	21	N
33445	M	White	63	Sita 100	21	Bladder cancer	138	Y
Placebo								
33057	M	White	43	Placebo	10	Biliary colic	103	N
33064	F	White	57	Placebo	154	Lung cancer	169	Y
33114	F	White	55	Placebo	5	Hyperglycemia	6	N
33945	F	Hispa	56	Placebo	97	Hyperglycemia	94	N
33844	F	White	56	Placebo	130	Change of bowel habit	169	N
33782	M	White	71	Placebo	23	Vision blurred	23	N
33937	M	White	57	Placebo	9	Abdominal pain	13	N

Based on the applicant's Table 12-10, Reference 020V1

Study P021

Table 98. Non-fatal clinical AEs that led to discontinuation in Study P021

Subject	Gender	Race	Age	Therapy (mg/d)	Study Day of Onset	Adverse Experience	Day Dropped	Serious
Sitagliptin 100 mg								
30034	M	Black	60	Sita 100	36	Prostate cancer	92	Y
30260	F	White	51	Sita 100	23	Intentional self-injury	23	Y
30655	M	White	65	Sita 100	71	Colon cancer	107	Y
30757	M	White	59	Sita 100	43	Hyperglycemia	51	N
30599	M	White	68	Sita 100	91	Depression	134	N
Sitagliptin 200 mg								
30032	F	Black	44	Sita 200	21	AV block 1st degree	43	N
30204	M	White	59	Sita 200	6	Renal Cell CA Stage Unspecified.	19	Y
30179	F	White	49	Sita 200	33	Angina Unstable	33	Y
30779	M	White	56	Sita 200	27	Rectal cancer	46	Y
Placebo								
30010	F	Black	55	Placebo	134	Respiratory Failure	133	Y
30221	F	White	42	Placebo	2	Tachycardia	12	N
30182	F	White	71	Placebo	138	Myocardial infarction	141	Y
31116	M	Hispa	61	Placebo	140	Cholecystitis acute	141	Y

Based on the applicant's Table 12-12 Reference 021V1

Although four sitagliptin-treated subjects were discontinued due to cancer, the different types of cancer and the onset early in the course of treatment suggest these neoplastic events were not caused by sitagliptin.

Study P023

Table 99. Non-fatal clinical AEs that led to discontinuation in Study P023

Subject	Gender	Race	Age	Therapy (mg/d)	Study Day of Onset	Adverse Experience	Day Dropped	Serious
Sita 100 mg								
38082	F	White	41	Sita 100	92	Arthralgia	126	N
38728	F	Black	52	Sita 100	38	Cholelithiasis	38	Y
38586	F	White	70	Sita 100	109	Breast Cancer	124	Y
38620	M	White	32	Sita 100	106	Gastroesophageal reflux disease	124	N
38496	M	White	46	Sita 100	119	Hemorrhagic stroke	119	Y
Placebo								
38209	M	Asian	51	Placebo	29	Myalgia	32	N
38178	M	White	58	Placebo	77	Diarrhea	83	N
38288	F	White	51	Placebo	99	Urticaria	98	N
38309	M	White	58	Placebo	34	Hypertension	54	N

Based on the applicant's Table 12-12, Reference P023V1

There were no clinical AEs that led to discontinuation in the sitagliptin 200 mg group.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Hypoglycemic events

Hypoglycemia is a common adverse event 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 an increase in endogenous GLP1 (such as that expected with DPP4 inhibition) to 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.

In the 12 weeks of Study P010, the investigator made a determination of whether a reported AE was "hypoglycemic AE" based on specific symptoms reported by the subject during study visits (investigator-determined). On the other hand, "hypoglycemia" events are reported based on symptoms noted in the hypoglycemia logs given to subjects (subject-reported). Table 100 shows the proportion of subjects with at least one episode of "hypoglycemia" or "hypoglycemic AE", in each treatment group.

Table 100. Proportion of subjects with investigator-reported hypoglycemic AEs and hypoglycemia in Study P010, including number of episodes and their severity

Treatment	Proportion of subjects with hypoglycemic AEs †	Proportion (%) of subjects with hypoglycemia *	Number of episodes	Severity
Placebo	3/124 (2.4)	3/125 (2.4)	3	2 Mi 1 Mo
Sita 5 mg bid	0	1/124 (0.8)	1	1 Se
Sita 12.5 mg bid	5/123 (4.1)	10/123 (8.1)	15	9 Mi 5 Mo 1 Se
Sita 25 mg bid	5/123 (4.1)	8/123 (6.5)	12	10 Mi 1 Mo 1 Se
Sita 50 mg bid	2/122 (1.6)	5/122 (4.1)	10	7 Mi 3 Mo
Glipizide	21/123 (17.1)	35/123 (28.5)	115	61 Mi 52 Mo 2 Se

† Hypoglycemic AEs are defined as investigator-determined based on specific symptoms presented by subjects at time of study visits.
* Hypoglycemia is based on symptoms reported in the subjects glucose logs, whether accompanied by capillary glucose reading or not.
Based on the applicant's Tables 8-14 and 8-17, Reference P010

The proportion of sitagliptin-treated subjects with hypoglycemic AEs was much lower than that of glipizide-treated subjects reaching statistical significance. The proportion of hypoglycemic AEs among sitagliptin-treated subjects was somewhat higher than in placebo-treated subjects, although not proportional to the sitagliptin dose. Eighty nine of the 156 episodes were accompanied by an explanation such as "skipped a meal" or "physical activity prior to the episode". Of the 156 episodes, only half had fingerstick glucose monitoring within 10 minutes of the episode; in 11 subjects, the glucose value was less than 60 mg/dL (9 glipizide-treated and 2 sitagliptin-treated subjects). There was no dose-related trend and the severity of the reported hypoglycemic episode was equally not dose related.

Table 101 shows the proportion of hypoglycemic AEs and subject-reported hypoglycemia events in the 12 weeks of Study P014.

Table 101. Proportion of subjects with investigator-reported hypoglycemic AEs and hypoglycemia in Study P014, including number of episodes and their severity

Treatment	Proportion (%) of subjects with hypoglycemic AEs	Proportion (%) of subjects with hypoglycemia	Number of episodes	Severity
Placebo	0 / 111	1 / 111 (0.9)	1	1 Mi
Sita 25 mg qd	1 / 111 (0.9)	2 /110 (1.8)	5	1 Mi 4 Mo
Sita 50 mg qd	1/ 110 (0.9)	6 / 110 (5.4)	7	4 Mi 3 Mo
Sita 100 mg qd	1 / 110 (0.9)	8 / 110 (7.3)	12	4 Mi 7 Mo 1 Se
Sita 50 mg bid	1/ 110 (0.9)	7 / 111 (6.3)	7	4 Mi 3 Mo

Based on the applicant's Tables 8-13 and 8-14, Reference P014

In this study the incidence of hypoglycemia is similarly low, although higher than placebo, and a trend appears to indicate a higher incidence of events with increasing dose of sitagliptin. The reported severity of the hypoglycemia episodes does not indicate a trend of higher severity with higher doses used.

Hypoglycemic AEs were analyzed in the Pooled Phase 3 studies. Pooling of the events is a useful strategy since the rates of events are low, and these Phase 3 studies were controlled, which facilitate assessment of the contribution of sitagliptin in causing hypoglycemia. The studies pooled were P019 (sitagliptin 100 mg daily combined with pioglitazone), P020

(sitagliptin 100 mg daily combined with metformin), P021 and P023 (sitagliptin 100 mg or 200 mg daily as monotherapy). Table 102 shows the incidence and proportion of subjects with hypoglycemic AEs in the Pooled Phase 3 studies.

Table 102. Incidence and proportion of hypoglycemic AEs among the treatment groups in the Pooled Phase 3 Studies

Treatment (mg qd)	Subjects exposed	# subjects with ≥ 1 episode	# of episodes	Subject -years	Total episodes / 100 subject-years	Difference in Proportions vs. control (%) (95% CI)	p-Value
Sita 100	1082	13	29	453	6.41	0.2 (-0.8, 1.2)	0.7
Sita 200	456	4	6	174	3.45	0.4 (-0.7, 1.5)	0.6
Control	778	7	8	310	2.58		

Based on the applicant's Table 2.7.4:59 Reference 2.7.4 Summary of Clinical Safety

A single subject in study P023 on sitagliptin 100 mg had 10 episodes interpreted as hypoglycemic AEs, all precipitated by exercise before breakfast. Most of these, however, had fingerstick glucose measurements ranging between 65 and 99 mg / dL. The analysis of incidence of hypoglycemia in the Pooled Phase 3 studies indicates no increased risk of hypoglycemia, regardless of the dose used.
Among subjects with chronic renal insufficiency that participated in Study P028, 3 out of 65 treated with sitagliptin had hypoglycemia, while one of 26 in the placebo group had hypoglycemia. Two of the 3 subjects with hypoglycemia in the sitagliptin group were also treated with insulin, while the single placebo-treated subject with hypoglycemia was also on insulin.

In conclusion, there is no objective evidence of increased risk of hypoglycemia in diabetic subjects treated with sitagliptin at doses of 200 mg daily or less, from the review of AEs reported by subjects or by investigators as hypoglycemia.

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.
Gastrointestinal disorders were reported for 142 subjects in the sitagliptin 100 mg dose group (13 %), 60 subjects in the sitagliptin 200 mg dose group (13%) and 79 subjects in the non-exposed group (10%) (Table 103).

Table 103. Incidence of selected gastrointestinal AEs in the Pooled Phase 3 Population

Adverse event	Sita 100 mg (%)	Sita 200 mg (%)	Non-exposed (%)
	N = 1082	N = 456	N = 778
GI disorders	72 (6.7)	27 (5.9)	34 (4.4)
Abdominal Pain	9 (0.8)	5 (1.1)	12 (1.5)
Abdominal Pain Lower	5 (0.5)	0	1 (0.1)
Abdominal Pain Upper	11 (1)	1 (0.2)	3 (0.4)
Diarrhea	33 (3)	12 (2.6)	18 (2.3)
Nausea	15 (1.4)	13 (2.9)	5 (0.6)
Vomiting	9 (0.8)	3 (0.7)	7 (0.9)

Adapted from the applicant's Table 2.7.4:61, reference 2.7.4. Summary of Clinical Safety.

Table 104. Incidence and statistical comparison of nausea among the treatment groups in the Pooled Phase 3 Studies

Treatment (mg qd)	Subjects exposed	# subjects with ≥ 1 episode (%)	Subject -years	N / 100 subject-years	Difference in Proportions vs. placebo (%) (95% CI)	p-Value
Sita 100	1082	15 (1.4)	453	3.31	0.8 (-0.1, 1.7)	0.103
Sita 200	456	13 (2.9)	174	7.47	2.3 (0.5, 4.2)	0.019
Placebo	778	5 (0.6)	310	1.61		

Adapted from the applicant's Table 2.7.4:62, reference 2.7.4. Summary of Clinical Safety

There was no statistical significance in the difference in proportion of nausea between the 100 mg versus the 200 mg dose groups. However, the difference between proportions of nausea between the 200 mg dose group and the non-exposed population of 2.3 % reached statistical significance. This is consistent with the profile observed in the clinical studies of exenatide. The onset of nausea occurred throughout the double-blind treatment period. There is no information to support the hypothesis that subjects with moderate or severe (one case only) nausea had an underlying diagnosis of gastroparesis. Except for one subject who discontinued study participation due to nausea, all other subjects reported improvement in this symptom with continued sitagliptin treatment. There was no relationship between nausea and vomiting (the latter had same incidence between treatment groups) and weight loss.
Constipation was not included as a "tier 1 symptom", subject to statistical analysis. The incidence of constipation was higher in sitagliptin groups: 1.8 %, 2.4% and 1 % for sitagliptin 100 mg qd, 200 mg qd and non-exposed, respectively.

7.1.3.3.3 Neurologic AEs

The applicant has designated tremor and dizziness as particular neurologic AEs of special interest, after findings of decreased activity, ataxia and tremors in dogs treated with sitagliptin at a dose of 50 mg / kg/ day. In both the Phase 2 and Phase 3 studies, there was no increase in AEs of the neurologic System Organ Class compared to non-exposed subjects.
Tremor was reported in 4 subjects treated with sitagliptin 100 mg qd dose (0.4%), in 2 subjects treated with 200 mg qd dose (0.4 %) and in one non-exposed subject. They were transient, mostly lasting one day, and not considered drug-related.
Dizziness was reported with slightly higher incidence in the sitagliptin 200 mg daily dose compared to either the 100 mg dose or the non-exposed subjects. This AE was also reported as mild and transient.

7.1.3.3.4 Skeletal muscle AEs

The applicant has designated myalgia and muscle weakness as AEs of special interest, due to findings of slight skeletal muscle degeneration in dogs exposed to sitagliptin at a dose of 50 mg/kg/day for 3 and 6 months, but not in the 1-year toxicology study.
Table 105 shows the incidence of myalgia and muscle weakness among the treatment groups in the Pooled Phase 3 studies. Serum creatine phosphokinase (CPK) was only

measured routinely in the Monotherapy studies P021 and P023. The table also shows incidence of elevated serum CPK in the pooled studies P021 and P023.

Table 105. Incidence of selected skeletal muscle related AEs in the Pooled Phase 3 Studies

Treatment	Myalgia	Muscle Weakness	Increased CPK (IU/L)*
Sita 100 mg qd	0.6 %	0.2 %	2.5 %
Sita 200 mg qd	1.5 %	0	0.7 %
Placebo	1.2%	0.1 %	1.7 %

*Pooled Phase 3 Monotherapy studies P021 and P023 only, increased CPK means > 3 X ULN

There is no safety signal related to injury to skeletal muscle suggested by the Pooled Phase 3 Population data.

7.1.3.3.5 Infections

DPP4 is identical to CD26, a lymphocyte membrane protein. Because of this fact, inhibition of DPP4 raises a theoretical concern of immune suppression. No increased rates of infections were observed in CD26 knock-out mice, or in animals treated with specific DPP4 inhibitors. Nevertheless, infection rates were monitored as AEs of special interest during the Phase 3 studies.

There was no overall increase in the incidence of AEs in the System Organ Class of Infections and Infestations among sitagliptin-treated subjects compared to non-exposed subjects in the Pooled Phase 3 Population. Nasopharyngitis and pharyngitis combined were seen in 5.7 % of sitagliptin subjects compared to 4.1 % incidence in the non-exposed subjects. These infections had the same average duration and severity among the treatment groups. Infections characteristic of decreased lymphocytic function (such as herpes virus infections) occurred at similar low rates among the treatment groups. Similarly, sitagliptin-treated subjects did not experience increased rates of fungal infections, and there were no reported cases of tuberculosis, cytomegalovirus or Epstein-Barr virus infections.

In the Long-Term Safety Population, there were small increases in some upper respiratory and urinary infections (Table 106):

Table 106. Incidence of infection-related AEs with a difference of 2% or greater in sitagliptin groups in the Long-Term Safety Population

AE	Sita 100		Sita 200		Non-exposed	
	N=429	(%)	N=27		N=154	
Bronchitis	24	5.6	0	0	1	0.6
Nasopharyngitis	40	9.3	1	3.7	8	5.2
Upper Respiratory Infection	49	11.4	4	14.8	11	7.1
Urinary Tract Infection	27	6.3	1	3.7	6	3.9

Based on the applicant's Table 2.7.4:40, Reference 2.7.4. Summary of Clinical Safety

There is indication of increased rates of infections (particularly upper respiratory infection) among subjects treated with sitagliptin in the Long-Term Safety Population. However, the relatively small sample size does not permit definite conclusions, particularly regarding dose dependence. Furthermore, the types of infections reported do not point to a specific cellular immune defect.

7.1.3.3.6 Urticaria, angioedema and skin lesions

Urticaria and angioedema were selected as AEs of special interest by the applicant because Substance P is a substrate of DPP4, among other proteolytic enzymes. There were no significant increases in incidence of urticaria in sitagliptin-treated subjects compared to non-exposed subjects in the Pooled Phase 3 Population. The only case of angioedema occurred in a subject in Study P019 treated for 79 days with sitagliptin 100 mg qd, but the subject had used a toxic disinfectant at home preceding the episode of angioedema. Toxicology studies in monkeys investigating other DPP4 inhibitors reported necrotic skin lesions in tail, digits, ears, nose and scrotum. In the Pooled Phase 3 studies, there were no cases of skin necrosis or vasculitis.

7.1.4 Other Search Strategies

The applicant conducted analyses of AEs in the Pooled Phase 3 Population by age (younger or older than 65 years), gender, and race (White, Black, Asian, Hispanic or Other). The analyses specifically investigated the following: subjects with at least one AE, with drug–related AEs, with SAEs, with drug-related SAEs, who discontinued due to AEs, who discontinued due to drug-related AEs, who discontinued due to SAEs and who discontinued due to drug-related SAEs. There were no differences in incidence of AEs by race or age. Females had slightly higher rates of at least one AE, but there were no differences among treatment groups.
Among sitagliptin-treated subjects with chronic renal insufficiency participating in Study P028, a higher incidence of coronary artery disease and congestive heart failure (5 of 65 subjects [7.7%]) were noted compared to the incidence in placebo-treated subjects (no subjects). Of these subjects, one had worsening coronary artery disease and died in the Phase B extension study of acute myocardial infarction, one had a myocardial infarction, and 3 had congestive heart failure. All 5 subjects had pre-existing history of heart disease, and there was an imbalance at baseline between the treatment groups regarding the prevalence of coronary disease and heart failure.
This reviewer also analyzed the types and incidence of AEs according to the dose of sitagliptin administered per kilogram of body weight. Although a wide range of dose/weight was observed in studies using 100 mg of sitagliptin qd (0.82 – 1.81 mg/kg/day) in the combination therapy studies P019 and P020 or up to 200 mg qd (0.72 – 2.81 mg/kg/day) in the monotherapy studies P021 and P023, no pattern of AEs emerged from this analysis.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The overall safety of sitagliptin 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.

Based on animal toxicity data, myopathy, hypotension, significant allergic events (e.g., anaphylaxis and urticaria) and infections were deemed events of clinical significance and were subject to immediate reporting during Phase 2 studies (Please refer to Section 7.1.3.3, in this review document).

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 Study Phase A and every 8 weeks during the extension studies (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.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant has used MedDRA dictionary Version 8.0 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 to the preferred term, particularly in cases of AEs leading to dropouts, and these events seem to have been appropriately classified.

7.1.5.3 Incidence of common adverse events

The best population for review of common AEs is the Pooled Phase 3 Population. This is a large pool of subjects that participated in four of the Phase 3 studies, with 1538 subjects treated for 18 to 24 weeks with sitagliptin 100 mg or 200 mg daily. The AEs in this group can be compared to AEs observed in 778 concurrent controls in these studies.

To provide an overview of the common AEs, it is useful to classify them according to the System Organ Class (SOC) categories listed in the MedDRA Version 8 (Table 107).

Table 107. Common AEs by System Organ Class categories in the Pooled Phase 3 Studies

System Organ Class Disorder	Sita 100 mg Exposed (N = 1082)		Sita 200 mg Exposed (N = 456)		Non-Exposed (N = 778)	
	n	(%)	n	(%)	n	(%)
Subjects with ≥ 1 AE	595	(55.0)	247	(54.2)	432	(55.5)
Blood and Lymphatic	8	(0.7)	2	(0.4)	1	(0.1)
Cardiac	21	(1.9)	8	(1.8)	18	(2.3)
Congenital, Familial and Genetic	2	(0.2)	0	(0.0)	2	(0.3)
Ear and Labyrinth	14	(1.3)	4	(0.9)	11	(1.4)
Endocrine	1	(0.1)	0	(0.0)	4	(0.5)
Eye	26	(2.4)	16	(3.5)	22	(2.8)
Gastrointestinal	142	(13.1)	60	(13.2)	79	(10.2)
General Disorders and Administration Site Conditions	58	(5.4)	21	(4.6)	37	(4.8)
Hepatobiliary	10	(0.9)	2	(0.4)	6	(0.8)
Immune System Disorders	10	(0.9)	5	(1.1)	3	(0.4)
Infections and Infestations	287	(26.5)	125	(27.4)	203	(26.1)
Injury, Poisoning, and Procedural Complications	50	(4.6)	26	(5.7)	35	(4.5)
Investigations	30	(2.8)	15	(3.3)	39	(5.0)
Metabolism and Nutrition	31	(2.9)	11	(2.4)	29	(3.7)
Musculoskeletal and Connective Tissue	114	(10.5)	58	(12.7)	89	(11.4)
Neoplasm Benign, Malignant and Unspecified	11	(1.0)	7	(1.5)	5	(0.6)
Nervous System	92	(8.5)	44	(9.6)	70	(9.0)
Pregnancy, Puerperium and Perinatal Conditions	0	(0.0)	0	(0.0)	1	(0.1)
Psychiatric	33	(3.0)	11	(2.4)	25	(3.2)
Renal and Urinary	26	(2.4)	8	(1.8)	22	(2.8)
Reproductive System and Breast	16	(1.5)	12	(2.6)	17	(2.2)
Respiratory, Thoracic and Mediastinal	59	(5.5)	28	(6.1)	40	(5.1)
Skin and Subcutaneous Tissue	58	(5.4)	26	(5.7)	24	(3.1)
Vascular Disorders	27	(2.5)	13	(2.9)	24	(3.1)

The Table excludes AEs observed after initiation of glycemic rescue therapy. Although a subject may have had 2 or more AEs, the subject is counted only once within a category. The same subject may appear in different categories.

Adapted from the applicant's Table 2.7.4:32 Reference 2.7.4 Summary of Clinical Safety

From Table 107, a slightly higher incidence of AEs in the sitagliptin groups compared to the placebo group were observed in some of the SOC groups. A brief and general discussion of the AEs in these SOC groups follows in the next six paragraphs.

The higher incidence of AEs in the Blood and Lymphatic Disorders relates to 5 subjects with anemia, 4 with hemoglobin levels not much lower than baseline and one with anemia secondary to gastrointestinal bleeding.

The higher incidence of AEs in the Gastrointestinal Disorders SOC in the sitagliptin-treated subjects reflected specific AEs of constipation, diarrhea, nausea and toothache.

The slightly higher incidence of adverse experiences in the Immune System SOC in the sitagliptin groups relative to the non-exposed group, was related to a range of specific adverse experiences, including a higher number of patients with adverse experiences of seasonal allergy and drug hypersensitivity (to non-study drug).

The slightly higher rate of AEs in the Neoplasms Benign, Malignant and Unspecified SOC

in the sitagliptin groups occurred in neoplasms originated in different tissues and organs and not a particular type. The overall incidence of 18 / 1538 (1.2 %) subjects in the 2 sitagliptin groups with AEs in this SOC differs from the incidence shown in Table 78 (12 / 1538 subjects or 0.8 %) because Table 107 includes non-serious events in this SOC: ocular neoplasm, skin papilloma, squamous cell carcinoma, and uterine leiomyoma. For 4 of 8 subjects in the sitagliptin groups who had malignant neoplasms, excluding subjects with basal or squamous cell skin cancer, clinical evidence of the neoplasm was present prior to randomization. In subjects with malignant neoplasms, the diagnosis occurred early in the double-blind treatment period, with all but 1 of 8 subjects diagnosed within 4 months of randomization. The diagnosis established latest during Phase A double-blind treatment was in a subject (AN 36124) in whom the diagnosis of lung cancer was made on Day 154; this subject had a history of heavy tobacco smoking and chronic bronchitis, and was found to have a 5 cm mass on a chest x-ray that was performed to evaluate his cough. None of the AEs in the Neoplasms Benign, Malignant, and Unspecified SOC was considered by the investigator to be drug-related. With the small difference in incidence observed, the range of tumor types observed, the presence of clinical findings pre-randomization in many subjects, and the diagnosis occurring early in the treatment period, a drug-related increase in AEs in this SOC is highly unlikely. The study period for the Pooled Phase 3 Studies was either 18 weeks or 24 weeks, which may not reflect sufficient time to detect cancers in subjects treated with a study drug. Because of the lag time for cancer detection, an appropriate population to complement this examination is the Pooled Long-Term Safety Population, consisting of 429 subjects treated with sitagliptin 100 mg qd, 27 subjects treated with sitagliptin 200 mg qd, or 154 subjects not exposed. This population was followed for at least one year. Eleven subjects (2.6%) in the sitagliptin 100 mg qd group, none in the 200 mg group and one (0.6%) in the non-exposed group had AEs in this SOC. However, from the 11 subjects only 2 had malignant conditions: one with breast cancer and one with basal cell carcinoma.

In the Respiratory, Thoracic, and Mediastinal SOC, a slightly higher incidence in the sitagliptin groups relative to the non-exposed group was observed. No particular AEs within this SOC had a higher rate; the slightly higher rate in this SOC was due to small differences in a range of specific terms.

A higher incidence of AEs in the Skin and Subcutaneous Disorder SOC was observed in the sitagliptin treatment groups relative to the non-exposed group. This higher rate was related to a slightly higher incidence in a range of specific AE terms (for most, only 1 to 2 subjects with the AE in a treatment group). In addition, the AE of rash (including the specific AE terms of rash, rash generalized, rash macular, rash scaly, and rash vesicular) was more often reported in the sitagliptin groups: rash was reported in 20 of 1538 (1.3%) subjects in the sitagliptin 100 mg and 200 mg groups, compared to 3 of 778 (0.4%) subjects in the non-exposed group. All of the AEs of rash were considered mild to moderate in intensity and no SAEs of rash were reported. In 17 of the 20 subjects, the rash resolved while the subject was still on study drug (with some subjects having stop dates for this AE during study Phase B). Four of the 20 subjects had rashes assessed as drug-related by the investigators; in 3 of these 4 subjects the rash resolved while subjects continued study drug therapy (in one subject, the rash resolved during continued study drug therapy in Phase B). One subject was discontinued due to the rash, which was reported to have resolved 2

months after discontinuation of study drug.

The most common AEs, observed with incidence of at least 3% and with higher incidence in at least one of the sitagliptin dose groups relative to the non-exposed subjects in the Pooled Phase 3 Population were diarrhea, nasopharyngitis, upper respiratory tract infection, [redacted] and headache. Of these, only upper respiratory tract infection was observed with an incidence greater than 5 % (generally termed "common") in all treatment groups.
It is this reviewer's view that only the 5 AEs listed in the paragraph above should be listed in labeling, to convey a useful list of potential AEs to prescribing physicians. Although the criteria to list these AEs are arbitrary, there is no clear evidence that a longer list of AEs manifesting themselves in sitagliptin treated subjects in clinical trials would be more informative to physicians or the public. On the other hand, a longer list using frequencies of 1% or 2% would be more confusing.

7.1.5.4 Common adverse event tables

This reviewer constructed a new Table of AEs based on the applicant's classification of MedDRA preferred AE terms under the System Organ Class (SOC) classification as present in the Summary of Clinical Safety Report as Table 2.7.4:33. The applicant's table only contains terms that have a minimum difference in the rate of occurrence between groups of 1%. This reviewer looked into all AEs for specific preferred terms, and combined terms that are so similar that their separation is difficult in clinical practice. Then only those combined terms with frequencies of greater than 1 % were listed in Table 108. Similar terms in a SOC that combined did not reach the frequency of 1 % were arbitrarily excluded. The reviewer did not combined terms from different SOCs (for example, kept urinary infection under the Infections and Infestations SOC and did not combine with AEs under the Renal and Urinary Disorders SOC). In preparing Table 108, AEs occurring after initiation of glycemic rescue therapy were excluded, due to likely confounding.
The overall sense is that the rates of AEs were very close among the 3 treatment groups and there are no events that can be easily singled out as consequence of sitagliptin treatment (Table 108).

Table 108. Specific AEs by system organ class with incidence ≥ 1 % in at least one group in the Pooled Phase 3 Population excluding data after initiation of glycemic rescue therapy

	Sita 100		Sita 200		Placebo	
	N	%	N	%	N	%
	1082		456		778	
Cardiac Arrhythmias						
Atrial fibrillation and flutter	2	0.2	2	0.4	0	0.0
Extra systoles, Supra Ventricular Extra systoles, Ventricular extra systoles	6	0.6	2	0.4	3	0.4
Palpitation	4	0.4	1	0.2	4	0.5
Sinus bradycardia	1	0.1	0	0.0	2	0.3
Supra Ventricular Tachycardia	0	0.0	1	0.2	0	0.0
Tachycardia	4	0.4	0	0.0	1	0.1
Total arrhythmia	17	1.6	6	1.3	10	1.3
Ear and Labyrinth						
Vertigo and Benign Positional Vertigo	9	0.8	0	0.0	9	1.2
Eye						
Blurred vision and reduced VA	4	0.4	5	1.1	5	0.6
Gastrointestinal Disorders						
Abdominal pain (general, upper, lower, discomfort, tenderness, stomach discomfort)	30	2.8	6	1.3	19	2.4
Constipation	20	1.8	11	2.4	8	1.0
Diarrhea and frequent bowel movement, gastroenteritis	44	4.1	13	2.9	28	3.6
Dyspepsia and GERD	14	1.3	6	1.3	9	1.2
Erosive esophagitis, esophagitis, reflux esophagitis, gastritis, gastritis erosive	6	0.6	7	1.5	7	0.9
Nausea	15	1.4	13	2.9	5	0.6
Toothache	9	0.8	5	1.1	3	0.4
General Disorders and Admin. Site Conditions						
Asthenia, fatigue and malaise	16	1.5	7	1.5	17	2.2
Chest discomfort and pain	8	0.7	5	1.1	3	0.4
Edema and peripheral edema	21	1.9	2	0.4	13	1.7
Infections and Infestations						
Acute sinusitis, nasopharyngitis, pharyngitis, strep pharyngitis, rhinitis, sinusitis, viral pharyngitis, URI	164	15.2	76	16.7	101	13.0
Bronchitis, acute bronchitis, lower URI	29	2.7	7	1.5	20	2.6
Cystitis, UTI, urethritis, pyelonephritis	23	2.1	16	3.5	14	1.8
Influenza	44	4.1	16	3.5	33	4.2
Skin infections *	43	4.0	19	4.2	28	3.6
Metabolism and Nutrition						
Hypoglycemia	13	1.2	4	0.9	7	0.9
Musculoskeletal and Connective Tissue						
Arthralgia	23	2.1	15	3.3	14	1.8
Back pain	32	3.0	12	2.6	23	3.0
Myalgia	7	0.6	7	1.5	9	1.2
Osteoarthritis	12	1.1	3	0.7	4	0.5
Pain in extremity	16	1.5	8	1.8	13	1.7
Nervous System Disorders						
Dizziness	17	1.6	13	2.9	12	1.5
Headache	39	3.6	18	3.9	28	3.6
Psychiatric Disorders						
Insomnia	10	0.9	5	1.1	9	1.2
Respiratory, Thoracic and Mediastinal Disorders						
Cough	25	2.3	10	2.2	17	2.2
Pharyngolaryngeal Pain	6	0.6	7	1.5	5	0.6
Nasal congestion, sinus congestion, upper respiratory tract congestion	10	0.9	8	1.8	4	0.5
Skin and Subcutaneous Disorders						
Pruritus	4	0.4	5	1.1	2	0.3
Rash, Rash generalized, rash macular, rash scaly, rash vesicular,	13	1.2	7	1.5	3	0.4
Vascular disorders						
Hypertension	15	1.4	9	2.0	14	1.8

* Includes Candida balanitis, body tinea, breast abscess, cellulitis, infective conjunctivitis, dermatophytosis, erysipela, eye lid folliculitis, folliculitis, fungal infection, fungal rash, fungal skin infection, furuncle, groin abscess, hordeolum, impetigo, nail infection, onychomycosis, otitis externa, paronichia, penile infection, pyoderma, pustular rash, scrotal abscess, skin Candida, skin infection, staphylococcal abscess, subcutaneous infection, tinea cruris, tinea infection, tinea pedis, tinea versicolor, vaginal candidiasis, vaginal mycosis, bacterial vaginitis, viral rash, vulvovaginitis

Based on the applicant's Table 2.7.4:33, Reference 2.7.4. Summary of Clinical Safety

The section of labeling describing AEs traditionally has a table that lists events occurring with greater frequency among the groups treated with the study drug as compared to

placebo or a control medication. The threshold used varies with the drug and the AE profile, but typically demonstrates the difference in observed rates of either 1 % or 2 %. If one considers significant a greater than 2 % difference between either treatment group and placebo (or non-exposed) the only AE that stands out from Table 108 is "Acute sinusitis, nasopharyngitis, pharyngitis, streptococcal pharyngitis, rhinitis, sinusitis, viral pharyngitis, and URI" with a difference of 2.2% between sitagliptin 100 mg and placebo (15.2 % minus 13 %) and 3.7 % between sitagliptin 200 mg and placebo (16.7 % minus 13 %). This is similar to the applicant's conclusion of combining nasopharyngitis and pharyngitis (the latter term also including pharyngitis streptococcal and pharyngotonsillitis) yielded a difference of 1.6 % (5.7 % in the sitagliptin groups against a rate of 4.1 % in placebo-treated subjects). The severity, duration and number of episodes of these infections were fairly similar across the 3 groups, as well as the number of subjects in whom the investigator attributed causality. There was no unusual increase in the rate of infections traditionally linked to dysfunction of T cells (as could be speculated based on homology between DPP4 and the T cell membrane CD26) in sitagliptin-treated subjects. Specifically, no increase in viral infections or cutaneous fungal infections has been observed. There were no reported cases of tuberculosis or deep fungal infections.
Nausea and constipation are two AEs that were observed with frequencies that yielded close to the 2% difference between groups. For constipation, 1.8% and 2.4 % for the sitagliptin 100 and 200 mg respectively, against 1 % in the placebo group, and for nausea, 1.4% and 2.9 % for the sitagliptin 100 and 200 mg respectively, against 0.6 % in the placebo group.
The applicant [redacted]

Of interest is the fact that DPP4 is strongly present in the serosal submucosal glands of the human bronchus, and that both Substance P and bradykinin are substrates of this enzyme (1). Given these facts, one would expect that inhibition of DPP4 would cause bronchoconstriction, mucus secretion and inflammation in a mechanism similar to that observed with drug-induced inhibition of angiotensin-converting enzymes. Although a small increase in incidence of upper respiratory infections among sitagliptin-treated subjects was observed, no increase in cough or lower respiratory infections has been detected in these studies.
The applicant also analyzed the incidence of AEs by SOC in subjects taking part of Studies P010, P014, P020 and P021 for at least one year (the Long-Term Safety Population). This is a "self-selected" population. Therefore there is greater potential for bias in the conclusions drawn, as compared to the Pooled Phase 3 studies. In addition, the majority of the subjects in the Long-Term Safety Population are the same participants in the Pooled

1 Van der Velden VHJ and Hulsmann. Peptidases: structure, function and modulation of peptide-mediated effects in human lung. Clinical and Experimental Allergy 1999; 29: 445-456.

Phase 3 Studies (those who took part in Studies P020 and P021). However, this analysis benefits from gathering one year or longer exposure data; some AEs are not expected to occur during a 4 to 6 months exposure, as was the case with the higher observed incidence of cardiovascular AEs in subjects exposed to rofecoxib.

Table 109 shows the AEs (grouped by SOC) that were seen with incidence among the sitagliptin groups ≥ 2 % above the incidence observed in the non-exposed subjects in the Long-Term Safety Population.

Table 109. Clinical AEs with incidence in sitagliptin groups ≥ 2 % above the incidence in non-exposed subjects in the Long-Term Safety Population

AE	Sita 100 (N=429)		Sita 200 (N=27)		Non-exposed (N=154)	
	N	%	N	%	N	%
Gastrointestinal Disorders						
Nausea	21	4.9	3	11.1	3	1.9
General Disorders and Administration Site Conditions						
Peripheral edema	20	4.7	1	3.7	3	1.9
Infections and Infestations						
Bronchitis	24	5.6	0	0	1	0.6
Nasopharyngitis	40	9.3	1	3.7	8	5.2
Upper Respiratory Tract Infection	49	11.4	4	14.8	11	7.1
Musculoskeletal and Connective Tissue Disorders						
Myalgia	17	4.0	1	3.7	3	1.9
Pain in extremity	19	4.4	0	0	3	1.9
Psychiatric Disorders						
Depression	13	3.0	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	17	4.0	0	0	4	2.6

These AEs are very consistent with those observed in the Pooled Phase 3 Population. The only new AE that had higher incidence in sitagliptin 100 mg (but not in subjects taking twice the dose) was depression. Of the 13 subjects with depression, 5 had history of depression prior to being randomized in the sitagliptin clinical studies. The following subjects dropped out due to depression or related terms:
On sitagliptin

- AN3394 on Sitagliptin 12.5 mg bid in Study P010: nervousness at day 16
- AN6904 on Sitagliptin 100 mg qd in Study P014: suicide attempt at day 47
- AN36481 on Sitagliptin 100 mg qd in Study P019: suicide attempt at day 41
- AN30599 on Sitagliptin 100 mg in Study P021: depression at day 134

On placebo or non-exposed

- AN3314 on Glipizide 10 mg qd in Study P010 at day 24

Some of the above dropout-related AEs were also considered SAEs.
Given the very low frequency of these events, there is no obvious association between treatment with sitagliptin and depression.
Peripheral edema appears to be more commonly observed among subjects treated with sitagliptin 100 mg daily, compared to those on 200 mg daily or to non-exposed. Such observation is misleading, however, as a comparison between the numbers in the two

populations would indicate that most subjects with reported edema in the Pooled Phase 3 Studies continued on in the Long-Term Safety Population, while most of those on placebo in the Pooled Phase 3 Population elected not to participate in the extension studies and were not counted in the Long-Term Safety Population.

The applicant compared the relative incidence of bronchitis between groups in the Long-Term Safety Population and the Pooled Phase 3 Studies. A higher incidence of bronchitis exists in the sitagliptin group in the Long-Term Safety Population, while the incidence of bronchitis was similar among groups in the Pooled Phase 3 Population. The analysis of the subjects that manifested such AE indicated that in the sitagliptin-treated subjects that remained in extension studies had more frequent history of recurrent bronchitis prior to randomization compared to those non-exposed to sitagliptin. Relative to the Long-Term Safety Population, the Pooled Phase 3 Population is substantially larger and fully randomized. The applicant compared the rate of events of bronchitis per subject-year between the subjects treated with sitagliptin 100 mg in the Pooled Long-Term Safety Population (0.057 events per subject-year of exposure) and the subjects treated with placebo in the Pooled Phase 3 Population (0.077 events per subject-year of exposure). The rate of events of bronchitis was similar.

Another consideration is that the higher rate of bronchitis in the sitagliptin treated compared to the non-exposed subjects in the Long-Term Safety Population could relate to a higher susceptibility with longer-term exposure to sitagliptin. If this were the case, the rate of events should increase over time post-randomization. This does not appear to have occurred: events of bronchitis were reported with a similar rate over time post-randomization, with the same rate observed prior to 180 days of drug exposure as occurred after 180 days of drug exposure. In addition, there was no increase in the incidence of more serious upper or lower respiratory tract infections such pneumonia.

7.1.5.5 Identifying common and drug-related adverse events

The table below shows the AEs reported as drug-related by investigators, which occurred with incidence ≥ 0.5 % in any of the treatment groups. To be included, the AE had to be considered at least possibly related to the study drug. No individual drug-related AEs occurred with incidence ≥ 1 % in any treatment group.

Table 110. Drug-related AEs with incidence ≥ 0.5 % in any treatment group in the Pooled Phase 3 Studies

	Sita 100 mg (N = 1082)		Sita 200 mg (N = 456)		Non-Exposed (N = 778)	
	n	(%)	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	103	(9.5)	43	(9.4)	78	(10.0)
Gastrointestinal Disorders	33	(3.0)	12	(2.6)	18	(2.3)
Constipation	5	(0.5)	4	(0.9)	3	(0.4)
Diarrhea	9	(0.8)	1	(0.2)	2	(0.3)
Nausea	6	(0.6)	4	(0.9)	2	(0.3)
General Disorders And Administration Site Conditions	17	(1.6)	3	(0.7)	9	(1.2)
Fatigue	3	(0.3)	1	(0.2)	4	(0.5)
Edema Peripheral	3	(0.3)	0	(0.0)	4	(0.5)
Investigations	14	(1.3)	2	(0.4)	10	(1.3)
Weight Increased	4	(0.4)	0	(0.0)	4	(0.5)
Musculoskeletal And Connective Tissue Disorders	4	(0.4)	5	(1.1)	4	(0.5)
Myalgia	1	(0.1)	3	(0.7)	1	(0.1)
Nervous System Disorders	18	(1.7)	8	(1.8)	15	(1.9)
Dizziness	4	(0.4)	3	(0.7)	2	(0.3)
Headache	7	(0.6)	4	(0.9)	7	(0.9)

Based on the applicant's Table 2.7.4:34, Reference 2.7.4. Summary of Clinical Safety

Again, as with the general analyses of AEs, nausea and constipation appear to occur more frequently in sitagliptin-treated subjects than in non-exposed subjects, but only slightly so. There is no clear dose response in any of these AEs when comparing incidences of AEs between the 100 mg and the 200 mg dose groups.

In Study P028, the most frequent AEs sorted by decreasing frequency observed at the 50 mg dose group are listed in Table 111.

Table 111. Frequent AEs observed in Study P028

AE	Total	Sita 25 mg	Sita 50 mg	Placebo /(Glipizide/Insulin)
	N	N (%)	N (%)	N (%)
Dizziness	7	2 (9.1)	3 (12.5)	2 (10)
Upper respiratory tract infection	8	2 (9.1)	3 (12.5)	3 (15)
Back pain	2	0	2 (8.3)	0
Cardiac failure	2	0	2 (8.3)	0
Diarrhea	11	4 (18.2)	2 (8.3)	5 (25)
Hemoglobin decreased	2	0	2 (8.3)	0
Headache	3	1 (4.5)	2 (8.3)	0
Urinary tract infection	5	1 (4.5)	2 (8.3)	2 (10)
Anemia	1	0	1 (4.2)	0
Aphthous stomatitis	1	0	1 (4.2)	0
Blood calcium decreased	2	0	1 (4.2)	1 (5)
Blood creatine phosphokinase increased	2	1 (4.5)	1 (4.2)	0
Blood creatinine increased	3	0	1 (4.2)	2 (10)

7.1.5.6 Additional analyses and explorations

Additional analyses and explorations are unnecessary given the very similar rates of AEs that occurred in the 2 groups of subjects treated with 100 mg and 200 mg of sitagliptin compared to subjects on placebo.

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.

A single subject experienced an adverse event from the list above (Acute renal failure), with a narrative as follows: Subject 6312, a 65-year-old white male with T2DM, chronic back pain, peripheral vascular disorder and hypertension, was randomized to the Sitagliptin 100-mg qd treatment group. Concomitant therapy included losartan potassium, ibuprofen, atorvastatin calcium and aspirin. On Day 55, the patient experienced bronchitis. The investigator felt that the bronchitis was definitely not related to study therapy. No action was taken regarding study therapy. The subject was treated with doxycycline and ibuprofen 1200 mg daily for fever and bronchitis. Subsequently, the subject recovered from bronchitis. On Day 59, the subject creatinine values were elevated at 1.8 mg/dL, which was determined to be a sign of ibuprofen-induced acute renal failure. On Day 60, study therapy was interrupted. Subsequently, the subject recovered from acute renal failure. On Day 61 serum creatinine was 1.4 mg/dL). Study therapy was restarted on Day 65. Serum creatinine on Day 71 was 1.2 mg/dL. The subject has been advised to avoid ibuprofen and other NSAIDs. The patient did not experience clinical symptoms related to the renal failure and was never hospitalized.
The single case of acute respiratory failure occurred in a placebo-treated subject, as a complication of worsening asthma and pneumonia.

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. In the Phase 3 studies chemistry and CBC were assessed at the screening and randomization visits, as well as every 6 weeks during Phase A of the studies and generally every 8 weeks during the Extension Study Phase B of the Phase 3 studies. Urinalysis and a lipid panel were performed every 24 weeks approximately for the Phase 2 and Phase 3 studies. The frequency of assessments for CBC and chemistry in the initial 12 weeks of the Phase 2 studies was higher, with blood collected every other week. The frequency of these assessments decreased to every 9 weeks approximately during the 40 week extensions of these Phase 2 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.

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

The applicant has performed analyses of laboratory values in the Pooled Phase 3 Population, the same population used for the controlled analysis of clinical AEs. This population is appropriate for analysis, for the following reasons: it comprises the bulk of the safety dataset, is large enough to detect more subtle signals of a drug effect on a particular laboratory value and is controlled. The subjects in the Pooled Phase 3 Population were participants in Studies P019 and P020 (examining the safety and efficacy of sitagliptin when added on to pioglitazone or metformin, respectively) and in Studies P021 and P023 (examining the safety and efficacy of sitagliptin in monotherapy) and the summaries reflect the collection of all safety laboratory data prior to initiation of glycemic rescue therapy. The time points of interest were Week 24 for the 24-week long studies P019, P020 and P021 and Week 18 for the 18-week long Study P023. Whenever applicable this review will include data after initiation of glycemic rescue therapy in the Pooled Phase 3 population, and will comment on the potential for confounding caused by the specific rescue treatment.

In addition, the applicant has analyzed the Pooled Long-Term Safety Population, presenting data from the pooled Phase 3 studies P020 and P021 with their extensions separately from the pooled Phase 2 studies P010 and P014 and their respective extensions. The data from the Pooled Long-Term Safety Population includes laboratory observations after initiation of glycemic rescue therapy.

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). 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

In the review of chemistry parameters, there were noteworthy changes noted in serum alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid, creatinine, and sodium and chloride levels. These changes from baseline to several timepoints throughout the studies were small, were not associated with clinical adverse events during the Phase 3 studies and are unlikely to have any clinical impact. The reason for their inclusion in this review is that they were consistent between the sitagliptin groups and they may represent trends to watch post-marketing.

Serum alkaline phosphatase

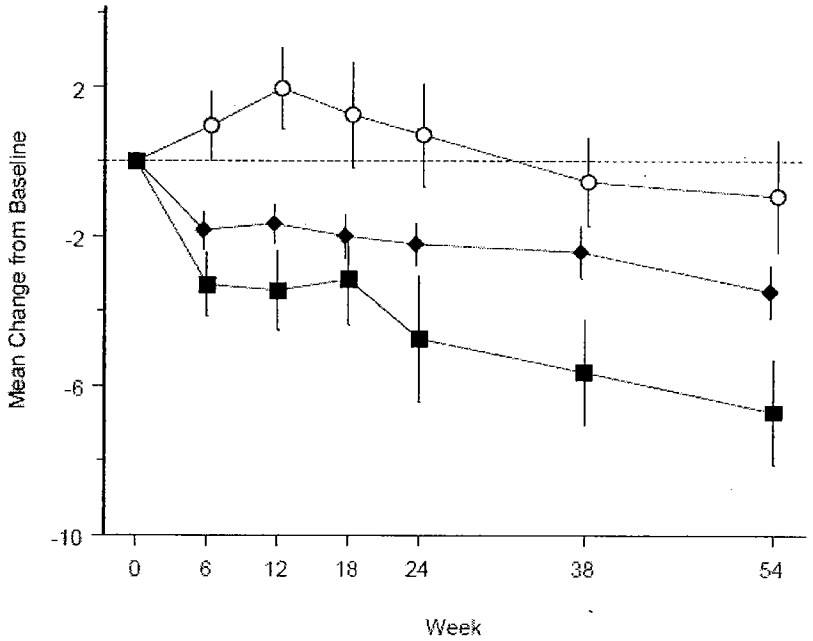
Mean serum concentrations of alkaline phosphatase tended to decrease over time in the sitagliptin-treated groups. Summary Statistics for change from baseline to timepoints throughout the studies in serum alkaline phosphatase in the Pooled Phase 3 Studies are shown in Table 112.

Table 112. Mean (SD) and median changes in serum alkaline phosphatase from baseline to several timepoints in the Pooled Phase 3 Studies

			Baseline	On Treatment	Change from Baseline		
Week	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Median	Range
6	Sita 100 mg	1041	56.7 (17.3)	54.2 (17.7)	-2.6 (0.3)	-3.0	-167.0 to 222.0
	Sita 200 mg	432	62.3 (18.2)	59.0 (17.8)	-3.3 (0.4)	-3.0	-39.0 to 36.0
	Non-Exposed	733	57.7 (16.7)	57.5 (16.3)	-0.2 (0.3)	0.0	-29.0 to 36.0
12	Sita 100 mg	998	56.6 (17.4)	53.5 (18.6)	-3.1 (0.4)	-3.0	-156.0 to 253.0
	Sita 200 mg	403	61.8 (18.1)	57.2 (16.7)	-4.6 (0.5)	-4.0	-50.0 to 46.0
	Non-Exposed	688	57.5 (16.7)	57.3 (17.0)	-0.2 (0.3)	0.0	-33.0 to 29.0
18/24	Sita 100 mg	951	56.3 (17.3)	52.2 (15.7)	-4.1 (0.3)	-4.0	-168.0 to 32.0
	Sita 200 mg	383	61.9 (18.1)	56.6 (19.1)	-5.3 (0.7)	-5.0	-49.0 to 152.0
	Non-Exposed	629	57.1 (16.2)	57.0 (17.1)	-0.1 (0.4)	-1.0	-30.0 to 47.0

A similar trend is noted for the mean change in serum alkaline phosphatase (IU/L) over time in the Phase 3 Cohort of the Long-Term Safety Population (Studies P020 and P021) (Figure 30). There was no significant difference between groups in the magnitude of change from baseline in serum alkaline phosphatase for sitagliptin treated subjects (mean decrease of 6.8 IU/L) and glipizide or placebo/metformin treated subjects (mean decrease of 6.4 IU/L).

Figure 30. Mean change in serum alkaline phosphatase (IU/L) from baseline up to 54 weeks in the phase 3 cohort of the Pooled Long-Term Safety Population by Treatment Group



♦ denotes sitagliptin 100 mg ■ denotes sitagliptin 200 mg in P021 only and ○ denotes non-exposed subjects

Applicant's Figure 2.7.4:2, Reference 2.7.4 Summary of Clinical Safety

The data indicates not only gradual, albeit slight, decreases in serum alkaline phosphatase over time in the sitagliptin groups compared to controls, but also a dose response, with subjects taking 200 mg of sitagliptin having a greater change in alkaline phosphatase from baseline compared to those in the 100 mg cohort.

The applicant measured bone specific alkaline phosphatase (a marker of bone formation) and C-telopeptide (a marker of bone resorption) in a subset of subjects in Study P021. The applicant noted reductions in bone-specific alkaline phosphatase that accounted for approximately 50 % of the reductions in total alkaline phosphatase seen in those sitagliptin groups: the subset of subjects treated with sitagliptin 100 mg had a mean decrease in bone specific alkaline phosphatase of 3.1 IU/L from baseline to week 24, whereas the sitagliptin 200 mg group had a decrease of 3.8 IU/L, compared to a mean decrease of 0.6 in the placebo group. Serum C-telopeptide also had shown slight reductions over time in sitagliptin subjects compared to placebo-treated subjects.

The applicant suggested as explanation for these findings that improvement in glycemic control and reduced glycosuria would lead to reduced calciuria, with reduction of PTH and 1, 25-dihydroxyvitamin D. A decrease in PTH would then explain the decrease in the bone-specific component of serum alkaline phosphatase, while improvement in liver function could explain the decrease in the hepatic component of alkaline phosphatase. This explanation, while speculative, is also reported in the medical literature. Nagasaka [2] and

2 Nagasaka S, et al. Effect of glycemic control on calcium and phosphorus handling and parathyroid hormone level in patients with non-insulin-dependent diabetes mellitus. Endocrine J 1995; 42(3):377-83.

Okazaki [3] observed that poorly controlled diabetics had elevated alkaline phosphatase, which decreased with treatment with diet, insulin and oral hypoglycemic agents. Although the decrease in serum alkaline phosphatase observed in sitagliptin studies is small and carries no clinical significance, the further decrease from week 24 to week 54 and lack of stabilization of serum levels at the end of one year in 149 subjects on sitagliptin 100 mg and in 27 subjects on sitagliptin 200 mg daily for over a year despite achievement of stable glycemic control is inconsistent with the explanation given. The lack of stabilization of alkaline phosphatase at the end of one year is somewhat concerning regarding potential clinical effects, particularly related to the continued decline in bone-specific alkaline phosphatase, such as subtle adynamic bone disease.
Furthermore, the FDA statistical reviewer and this reviewer conducted an analysis of the laboratory data to investigate a possible relation between the magnitude of glycemic improvement (measured as a reduction from baseline in HbA1c) and the decrease in serum alkaline phosphatase. No relation between the variations in the 2 laboratory parameters was apparent from this analysis.
On the other hand, when focusing on increased alkaline phosphatase as laboratory AEs among those who had this analyte measured in the Pooled Phase 3 Population, we note that 6/1066 (0.6%) subjects in sitagliptin 100 mg, 1 / 448 (0.2 %) in the sitagliptin 200 mg and 1 / 761 (0.1%) subjects in the placebo had such event. There were no differences among treatment groups in the incidence of increased ALT or AST or bilirubin as AEs, assuaging concerns about potential liver toxicity. In 4 of the sitagliptin-treated subjects, the serum alkaline phosphatase returned to normal despite continued sitagliptin treatment, in 2 the elevation persisted slightly above baseline and 1 subject had liver metastases from pancreatic cancer.

Serum AST / ALT

Very small mean decreases in both ALT and AST from baseline to weeks 6 and 12 of study were noted in all groups, but the mean decreases were greater in the sitagliptin groups, with a dose-response. Like the hepatic component of the serum alkaline phosphatase, this decrease can represent slight improvement of underlying non-alcoholic steatohepatitis that is observed in patients with insulin resistance and T2DM.

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3 Okazaki R, et al. Metabolic improvement of poorly controlled noninsulin-dependent diabetes mellitus decreases bone turnover. JCEM 1997; 82(9):2915-20.

Table 113. Changes in liver enzymes (IU/L) from baseline to week 12 and 18/24 in the Pooled Phase 3 Studies, by treatment group

Liver enzyme	Week	Sita 100 mg			Sita 200 mg			Non-exposed		
		N	Mean (SD)	Change from baseline	N	Mean (SD)	Change from baseline	N	Mean (SD)	Change from baseline
AST	Baseline	1041	15.8 (7)		433	16.2 (6.1)		733	15.8 (6.1)	
	12	998	15.2 (7.3)	-0.5	403	15.3 (5.3)	-0.8	688	15.4 (5.8)	-0.4
	18/24	951	15.3 (6)	-0.4	383	15.4 (7)	-0.7	629	15.8 (6.3)	0
ALT	Baseline	1041	19.1 (10)		433	19.6 (9.1)		733	18.8 (8.9)	
	12	998	17.9 (11.5)	-1.1	403	17.8 (8.5)	-1.8	688	18.1 (8.6)	-0.7
	18/24	951	17.8 (9)	-1.1	383	17.9 (10.3)	-1.7	629	18.4 (8.9)	-0.3

Adapted from the applicant's Tables 2.7.4:66 and 2.7.4: 67

Unlike the trend noted with the decrease in serum alkaline phosphatase, there is stabilization of the liver transaminases from week 12 to week 18 or week 24. The serum transaminases continue to remain stable after the initial decrease even at week 54 for the selected subjects who are part of the Phase 3 cohort of the Long-Term Safety Population.

Uric acid

In the Pooled Phase 3 Studies, mean uric acid concentrations increased slightly and early into the studies in both 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. Between weeks 24 and 38, further mean increases in uric acid levels were observed in all groups that constituted the Phase 3 cohort of the Long-Term Safety population, a subset of subjects in studies P020 and P021. The placebo/ glipizide group had a mean increase of 0.6 mg/dL (from baseline to week 38), whereas the sitagliptin groups had a mean increase in uric acid of about 0.3 mg/dL. 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.

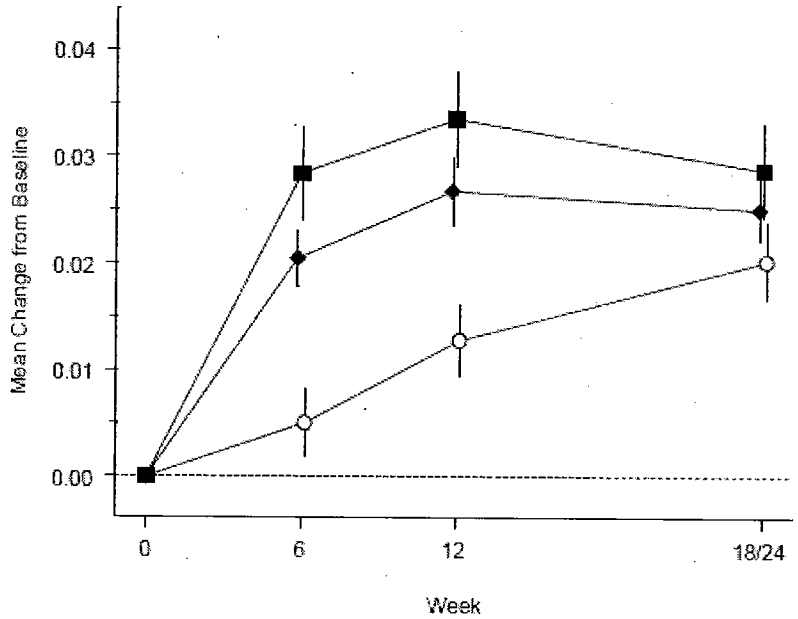
Serum creatinine

Pooled Phase 3 Population

Very slight increases in serum creatinine were noted in all treatment groups by weeks 18 or 24 in the Pooled Phase 3 Population. The mean change by the end of the studies compared to baseline was the same for all groups. However at both weeks 6 and 12 subjects on sitagliptin had slightly higher increases compared to placebo (mean change of 0.02 to 0.03 mg/dL from baseline, compared to a mean change of less than 0.01 mg / dL in the placebo group). Creatinine clearance decreased slightly from baseline to week 18 or 24 in all treatment groups by a mean (SD) of 3.0 (0.3), 3.1 (0.5) and 2.6 (0.4) mL/min, respectively for the sitagliptin 100, sitagliptin 200 mg and placebo. In the smaller subset of the Phase 3

cohort of the Long-Term Safety Population, there was a slight increase in mean serum creatinine in both sitagliptin groups of about 0.03 mg/dL from baseline, compared to no change in placebo. In subjects with normal renal function these changes are probably not clinically significant.

Figure 31. Mean change from baseline in serum creatinine over time in the Pooled Phase 3 Studies by treatment group.



♦ denotes sitagliptin 100 mg, ■ denotes sitagliptin 200 mg and ○ denotes placebo
Adapted from the applicant's Figure 2.7.4:9, Reference 2.7.4 Summary of Clinical Safety

Subjects with chronic renal insufficiency

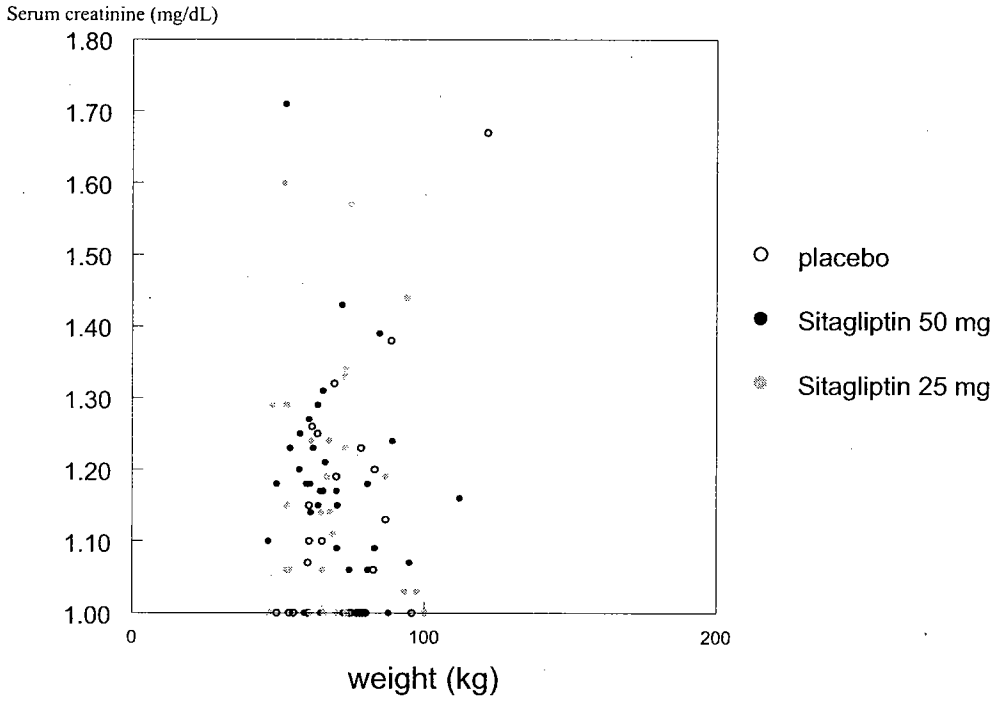
Study P028 looked at effects of sitagliptin in diabetic subjects with chronic renal insufficiency. Subjects randomized to sitagliptin received a daily dose of 25 mg if their calculated creatinine clearance was < 30mL / min (severe renal insufficiency or dialysis) or 50 mg of sitagliptin if their calculated creatinine clearance was ≥ 30 but less than 50 mL/min (moderate renal insufficiency). In that study the mean placebo-subtracted increase in serum creatinine from baseline to week 12 in both sitagliptin groups was larger than that seen in the Pooled Phase 3 Studies. By week 12, serum creatinine increased from a mean (SD) 2.05 (1.06) to 2.14 (1.15) in the pooled sitagliptin groups, compared to a mean increased from 2.05 (0.93) to 2.11 (0.96) in the placebo group, excluding subjects on dialysis. There were 12 subjects on dialysis in the sitagliptin 25 mg and 5 subjects on dialysis in the placebo group, adequately balanced with the 2:1 randomization favoring sitagliptin treatment. These increases were generally not accompanied by changes in BUN, phosphorus, chloride or bicarbonate.
In Study P028, both the 25 mg and the 50 mg groups had similar increases in mean serum creatinine, after excluding subjects on dialysis from the 25 mg dose group (Table 114). The difference in serum creatinine was about twice that seen in the placebo group. The mean increase did not correlate with age, gender, weight (Figure 32), body mass index or racial

groups. The increase in serum creatinine also did not correlate with the baseline serum creatinine, in any of the groups.

Table 114. Serum creatinine changes from baseline to week 12 in Study P028, by dose of sitagliptin, excluding subjects on dialysis

Treatment		Baseline	Week 12	Change from baseline to week 12
	N	Mean (SD)	Mean (SD)	Mean (SD)
Sitagliptin 25 mg	14	3.21 (1.2)	3.33 (1.4)	0.12 (0.6)
Sitagliptin 50 mg	34	1.53 (0.4)	1.65 (0.5)	0.11 (0.2)
Placebo/(Glipizide/Insulin)	20	2.05 (0.9)	2.11 (1.0)	0.06 (0.2)

Figure 32. Scatterplot of changes in serum creatinine (mg/dL) against body weight (kg) according to sitagliptin dose used in Study P028



The applicant speculates that the increase in serum creatinine relates to reduced tubular secretion of creatinine, rather than a change in glomerular filtration rate, in a mechanism similar to the effect of cimetidine on creatinine tubular secretion. There was a slightly higher incidence of AEs of increased serum creatinine among the sitagliptin 100 mg group (0.7%) compared with the sitagliptin 200 mg and non-exposed groups (0.4% for both treatment groups) in the Pooled Phase 3 Population. All of the sitagliptin 100 mg qd subjects in whom these AEs were reported participated in P020 in which there were more stringent protocol-specified discontinuation criteria for serum creatinine and estimated creatinine clearance (due to the combination with metformin therapy). Two subjects had creatinine values that returned to baseline levels while on study drug; 3 subjects had either elevated pre-randomization values or values that began to rise prior to randomization; 1 subject had an AE of increased serum creatinine associated with a value that was lower than the pre-randomization value; and one subject had stable creatinine values throughout

the trial, but creatinine clearance met prespecified discontinuation criteria. Four of these sitagliptin 100 mg subjects discontinued due to increased serum creatinine, related to protocol-specified discontinuation criteria. Two subjects in the sitagliptin 200 mg group had AEs of increased serum creatinine that subsequently returned to baseline levels while continuing study drug.

There was also a higher incidence of adverse experiences of decreased creatinine clearance among the sitagliptin treatment groups compared with the non-exposed subjects, occurring in 6 (0.6%), 3 (0.7%), and 2 (0.3%) patients in the sitagliptin 100 mg, sitagliptin 200 mg, and non-exposed groups, respectively. Within the sitagliptin 100 mg group, 4 subjects had creatinine clearances that returned to baseline levels while continuing study drug; 1 subject had a decreased pre-randomization creatinine clearance value and a subsequent value that met protocol-specified discontinuation criterion for creatinine clearance; and 1 subject had a creatinine clearance value that led to discontinuation.

In the sitagliptin 200 mg group, 3 subjects had adverse experiences of decreased creatinine clearance: 2 of these subjects had values that were < 60 mL/min prior to randomization, which decreased slightly during the double-blind treatment period, while 1 subject had creatinine clearance values that returned to baseline values after the adverse event.

While increases in serum creatinine were probably devoid of clinical significance in subjects with normal underlying renal function, the increase in serum creatinine and / or a decrease in creatinine clearance in patients with severely impaired renal function are of a magnitude that could be associated with faster deterioration of renal function. Our recommendation is to request a study that could best address the mechanism of increased serum creatinine, by measuring directly the glomerular filtration rate.

Sodium and Chloride

There were very slight increases in both serum sodium and chloride (0.5 to 0.6 mEq/L) concentrations from baseline to week 6 in the sitagliptin groups compared to placebo and this difference remained constant through the studies duration. Since such difference was not seen in the Pooled Long-Term Safety Population, where the control group received active treatment, the applicant attributes the slight mean increase in sodium to an improvement in hyperglycemia.

Blood urea nitrogen

There was a higher incidence of increased blood urea nitrogen reported as AE in the sitagliptin 200 mg group (5/448 or 1.1%) compared to both the placebo group (2/761, or 0.3%) and the sitagliptin 100 mg group (none of 1065 subjects). The increased BUN resolved without study drug discontinuation and there were no concurrent increases in serum creatinine or occurrence of gastrointestinal bleeding. No subject discontinued due to increased BUN.

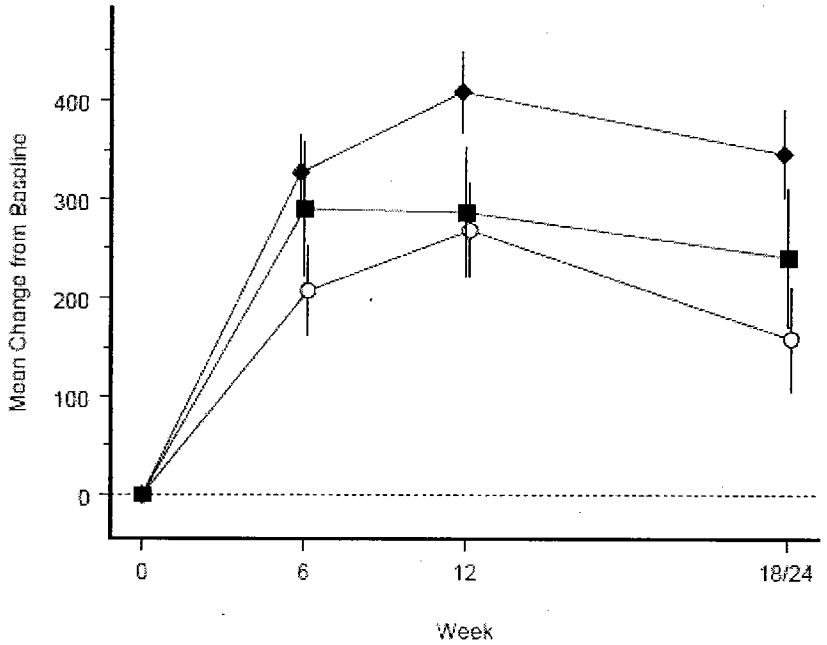
Also there were noteworthy changes in selected parameters of the complete blood count.

White Blood Cell Count (WBC) and Absolute Neutrophil Count (ANC)

A small increase from baseline to week 6 was observed in both WBC and ANC for all treatment groups, with slightly larger increases in both WBC (Figure 33) and ANC among

the sitagliptin groups. These were not dose dependent. The number of white cells remained relatively constant from week 6 to week 18 or 24. There were no increases in bands or other less mature forms of neutrophils.

Figure 33. Mean change from baseline in WBC count (cells /µL) over time in the Pooled Phase 3 Studies (Mean ± SE)



♦ denotes sitagliptin 100 mg, ■ denotes sitagliptin 200 mg and ○ denotes placebo
Adapted from the applicant's Figure in page 138, Reference R9

There was a smaller magnitude increase in mean absolute monocyte counts that parallels the curves seen in Figure 33 above.

These changes in white cell count or their fractions of neutrophils and monocytes are not necessarily a reaction to episodes of upper respiratory infection or nasopharyngitis. There is no clear explanation for this finding. Exendin-4, a GLP1 analog resistant to DPP4 metabolism, has been shown to acutely increase plasma cortisol levels. While this could be the mechanism by which neutrophils and overall white cell counts increase, this explanation remains hypothetical.

After week 30 in the Pooled Long-Term Population, the WBC and ANC in sitagliptin-treated subjects tended to be similar to those parameters in non-exposed subjects.

Hemoglobin

There were small decreases in mean serum hemoglobin among sitagliptin-treated subjects compared to placebo-treated subjects in the Pooled Phase 3 Population. The mean (SE) decreases from baseline to week 18 or 24 in serum hemoglobin were 0.14 (0.02), 0.22 (0.04) and 0.08 (0.03) for the sitagliptin 100 mg, 200 mg and placebo groups, respectively. In the Phase 3 Cohort of the Long-Term Safety Population, there were no differences in the mean changes in serum hemoglobin from baseline to one year of exposure among the treatment groups.

In the Hematology laboratory values category, greater incidence of AEs of decreased

hemoglobin was observed in the sitagliptin 100 mg group, but not in the sitagliptin 200 mg group, compared to the non-exposed group. Among the 6 subjects with the AE of decreased hemoglobin, the value returned to the pre-randomization range in 5 subjects while they continued on study drug, either during Phase A or after entry into Phase B.

No clinically meaningful difference was seen in the incidence of overall laboratory AEs, and only small differences in the incidence of specific laboratory AEs, were observed, as highlighted in this review. In general, where a higher incidence with sitagliptin relative to non-exposed subjects was observed, these reflected subjects with transient abnormalities that resolved subsequent to the abnormality considered by the investigator as an AE. No meaningful differences in the occurrence of specific laboratory AEs were observed. The only laboratory changes seen that may need to be further explored are the persistent decreases in serum alkaline phosphatase in the general population of diabetics, and the elevation in serum creatinine reported in the diabetics with chronic renal insufficiency.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 115. Incidence (%) of subjects with laboratory values meeting pre-defined limits of change in the Pooled Phase 3 Population, including data after initiation of glycemic rescue therapy

Parameter*	Sita 100 mg		Sita 200 mg		Non-exposed	
	n/N	%	n/N	%	n/N	%
Alkaline Phosphatase	6/1057	0.6	5/448	1.1	8/754	1.1
Either AST or ALT	7/1057	0.7	2/448	0.4	5/754	0.7
Uric Acid	12/1057	1.1	4/448	0.9	7/754	0.9
Creatinine	39/1057	3.7	16/448	3.6	19/754	2.5
WBC	58/1054	5.5	20/447	4.5	33/755	4.4
ANC	30/1048	2.9	12/446	2.7	11/755	1.5
Hemoglobin	85/1054	8.1	35/447	7.8	36/755	4.8

Adapted from the applicant's Table2.7.4:44, Reference Appendix of 2.7.4 Summary of Clinical Safety
*Criteria used as predefined limits of change for the different parameters used in the Table:
Alkaline Phosphatase (≥ 1 value increase ≥ 50 % from baseline and > ULN)
ALT or AST (either 1 value or last value >ULN and an increase >3-fold increase from baseline)
Uric Acid (≥ 1 value > ULN and ≥ 50 increase from baseline)
Creatinine (≥ 1 value ≥ 0.3 mg /dL increase from baseline)
WBC (≥ 1 value ≥ ULN and ≥ 20 % change from baseline)
ANC (≥ 1 value ≥ ULN and ≥ 20 % change from baseline)
Hemoglobin (≥ 1 value decrease ≥ 1.5 g/dL from baseline)

The increased frequency of serum hemoglobin decreases beyond the predefined limits of change among sitagliptin subjects cannot be readily explained. Only a few subjects in the sitagliptin groups had clear explanation for the decreased hemoglobin, usually related to episodes of gastrointestinal bleeding (for example, diverticular disease and colon carcinoma). Most of the episodes of decreased serum hemoglobin resolved during the studies with return of the values to baseline and did not result in anemia. There is no evidence that decreases in serum hemoglobin levels were secondary to hemodilution.
It is important to note the changes in BUN and creatinine that occurred in Study P028, as shown in Table 116.

Table 116. Subjects exceeding pre-defined limits of change in BUN and creatinine in Study P028, excluding data after initiation of glycemic rescue therapy

Lab Test	Predefined Limits of Change†	Treatment	n / N (%)	(95% CI)‡
BUN (mg/dL)	One value with an increase ≥ 50% and > ULN	Sitagliptin	8/ 52 (15.4)	5.9 (-14.9, 26.6)
		Placebo	2/ 21 (9.5)	
	Last value with an increase ≥50% and > ULN	Sitagliptin	5/ 52 (9.6)	4.9 (-13.9, 23.6)
		Placebo	1/ 21 (4.8)	
Serum Creatinine (mg/dL)	One value with an increase ≥ 0.3 mg/dL	Sitagliptin	15/ 52 (28.8)	-4.5 (-28.2, 19.3)
		Placebo	7/ 21 (33.3)	
	Last value with an increase ≥ 0.3 mg/dL	Sitagliptin	13/ 52 (25.0)	10.7 (-11.9, 33.3)
		Placebo	3/ 21 (14.3)	

† Increases or decreases are relative to baseline; last value = last on-treatment value in Phase A.
‡ 95% CI computed only for those criteria with 2% incidence in one or more treatment group.
ULN = upper limit of normal.
Subjects on dialysis at randomization are excluded from the analysis of BUN and serum creatinine.

From the subjects in Stratum 1, who had creatinine clearance at baseline ≥ 30 mL/ min and who received sitagliptin at 50 mg qd or placebo, more subjects in the sitagliptin group had to have their sitagliptin dose lowered due to decreased calculated clearance during the study, as shown in Table 117.

Table 117. Number and proportion of subjects with moderate renal insufficiency who required dose adjustment due to creatinine clearance < 30 mL/min

Treatment	N†	N (%)
Sitagliptin	37	6 (16.2)
Placebo	15	1 (6.7)

† Total number of patients in Stratum 1.

This suggests that patients with moderate renal insufficiency need to be closely monitored and have dose readjusted based on the threshold of creatinine clearance < 30 mL/min. There are no safety data on exposure to 50 mg qd in subjects with severe renal insufficiency or on dialysis.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Laboratory SAEs

There was one laboratory SAE in each of the sitagliptin groups, compared to none in the non-exposed group that occurred in the Pooled Phase 3 Studies.
One subject treated with sitagliptin 100 mg in Study P021 (AN30139) had an SAE of increased lipase that was observed during an emergency evaluation for abdominal pain and resulted in hospitalization.
One subject (AN38401) treated with sitagliptin 200 mg in Study P023 had a SAE of decreased sodium and potassium, likely related to use of diuretics.

Laboratory AE	Sita 100 mg	Sita 200 mg	Non-exposed
SAEs	1/1066 (0.1%)	1 / 448 (0.2 %)	0 / 763 (0%)
Discontinued due to laboratory AEs	7/1066 (0.7%)	0/448 (0%)	4/763 (0.5%)

Laboratory AEs leading to subject discontinuation

Study P010

- Subject AN3350, a 34 year old white male randomized to sitagliptin 5 mg bid, discontinued because of hyperglycemia
  - FPG was 128 to 145 at screening and 239 at randomization
  - FPG rose to 324 on day 20
  - FPG was 269 on day 37 and the subject was discontinued on day 43.

- Subject AN3481, a 49 year old white male randomized to sitagliptin 50 mg bid, discontinued because of increased creatinine phosphokinase
- CPK was 45 (normal) at randomization
- CPK was 183 at week 3
- CPK was 1729 IU/L at week 5
- CPK was 199 IU/L 4 days later (2 days off sitagliptin) without symptoms or physical findings.

Study P010 X1 (extension to Study P010)

- Subject AN2648, randomized to sitagliptin 50 mg bid / 100 mg qd discontinued because of increased ALT.
  - ALT of 47 IU/L and AST 40 IU/L at screening
  - ALT/AST started to increase above this range after day 172
  - ALT was 108 IU/L and AST 55 IU/L on day 184: study medication was interrupted
  - ALT 78 and AST 30 on day 188
  - ALT 49 and AST 40 on day 225, sitagliptin treatment resumed
  - ALT 41 and AST 24 on day 245
  - ALT 81 and AST 52 on day 362
  - Remained in same range until day 400, when subject was discontinued.

- Subject AN3434, a 64 year old white male randomized to placebo/sitagliptin in Study P010X1, discontinued because of thrombocytopenia.
  - platelet counts near or slightly below the LLN (LLN: 125,000/mm^3) throughout the study
  - 138,000/ mm^3 at baseline on Day 1
  - 119,000/ mm^3 at Week 25
  - 107,000/ mm^3 at the discontinuation visit, Week 27

- The decreased platelets at Week 16 (113,000/ mm^3) and at Week 25 (119,000/ mm^3) were reported by the investigator as laboratory AEs possibly related to study drug, and the subject was discontinued due to this laboratory AE at Week 27. No other hematological laboratory AEs were reported for this subject.

- Subject AN2058, a 47 year old white female randomized to sitagliptin 12.5 mg bid / 100 mg qd due to increased CPK, was discontinued prior to converting to sitagliptin 100 mg qd
  - CPK was 122 IU/L at screening (ULN = 120 IU/L)
  - CPK was 133 on day 67
  - CPK was 149 on day 91
  - Subject complained of muscle soreness on day 96
  - CPK was 199 on day 120
  - CPK of 141 on day 149 (discontinuation visit). Physical exam showed muscle weakness.

- Subject AN3480 a 57 year old Hispanic male randomized to glipizide was discontinued because of increased AST/ALT and alkaline phosphatase on day 263.

No subject was discontinued due to laboratory AEs from dose collapse to the end of Study P010 Extension.

Study P014

- Subject AN6898, a 46 year old white male on sitagliptin 50 mg bid was discontinued due to increased fasting glucose.
- His FPG ranged from 198 to 267 before randomization
- FPG was 216 on day 17 and rose to 266 on day 56, when he was discontinued.

No subject was discontinued due to laboratory AEs during the extension of Study P014.

Study P020

Table 118 shows subject discontinuation from Study P020 due to laboratory AEs. Most of the subjects discontinued due to laboratory AEs were participants in Study P020.

Table 118. Laboratory AEs leading to subject discontinuation in Study P020

Subject	Gender	Race	Age	Therapy (mg/d)	Study Day of Onset	Adverse Experience	Day Dropped	Serious
Sitagliptin 100 mg								
33184	F	Hispanic	43	Sita 100	11	ALT increased	14	N
33315	M	white	57	Sita 100	11	ALT increased	17	N
33128	F	white	58	Sita 100	124	Blood creatinine increased	130	N
33199	M	white	75	Sita 100	43	Blood creatinine increased	46	N
33734	F	Hispanic	63	Sita 100	141	Creatinine clearance decreased	149	N
33827	F	Asian	52	Sita 100	13	Blood creatinine increased	31	N
33847	F	Asian	57	Sita 100	171	Blood creatinine increased	171	N
Placebo								
33190	M	black	44	Placebo	8	Blood creatinine increased	17	N
33593	F	white	37	Placebo	147	Fasting glucose increased	146	N
33668	M	white	55	Placebo	134	Fasting glucose increased	160	N

Based on the applicant's Table 12-11, Reference 020V1

From the subjects randomized to sitagliptin, 2 subjects (AN33184 and AN 33315) were discontinued due to increased ALT, but had increased ALT prior to baseline. Five other subjects were discontinued due to increased creatinine or decreased calculated creatinine clearance. Of these 5, 3 (AN33847, AN33827 and AN33734) were discontinued due to the more rigid criteria imposed by the protocol prescribed use of metformin, even though these increases in serum creatinine were very small. The fourth subject (AN33199) had been diagnosed with obstructive uropathy (bilateral nephrolithiasis) after the serum creatinine had increased from 1.1 to 1.5 mg/dL. The fifth subject (AN33128) had an increase in serum creatinine from 1 – 1.3 (screening and baseline) to 1.7 mg/dL at day 130, persisting for 3 weeks after discontinuation, from reasons unknown. The 3 subjects randomized to placebo were discontinued due to the following laboratory AEs: AN33190 due to increased serum creatinine, and AN33593 and 33668 due to increased fasting blood glucose.

Study P021

- Subject AN30249 on placebo was discontinued due to increased ALT.
  - ALT increase was noted by day 44. The subject discontinued study therapy on day 55, with progressive normalization of AST and ALT by day 104.

Study P023

There were no discontinuations due to laboratory AEs in Study P023.

7.1.7.4 Additional analyses and explorations

The analyses of laboratory findings in the Pooled Phase 3 Population revealed dose-dependent decreases in serum alkaline phosphatase and increases in serum creatinine. While there is no known clinical implication for the magnitude of decrease in serum alkaline phosphatase, the dose dependent increase in serum creatinine in subjects treated

with sitagliptin compared to placebo may represent a safety issue. Of particular concern is the fact that serum creatinine increased to a greater magnitude in subjects with chronic renal insufficiency who were not on dialysis, even though the dose of sitagliptin was adjusted for their baseline creatinine clearance.

7.1.7.5 Special assessments

For this review, the applicant included the following events: 1) subjects who discontinued for elevated liver enzymes (either based on protocol-defined criteria or due to a reported AE of increased liver enzymes and 2) subjects whose ALT or AST laboratory values met PDLC criteria for last measurements of ≥ ULN and ≥ 2-fold increase from baseline (last measurement while the subject was on study medication: for the Pooled Phase 3 Population this visit could be the start of glycemic rescue therapy, while in the Long-Term Safety Population, the last observed value while the subject was on study medication, regardless of rescue therapy).

Elevation of serum transaminases

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On sitagliptin

Subject ID	Baseline/pre-randomization		Peak		Study Day	Comment
	ALT	AST	ALT	AST		
Study P010 and extensions						
AN2171	24-30	23-25	104	26	427	Met PDLC at last visit. Subject discontinued due to prohibited use of warfarin / prednisone day 456 with ALT 20 AST 16 on day 462
AN2648	31-47	24-40	108	55	184	Met PDLC at last visit. Sitagliptin interrupted, with ALT 49, AST 40 at day 225; sitagliptin resumed ALT 81 AST 52 at day 362, subject discontinued day 400
AN3417	Normal	Normal	30	27	463	Met PDLC at last visit. ALT/AST normal on day 527 when metformin started. ALT 80 AST 62 on day 611, subject discontinued due to lack of efficacy with ALT 62 AST 33 and nl. 2 months later
Study P014 and extensions						
AN5067	21	N/A	73	26	95	Met PDLC at last visit Phase A; subject did not continued to extension; ALT 30 on day 110
AN6446	68	44	101	69	369	**Discontinued due to AE of increased ALT/AST**; ALT 62 AST 37 on day 375 and ALT 46 AST 24 day 400,; reason for increase unknown
Study P015						
AN7544	14	13	90	16	28	Met PDLC at last visit. ALT unconfirmed on sitagliptin, because subject crossed over to placebo, per study design
Study P020						
AN33589	17	10	55	17	168	Met PDLC at last visit. Final study visit in Phase A. Subject elected not participate in extension.
AN33061	31	19	94	69	379	**Reported as laboratory AE**. Week later study drug discontinued due to upper abdominal pain. Day 392: ALT 79 AST 42
Study P021						
AN30244	40	62	64	145	127	Met PDLC 3XULN. Hepatomegaly. Day 131: returned to baseline while on sitagliptin. Subject discontinued: non-compliance.
AN30304	23	21	250	145	70	**LFT elevation reported as SAE**. Withdrew consent day 70. Hepatosplenomegaly at baseline, biliary obstruction day 83. NASH by biopsy day 99: portal inflammation with eosinophils (+).
AN30757			290	285	47	Met PDLC at last visit. Gallbladder necrosis and cholecystectomy day 40. Subject discontinued for hyperglycemia day 52. Day 55: normal ALT/AST.
AN30779 (sitagliptin 200 qd)	13	11	27	36	47	Met PDLC at last visit. Subject discontinued: anemia, weight loss and colon CA. Day 54: normal ALT/AST.
AN31044 (sitagliptin 200 qd)	11	13	107	90	169	Met PDLC at last visit. Cholelithiasis day 167. Normal AST and ALT during Phase B until day 283 when discontinued for hyperglycemia.
Study P023						
AN38107	37	29	105	94	92	Met ALT/AST discontinuation criteria day 100. Day 113: ALT 59 AST 49. (-) hepatitis, no increase in alcohol intake.
AN38077 (sitagliptin 200 qd)	21	17	103	46	127	Met ALT/AST discontinuation criteria. Day 139. Day 140: ALT 41 AST 27. Viral hepatitis negative. No explanation for increased ALT/AST.

On Placebo or Active Control

Subject ID	Baseline/pre-randomization		Peak		Study Day	Comment
	ALT	AST	ALT	AST		
Study P010 and extensions						
AN3480 (on Glipizide)	55	45	137	158	177	**Discontinued due to AE of increased ALT/AST.** Glipizide held from day 180-239. On day 239, ALT 43 AST 31, glipizide use restarted. On day 261 ALT 77 AST 72 and subject was discontinued.
Study P019						
AN36261	6	11	37	32	165	Met PDLC at last visit. ALT and AST returned to normal 8 days after discontinuation of placebo.
Study P020						
AN33244	8	11	40	40	169	Met PDLC at last visit Phase A (on placebo); values returned to normal during Phase B on metformin and glipizide.
Study P021						
AN30249	16-42	19-26	79	61	55	**Discontinued for laboratory AE.** Negative for viral hepatitis, gradual decrease until day 104, when ALT 24 AST 21.
AN30944	13	18	47	29	146	Met PDLC at last visit. Final study visit in Phase A. when starting glycemic rescue therapy. On day 175 ALT 26 AST 21.
Subjects discontinued prior to initiation of study drug due to increased liver enzymes						
AN36486						
AN33184						
AN33315						

From the table above, we note that 15 subjects treated with sitagliptin had elevation of either ALT or AST or both, that met PDLC at the last visit or resulted in discontinuation due to a laboratory AE, as compared to 8 subjects not exposed to sitagliptin. These data do not support a conclusion that sitagliptin has hepatotoxic properties. It is likely that these subjects represent outliers and that the effect of sitagliptin on liver enzymes is no different than that found with other anti-hyperglycemic agents (such as PPAR agonists and metformin) and lipid lowering agents. For the majority of subjects the improved glycemic control results in less glucose toxicity and less insulin resistance, contributing to improvement of non-alcoholic steatosis that is so prevalent in T2DM, in particular in obese patients with T2DM.[4] It is interesting to note that the second most common reason for exclusion of subjects in the studies was the presence of abnormal liver enzymes, above the pre-determined, arbitrary, threshold of > 2 times the ULN. Thus, 69 subjects (6.5%) of 1066 non-randomized in Study P021, 39 subjects (4.5%) of the 866 subjects non-randomized in Study P023 met this criterion for exclusion. These rates are not different from the rates described in the studies.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

4 Tolman KT, Fonseca V et al. Narrative review: Hepatobiliary disease in type 2 diabetes mellitus. *Ann Intern Med* 2004: 141:946-956.

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 represent issues of safety.

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

The population selected for the analyses of vital signs is the Pooled Phase 3 Studies, which represent the large experience with sitagliptin use, at the doses proposed for marketing, and in a controlled fashion.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 119 shows baseline and on treatment changes in selected vital signs in the Pooled Phase 3 Population. No clinically significant changes in vital signs were observed with sitagliptin treatment at either 100 mg or 200 mg daily, compared to placebo.

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Table 119. Mean (SD) changes in vital signs in the Pooled Phase 3 Population

			Baseline	On Treatment	Change from Baseline		
Vital Sign	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Median	Range
Body weight (kg)	Sita 100 mg	931	87.2 (18.1)	87.0 (18.3)	-0.2 (0.1)	-0.1	-18.5 to 12.1
	Sita 200 mg	374	85.9 (19.6)	85.8 (19.5)	-0.1 (0.2)	0	-17.7 to 21.8
	Placebo	601	86.2 (17.6)	86.0 (17.6)	-0.3 (0.1)	-0.2	-13.3 to 11.0
BMI (kg/m^2)	Sita 100 mg	930	31.0 (5.2)	30.9 (5.3)	-0.1 (0)	0	-7.2 to 5.3
	Sita 200 mg	374	30.9 (5.4)	30.9 (5.4)	0 (0.1)	0	-5.3 to 8.2
	Placebo	600	30.9 (5.1)	30.8 (5.1)	-0.1 (0)	-0.1	-6.1 to 4.2
Systolic BP (mmHg)	Sita 100 mg	953	128.2 (14.2)	127.1 (14.0)	-1.0 (0.4)	-0.5	-41.0 to 61.5
	Sita 200 mg	382	127.7 (13.4)	127.2 (14.3)	-0.5 (0.7)	0	-42.0 to 67.0
	Placebo	629	129.9 (14.1)	129.6 (14.3)	-0.4 (0.5)	0	-43.5 to 45.0
Diastolic BP (mmHg)	Sita 100 mg	953	77.9 (8.4)	77.5 (8.1)	-0.3 (0.3)	0	-41.5 to 37.0
	Sita 200 mg	382	78.4 (8.2)	77.7 (8.4)	-0.7 (0.4)	0	-25.0 to 27.0
	Placebo	629	78.4 (8.5)	78.3 (8.2)	-0.1 (0.3)	0	-30.0 to 29.0
Pulse Rate (beats/min)	Sita 100 mg	949	72.9 (9.3)	73.1 (9.4)	0.2 (0.3)	0	-44.0 to 34.0
	Sita 200 mg	382	72.2 (9.0)	72.4 (8.6)	0.2 (0.4)	0	-36.0 to 28.0
	Placebo	629	72.2 (8.9)	72.2. (9.8)	0.0 (0.3)	0	-28.0 to 27.0
Respiration (breaths/min)	Sita 100 mg	884	17.0 (2.7)	16.9 (2.6)	-0.2 (0.1)	0	-12.0 to 12.0
	Sita 200 mg	364	17.0 (2.6)	17.0 (2.9)	0 (0.1)	0	-8.0 to 19.0
	Placebo	571	17.0 (2.8)	17.0 (2.6)	-0.1 (0.1)	0	-10.0 to 10.0
Temperature (°C)	Sita 100 mg	877	36.5 (0.4)	36.5 (2.1)	0.1 (1)	0	-2.8 to 1.9*
	Sita 200 mg	364	36.5 (0.4)	36.5 (0.4)	0 (0)	0	-1.3 to 1.3
	Placebo	571	36.5 (0.4)	36.5 (0.4)	0 (0)	0	-1.8 to 2.0

* excludes subject AN 33165, whose temperature was recorded in error in the CRF.

No changes were seen in vital signs assessed in subjects treated with sitagliptin compared to placebo in the 18 or 24 weeks of the Pooled Phase 3 Studies. This is in contrast to the findings in subjects treated with exenatide in clinical studies, who lost from baseline to week 30 between 2 and 3 kg compare to placebo. This difference can be related to the limited physiologic augmentation of GLP-1 obtained with DPP4 inhibition, as contrasted to the supra-physiologic GLP1 activity achieved with the administration of the GLP1 analog exenatide.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no shifts from normal to abnormal in the analyses of vital signs in the Pooled

Phase 3 Population that were clinically meaningful

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no subjects discontinued due to vital signs abnormalities. One sitagliptin-treated subject (100 mg qd) and one placebo subject were discontinued due to perceived palpitation or tachycardia, but these were reported as AEs.

7.1.8.4 Additional analyses and explorations

Analyses in vital signs in subjects with chronic renal insufficiency that participated in Study P028 did not reveal significant changes or trends from baseline to end of study.

7.1.9 Electrocardiograms (ECGs)

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

All testing and reports are based on the ITT population. ECG testing was conducted at baseline and at Week 24 for Studies P019, P020, and P021or week 18 for Study P023. While electronic versions of the ECG were transmitted to and interpreted by a central laboratory for consistency, the ECG tracings were also assessed by investigators; if clinically significant changes occurred, these were reported as clinical or "other" AEs. The following changes were made in the Phase 3 protocols after the results of PN032 (a positive-controlled QTc study in healthy subjects) demonstrated small mean increases (maximum 8.2 msec above a mean of 406 msec) in QTc intervals following a sitagliptin dose of 800 mg (8-fold the clinical dose of 100 mg qd). Measurements of pre-dose and 2- to 6-hour post-dose ECG to be obtained at Week 18 / Week 24 were added (but not on days tested with a meal tolerance test, due to potential confounding effects of food on heart rate).

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

Similar to the analyses of AEs and laboratory findings, ECG data were reviewed in the Pooled Phase 3 Studies. This population comprises a substantial number of subjects, studied in placebo-controlled studies for either 18 weeks (one study) or 24 weeks (3 studies). In addition, Study P032 was a study designed to investigate effects different doses of sitagliptin on the corrected QT (QT_c) interval in healthy volunteers and the results of that

study are also reviewed in this section.

Study P032

Two doses of sitagliptin were tested on their effects on the QT_c interval: 100 mg and 800 mg. These were given as single doses (placebo- and moxifloxacin-controlled, double-blind, double dummy) in a crossover design with 7 days washout between doses. Seventy four subjects completed the study. Moxifloxacin was used as a positive control, to test the sensitivity of the ECG criteria used in the study. ECGs were performed pre-dose and in multiple timepoints up to 12 hours following the dose, concomitant with venous sampling for assessment of drug concentrations. The QT interval was corrected according to Fridericia ($QT/RR^{1/3}$).

Following sitagliptin 100 mg, the dose proposed for marketing, there was no increase in QT_c observed at any time point. The supra-therapeutic 800 mg dose was associated with a small but detectable increase in QT_c. The maximum mean increase in the placebo-corrected change in QTc from baseline was 8.0 ms (the upper bound of the one-sided 95% confidence interval was 10.6 ms) and occurred at 3 hours post-dose (corresponding to plasma sitagliptin concentrations ~11-fold higher than maximal concentrations following a 100 mg dose). At the prespecified time point of 1 hour, the mean change in QT_c from baseline was 3.7 ms (the upper bound of the one-sided 95% confidence interval was 6.2). There were no extreme values in this study and categorical analysis of the data did not demonstrate any differences in maximum QT_c (> 450 ms, > 480 ms, and > 500 ms), nor any differences in the maximum QT_c change from baseline (> 30 ms and > 60 ms) across the 2 doses of sitagliptin and placebo.

The sensitivity of the assay to detect modest increases in QT_c interval was established with the active control moxifloxacin. The mean placebo-corrected QT_c change from baseline associated with moxifloxacin ranged from 7.0 ms (90% CI: 4.4 ms, 9.5 ms) at 0.5 hours post-dose to 13.9 ms at 3 hours post-dose (90% CI: 11.3 ms, 16.4 ms). Administration of moxifloxacin is associated with an increase in QTc interval, clearly demonstrating the sensitivity of the methods used in this study.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

As shown in Table 120, there were no changes in QT_c interval from baseline to the last visit in each of the Phase 3 studies, compared to the QT_c observed in placebo-treated subjects.

Table 120. Changes in QT corrected interval (ms) from baseline in the Pooled Phase 3 Studies, excluding data after initiation of glycemic rescue therapy

		Baseline	On Treatment	Change from Baseline		
Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Median	Range
Sita 100 mg	958	417 (25)	426 (23)	9.6 (0.5)	3	0 to 161
Sita 200 mg	405	419 (23)	427 (23)	8.7 (0.6)	1	0 to 76
Placebo	685	416 (26)	425 (24)	9.2 (0.5)	1	0 to 73

Table 121 shows the change from baseline in QT_c for a subset of subjects who had ECG at the expected T_{max} of sitagliptin, an interval of 1 to 6 hours post-dose in the Pooled Phase 3 Studies.

Table 121. Changes from baseline in QT corrected interval (ms) at T max in the Pooled Phase 3 Studies, excluding data after initiation of glycemic rescue therapy

		Baseline	On Treatment	Change from Baseline		
Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Median	Range
Sita 100 mg	81	417 (29)	418 (21)	1 (3)	-3	-64 to 95
Sita 200 mg	63	416 (22)	417 (22)	0.4 (2)	2	-45 to 71
Placebo	66	419 (24)	415 (20)	-4 (3)	-3	-91 to 34

The same conclusion also applies to subjects with chronic renal insufficiency treated with sitagliptin in Study P028.
Sitagliptin has been shown to be a P-glycoprotein (PgP) substrate, and a PK study in healthy volunteers (P037) has shown increase in C_{max} of 68 % when co-administered with maximally tolerated doses of cyclosporin A (a potent PgP inhibitor), namely 600 mg. The applicant did not conduct a study to investigate effects of sitagliptin on QT interval prolongation with the concomitant use of cyclosporin A or others PgP inhibitors (quinidine, ketoconazole, clarithromycin, or atorvastatin), which is a departure from the ICH Guidance E14QT (2005) ("Alternatively, if the concentrations of a drug can be increased by drug-drug or drug-food interactions involving metabolizing enzymes (e.g., CYP3A4, CYP2D6) or transporters (e.g., P-glycoprotein), these effects could be studied under conditions of maximum inhibition"). However, because the study tested effects of sitagliptin at 200 mg, a dose not proposed for marketing), it is unlikely that the proposed dose of 100 mg daily, even if used with these PgP inhibitors, would lead to significant prolongation of QT interval and cardiac arrhythmias.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The proportion of subjects with at least one QT_c interval $\geq$ 500 ms was similar among treatment groups, with between 0.2 and 0.5 %. These subjects had QT_c intervals prior to randomization that were very close to 500 ms. The proportion of subjects with QT_c interval increases from baseline by 30 or 60 ms was also similar among groups.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

There were no marked outliers or subjects discontinued from studies due to ECG abnormalities.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

Sitagliptin, being a small molecule, is unlikely to generate an immune response. On the other hand, sitagliptin exerts its metabolic effect by inhibition of DPP4, which is identical to CD26, a T lymphocyte surface glycoprotein. This fact prompted the applicant to be particularly vigilant to effects of sitagliptin on infections or other immune disorders in the clinical studies. No increased risk of infections or immune disorders has been observed.

7.1.11 Human Carcinogenicity

The review of the sitagliptin clinical studies did not reveal an increase risk of neoplasia (Please refer to Section 7.1.2 and Table 77).
Please see Dr. Bourcier's toxicology review for a complete discussion of the applicant's carcinogenicity program. Sitagliptin was found to increase risk of hepatic neoplasia in rat toxicity studies, when exposed to a dose of 500 mg/kg/day, corresponding to 250 times the human dose and a 58-fold greater exposure than that achieved with the maximum recommended human dose. This dose was associated with hepatotoxicity in those animal studies. In addition, no evidence of genotoxicity or mutagenicity with sitagliptin was found and no trend to cause tumors was evident in mice studies with the MTD of 500 mg/kg/day for 2 years.

7.1.12 Special Safety Studies

As discussed in Section 7.1.9.2 in this review document, the applicant has conducted a clinical study to assess effects of sitagliptin on the QT_c interval in healthy volunteers. That study did not demonstrate prolongation of the QT_c interval that would merit concerns for arrhythmias or Torsades.
There is no substantial clinical experience with this pharmacological class, beyond what

has been observed in this application, since sitagliptin is a first in class new molecular entity. FDA has recently notified manufacturers that they have "received data indicating that the administration of DPP4 inhibitors to monkeys has resulted 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. These are being investigated in a 6-month monkey toxicity study by the applicant. There is no indication of analogous safety signals observed in the sitagliptin clinical studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Based on the 2-week post study telephone contact and based on the direct follow up of subjects who had sitagliptin discontinued or held during the clinical studies, there is no indication of withdrawal or rebound symptoms.
The potential for abuse was not investigated in the sitagliptin development. No effect on the Central Nervous System was detected to suggest an abuse potential. Unlike Exenatide, which is a GLP-1 analog that was shown to cause weight loss, sitagliptin has not demonstrated capacity to decrease weight, and therefore use (or abuse) for weight loss is not anticipated. There were no CNS AEs to suggest impairment of mental ability or ability to drive or operate machinery.

7.1.14 Human Reproduction and Pregnancy Data

The sitagliptin development did not provide evidence of effects on reproduction and pregnancy. Only one subject (AN5041) in Study P014 was pregnant when she took a single dose of sitagliptin 50 mg. She was discontinued from the study and gave birth to a healthy male after a full term unremarkable pregnancy.
Preclinical development and reproductive toxicity studies indicate that sitagliptin does not affect fertility in female or male rats at the limit dose of 1000 mg/kg/day but does slightly increase the incidence of rib abnormalities at this dose with a NOEL for developmental toxicity in rats of 250 mg/kg/day. There was no effect on fetal development in rabbits at 125 mg/kg/day. The applicant classified sitagliptin as a Pregnancy Category B for labeling purposes.
Sitagliptin is secreted in the milk of lactating rats. It is not known whether sitagliptin is secreted in human milk. Therefore it should not be used by a woman who is nursing. Please see Dr. Bourcier's review for a complete discussion on the effects of sitagliptin on reproduction in animal studies.

7.1.15 Assessment of Effect on Growth

The youngest subjects enrolled in the Phase 3 studies were 18 years old, and therefore no effect of sitagliptin on linear growth can be inferred from these studies.
Diprotin A, another DPP4 inhibitor, was shown to inhibit the degradation of human growth

hormone releasing hormone GRH (1-44)-NH2 to GRH (3-44)-NH2 in in-vitro experiments.[5]

7.1.16 Overdose Experience

No overdose in excess of 400 mg occurred during the Phase 2 or Phase 3 studies. In Phase 1 studies, single doses of 800 mg or 10-day dosing with 600 mg daily of sitagliptin has been well tolerated in healthy volunteers. There has been more substantive experience with a dose of 200 mg daily, in healthy obese middle age volunteers during Phase 1 studies as well as in diabetics during Phase 3 studies, without dose-dependent events related to safety or tolerability.

Sitagliptin has a wide therapeutic margin; thus, the potential for toxicity as a result of overdose is limited. Since single doses up to 800 mg have been well-tolerated in Phase 1 studies, hence accidental exposure to doses of up to 800 mg are unlikely to result in clinical sequelae. There is no clinical experience with doses above 800 mg.

In the event of an overdose, the applicant proposes to employ usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3 to 4 hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

7.1.17 Postmarketing Experience

Sitagliptin has not been approved anywhere, and no post-marketing experience exists with the use of sitagliptin.

7.2 Adequacy of Patient Exposure and Safety Assessments

The overall exposure to sitagliptin in the 34 clinical studies that are part of this development program is 3276 subjects, with a cumulative exposure of 1339 subject-years (see Table 122). The applicant presented a discussion of the probability of detecting uncommon AEs, as follows.

The probability entries are calculated using cumulative Poisson probability distribution $p = 1 - \sum_{i=1}^{x} \frac{\mu^i e^{-\mu}}{i!}$, where x is the number of observed cases, μ the background rate. For example, if the background rate of an AE is 1:1000 and there are 1000 patient-years of experience, then there is a 26% probability of observing 1 event and an 8% probability of

5 Frohman LA, Downs TR et al. Dipeptidylpeptidase IV and trypsin-like enzymatic degradation of human growth hormone-releasing hormone in plasma. J Clin Invest. 1989 May; 83(5): 1533–1540

observing 2 events.
The applicant concludes that relatively uncommon AEs would be detected in this development program; rare events, on the other hand could be missed and will only be detected through exposure of a larger population and with more prolonged treatment duration.

Table 122. Exposure to sitagliptin in different phases of the clinical development

Clinical Trial†	Total Subjects/ Any dose on Sitagliptin‡	Dosage Range of Sitagliptin	Range of Days on Sitagliptin	Mean Number of Days on Sitagliptin
Phase 1	557	1.5 mg to 800 mg	1 to 28	5.9
Phase 2	1116	5§ mg to 400 mg	1 to 419	229.7
Phase 3	1603	25§ mg to 400 mg	1 to 216	142.9

† Includes patients from Phase 1 studies; Phase 2 studies P010, P014, P015, and Japan study RC431A201; and Phase 3 studies P019, P020, P021, P023, and P028.
‡ Although some patients may have taken two or more different dosages, they have been counted only one time each.
§ Includes both protocol specified doses and actual doses taken during the study.

Adapted from the applicant's Table1, reference Risk Management Plan

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The overall exposure to sitagliptin in the 34 clinical studies that are part of this development program is 3276 subjects, with a cumulative exposure of 1339 subject-years. Of these subjects, 2719 were patients with T2DM. From the 2719 diabetic patients, 1116 were treated with sitagliptin doses from 10 to 100 mg qd in Phase 2 studies of up to 12 weeks duration and 1538 subjects were treated with sitagliptin 100 mg (n= 1082) or 200 mg qd (n= 456) for 18 or 24 weeks Phase 3 studies. A subset of subjects from both the Phase 2 and the Phase 3 studies elected to participate in extensions of these studies. This subset is referred to as the Pooled Long-Term Safety Population. This Long-Term Safety Population consists of 429 subjects treated with sitagliptin 100 mg qd, and 27 subjects treated with sitagliptin 200 mg qd for periods of over one year. An additional 65 subjects with both T2DM and chronic renal insufficiency were treated with either 25 mg or 50 mg qd of sitagliptin, based on their creatinine clearance.
The exposure to sitagliptin in the Phase 3 studies is shown in Table 73.

7.2.1.1 Study type and design/patient enumeration

Table 123 is a comprehensive list of all clinical studies conducted in the development of sitagliptin and these studies are described in the new drug application.

Table 123. Listing of all studies conducted in the clinical development of sitagliptin

Study #	Study Population			Study Goal	Study Design
	M	F	Age range		
P001	34	0	18-45	PK	DB, R, PC, SAD (1.5 to 600 mg)
P003	20	18	18-80	PK in healthy obese and elderly	DB, R, PC, Single dose (50 mg)
P004	70	0	18-45	PK/PD of multiple doses	DB, R, PC, 10 days (25 to 400 qd; 800 mg d1 and 600 mg d3-10; 300 bid
P005	42	16	33-60	PK/PD in T2DM	DB, R, PC, Single dose (25mg, 200 mg or PBO)3-period crossover
P006	6	6	18-56	PK of 2 formulations	Open label, R, 2-period crossover, single 50 mg dose (tablet vs dry filled capsule)
P007	12	20	45-65	PK/PD in obese middle age	DB, R, PC, 28-day dosing of 200 mg bid or PBO
P008	20	10	27-70	PK in 24 subjects with chronic renal insufficiency/ 6 healthy	Open label, 2-part study: Part 1: 50 mg single dose in normal, mild, moderate and severe CRI; Part 2: 6 subjects with ESRD receive 2 50-mg doses 1 week apart
P009	6	0	27-43	PK radioactive elimination study	Single center, open label, single period 83 mg [14C]sitagliptin
P010	405	338	21-76	Phase 2: Safety/Efficacy in T2DM	MC, DB, R, PC and AC, PG, dose ranging study 5 – 50 mg bid /PBO or glipizide 5-20 mg bid / PBO X 12 weeks
P010X1	276	233	21-76	Extension to Study P010	40 week study: all sitagliptin groups collapsed dose to 100 qd/PBO or glipizide. Metformin rescue per protocol
P011	7	12	39-67	Safety in mild to moderate hypertension	R, DB, Double dummy, PC, 3-period crossover, 50 -100 bid or PBO X 5 days
P012	7	6	18-60	Effect on metformin PK and concomitant use PD	DB, double-dummy, PC, 3-period crossover, with 50 mg bid/PBO, with metformin 500 bid/PBO X 7 days
P013	18	0	20-46	PK/PD in Japanese male subjects	DB, R, PC, SAD, 4-period study with 5 – 400 mg
P014	288	267	23-74	Dose ranging for safety / efficacy	MC,DB,R, PC, 24-wk dose ranging 25-100 mg qd or 50 bid vs. PBO
P014X1	183	155	26-74	Extension to Study P014	40 week study: those on placebo switched to metformin (and sitagliptin PBO) and those on sitagliptin had dose collapsed to 100 mg qd (and metformin PBO)
P015	10	18	38-71	Combination with metformin: safety / efficacy	DB, R, PC, crossover study with 50 mg bid (or PBO, random sequence) and metformin X 4 weeks per period
P016	8	0	20-44	PK Absorption in gastric, enteric and colonic mucosa	Open label, 3-period, fixed sequence 50 mg delivered with [redacted] devices to stomach, distal small bowel or colon
P017	10	10	47-71	PK and safety in moderate hepatic insufficiency	Open label, single dose of 100 mg study in subjects with Child-Pugh's score 7-9, vs healthy controls
P018	16	20	24-34	PK effects on digoxin plasma concentration	DB, R, PC, 2-period crossover 0.25 mg digoxin and 100 or 200 mg sitagliptin (or PBO) X 10 days
P019	196	157	24-87	Efficacy with pioglitazone	Phase 3, MC, DB, R, PC, 100 mg (or PBO) with pioglitazone 30-45 mg X 24 wks
P020	301	400	19-78	Efficacy with metformin	Phase 3, MC, DB, R, PC, 100 mg (or PBO) with metformin ≥ 1500 mg X 24 wks
P021	383	358	18-75	Efficacy in monotherapy	Phase 3, MC, DB, PC, 10 mg, 200 mg (or PBO) X 24 wks with metformin rescue
P022	6	6	18-45	PK effect on warfarin PK	R, open label, 2-period crossover with 30 mg warfarin with or without 11 days of sitagliptin 200 mg qd
P023	383	238	27-76	Efficacy in monotherapy	MC, DB, R, PC, 100 mg, 200 mg or PBO (randomized 2:2:1) X 18 weeks
P025	9	3	21-40	Effect on simvastatin PK	R, open label, 2-period crossover 20 mg simvastatin with or without 5 days of sitagliptin 200 mg qd
P026	0	18	19-43	Effect on contraceptives PK and safety	Open label, 28-day study of triphasic EE2/NET with 200 mg (or PBO) X 21 days
P027	6	6	41-54	Bioequivalence between 2 forms of sitagliptin	Open label, R, 2-period, single 100 mg dose [redacted] , vs. monohydrate- final market image tablets)
P028	47	44	41-92	Safety in Chronic renal insufficiency	MC, DB, R, PC, 25 or 50 mg (versus PBO) X 12 wks (phase A) and 42-wk extension (PBO to glipizide)
P029	9	13	23-56	PK, effects of food on bioavailability	DB, fixed sequence, 3-period crossover with IV 25-100 mg (or PBO) (Part A) and 100 mg PO fasting, post-prandial and IV fasting (Part B)
P031	4	5	22-44	Effect on glyburide PK	R, open label, 2-period crossover 1.25 mg glyburide before or after 6 days of sitagliptin 200 mg qd
P032	43	43	18-47	Effect on QT interval	R, DB, PC, double dummy, 4-period crossover with single doses of 100 mg, 800 mg, 400 mg moxifloxacin or placebo
P033	5	5	23-45	PK dose proportionality	Open label, R, 5-period crossover with single doses of 25 - 400 mg
P034	8	4	21-44	Effect on rosiglitazone PK	R, open label, 2-period crossover 4 mg rosiglitazone before or after 5 days of sitagliptin 200 mg
P037	8	0	18-32	Effect of cyclosporin on sitagliptin PK	Open label, R, 2-period crossover, with single dose sitagliptin 100 mg following cyclosporin 600 mg or not
RC431	95	56	27-69	Efficacy in Japanese diabetics	MC, R, DB, PC, 100 mg vs. PBO X 12 weeks

DB: double-blind
R: randomized
PC: placebo-controlled
AC: active-controlled
SAD: single ascending dose
MC: multicenter
PBO: placebo

7.2.1.2 Demographics

The demographic characteristics of participant subjects in the Pooled Phase 2 studies P010 and P014 are shown in Table 124, and the demographic characteristics of those participating in the Pooled Phase 3 studies are shown in Table 125.

Table 124. Demographic characteristics of subjects in the Pooled Phase 2 Studies P010 and P014

		Placebo				Sitagliptin*				Glipizide (Study P010 only)	
		P010	P014	Total	%	P010	P014	Total	%	P010	%
Gender	Male	78	70	148	62.7	257	218	475	50.6	70	56.9
	Female	47	41	88	37.3	238	226	464	49.4	53	43.1
Race	Asian	3	1	4	1.7	22	2	24	2.6	6	4.9
	Black	10	8	18	7.6	31	26	57	6.1	4	3.3
	Multi-racial	9		9	3.8	32		32	3.4	8	6.5
	White	83	87	170	72.0	325	381	706	75.2	75	61.0
	Other	20	15	35	14.8	85	35	120	12.8	30	24.4
Age	Mean	55.3	55.9	55.6		55.5	55.4	55.5		54.7	
	SD	9.7	9.3	9.5		9.3	9.3	9.3		10.7	

* All doses combined

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Table 125. Demographic characteristics of subjects in the Pooled Phase 3 Population

Age(years)					
Treatment	N	Mean	SD	Median	Range
Sitagliptin 100 mg	1082	54.4	10.2	55.0	19.0 to 80.0
Sitagliptin 200 mg	456	55.2	9.7	56.0	18.0 to 75.0
Placebo	778	55.2	10.2	55.5	23.0 to 87.0
All	2316	54.8	10.1	55.0	18.0 to 87.0

Age Categories				
Treatment	<65 years N (%)	65 to 74 years N (%)	≥75 years N (%)	Total N
Sitagliptin 100 mg	896 (82.8)	175 (16.2)	11 (1.0)	1082
Sitagliptin 200 mg	374 (82.0)	81 (17.8)	1 (0.2)	456
Placebo	637 (81.9)	126 (16.2)	15 (1.9)	778
All	1907 (82.3)	382 (16.5)	27 (1.2)	2316

Gender			
Treatment	Male N (%)	Female N (%)	Total N
Sitagliptin 100 mg	598 (55.3)	484 (44.7)	1082
Sitagliptin 200 mg	221 (48.5)	235 (51.5)	456
Placebo	443 (56.9)	335 (43.1)	778
All	1262 (54.5)	1054 (45.5)	2316

Race						
Treatment	White N (%)	Black N (%)	Hispanic N (%)	Asian N (%)	Other N (%)	Total N
Sitagliptin100 mg	684 (63.2)	68 (6.3)	188 (17.4)	99 (9.1)	43 (4.0)	1082
Sitagliptin 200 mg	278 (61.0)	23 (5.0)	92 (20.2)	44 (9.6)	19 (4.2)	456
Placebo	483 (62.1)	54 (6.9)	136 (17.5)	70 (9.0)	35 (4.5)	778
All	1445 (62.4)	145 (6.3)	416 (18.0)	213 (9.2)	97 (4.2)	2316

SD = Standard Deviation.

From the applicant's Table 2.7.4: 9 Reference 2.7.4 Summary of Clinical Safety

In addition, Table 126 shows the distribution of subjects participating in individual studies that comprised the sitagliptin development, according to the disease or syndrome for which sitagliptin was being tested.

Table 126. Distribution of subjects exposed to sitagliptin in all clinical studies, according to the disease or syndrome in which sitagliptin was being tested

Study	Phase	Healthy	Chronic Renal Insufficiency	Hepatic Insufficiency	Hypertension	Diabetics
P001	1	34				
P003	1	38				
P004	1	70				
P005	1					58
P006	1	12				
P007	1	32				
P008	1	6	24			
P009	1	6				
P010	2					492
P010X1	2					80
P011	1				19	
P012	1	13				
P013	1	18				
P014	2					441
P015	2					28
P016	1	8				
P017	1			20		
P018	1	36				
P019	3					175
P020	3					464
P021	3					488
P022	1	12				
P023	3					411
P025	1	12				
P026	1	18				
P027	1	12				
P028	2					65*
P029	1	22				
P031	1	9				
P032	1	86				
P033	1	10				
P034	1	12				
P037	1	8				
RC431	2					75
Total		474	24	20	19	2777

* Diabetics with chronic renal insufficiency

7.2.1.3 Extent of exposure (dose/duration)

Table 73 and Table 75, in Section 7.1 above, show exposure data to sitagliptin in the Pooled Phase 3 Population and in the Pooled Long-Term Safety Population, respectively. The mean exposure to sitagliptin 100 mg in the Pooled Phase 3 Studies was 615.2 subject-years (1538 subjects treated for a mean 146 days, or 0.4 years) and the mean exposure to

sitagliptin 200 mg in the Pooled Phase 3 Studies was 169.6 subject-years (456 subjects treated for a mean 136 days).
In the Pooled Long-Term Safety Population, the mean exposure to sitagliptin 100 mg was 577 subject-years (429 subjects treated for a mean 491 days) and the mean exposure to 200 mg was 27.6 subject-years (27 subjects treated for a mean 373 days).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary sources of clinical data were submitted for review. The clinical reviewer conducted a literature search for evidence of safety concerns with sitagliptin or other DPP4 inhibitors.

7.2.2.1 Other studies

There were no additional studies conducted with sitagliptin, other than the ones reported under this application. This clinical reviewer has enriched the review of sitagliptin by comparing the data from the clinical studies to the data obtained from clinical studies investigating safety and efficacy of vildagliptin, a similar DPP4 inhibitor.

7.2.2.2 Postmarketing experience

Sitagliptin is not yet marketed anywhere in the world. Sitagliptin is the first DPP4 inhibitor submitted as a new drug application.

7.2.2.3 Literature

The applicant has provided relevant references to the review of sitagliptin. The clinical reviewer has also searched the medical literature for additional references to address specific issues of review, and these references are provided in footnotes and in the References section of this document.

7.2.3 Adequacy of Overall Clinical Experience

The sitagliptin clinical experience regarding extent and duration of exposure needed to assess safety is adequate, according to the ICH E1 guidance. ICH E1 mentions a total exposure of about 1500 subjects, with 300-600 for 6 months and 100 for one year for products intended to treat chronic conditions. The Division of Metabolism and Endocrinology Products has traditionally requested more substantive safety experience in

the development of products intended for the treatment of T2DM, for which the applicant generally complied with.
The design of studies intended to demonstrate the safety and efficacy of sitagliptin for the indications proposed (in monotherapy and in combination with PPAR agonists and with metformin) is adequate.
The applicant evaluated effects of sitagliptin in older subjects, in subjects with chronic renal insufficiency and in hepatic insufficiency, thus being able to provide a more comprehensive view of potential safety issues in these populations.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see Dr. Bourcier's toxicology review for details of the adequacy of preclinical testing of sitagliptin. In general, preclinical testing for sitagliptin was adequate, and an important toxicity study in monkeys is still ongoing at the time of this review.

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing performed routinely in the studies was adequate to elicit adverse events and other clinical, electrocardiographic and laboratory parameters that could represent a safety concern.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see Dr. Wei's Biopharmacology review for details on the adequacy of the sitagliptin PK evaluation program. The overall program is adequate to learn about the PK of sitagliptin and effects of meals and interactions with relevant classes of drugs. However, there is no significant experience of the concomitant use of sitagliptin with insulin and insulin analogs, and a limited experience with oral insulin secretagogues. This is an important issue because sitagliptin indirectly stimulates endogenous insulin and although the risk of hypoglycemia is small when used in monotherapy or in combination with insulin sensitizing drugs, the risk of hypoglycemia with other insulin secretagogues (that do not stimulate insulin secretion in a glucose-dependent manner) is unknown. This deficiency can be addressed as a post-marketing commitment.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant has adequately collected data on potential adverse events that could be resulting from exposure to any new drug/ drug class. For this purpose the applicant has

conducted a QT interval study and studies in chronic renal insufficiency and chronic liver dysfunction. In addition, the applicant planned for and gathered information on AEs expected based on mechanism of action (such as hypoglycemia, for insulin secretagogues). On the other hand, Study P028 isolated findings of increased serum creatinine (some with clinical significance) in a population with already impaired kidney function should have prompted a study to evaluate whether the kidney function has been impaired or the finding corresponds to an artifact (likely related to decreased creatinine tubular secretion). The fact that these individuals with an increase in serum creatinine of a greater magnitude did not have other accompanying laboratory signs of worsened renal function (increased BUN, decreased bicarbonate, for example) is reassuring, but does not obviate the lack of direct assessment of GFR in a controlled setting. The importance of this issue comes from the prevalence of renal impairment in T2DM, and the possible impact on the health of patients taking sitagliptin to achieve better glycemic control.

7.2.8 Assessment of Quality and Completeness of Data

The overall assessment of the application and study reports regarding the safety of sitagliptin is that sufficient data to assess risk to benefit profile of sitagliptin has been provided. Data that is as complete and of good quality is available for review, and the applicant provided in the study report important analyses of the safety data. More can be learned from postmarketing exposure to thousands (and possibly millions) more patients, particularly regarding sitagliptin risks in causing rare events.

7.2.9 Additional Submissions, Including Safety Update

Table 127 shows the cutoff dates for inclusion of safety data in the original application and in the 4-month safety update report (SUR). The SUR contains 1-year data from Studies P021 and P020, and these data partially overlap with the data obtained from the Pooled Long-Term Safety Population. There is no overlap in the listing of SAEs from the Worldwide Adverse Experience Surveillance (WAES) reports between the original application and the SUR.

Table 127. Reporting Periods for Safety Data in the Original Application and in the SUR

	Visit or Date Cutoff for the Original Application	Visit or Date Cutoff for the SUR
P021 (monotherapy study)	Visit 9 (Week 24)	Visit 13 (Week 54)
P020 (combination with metformin)	Visit 8 (Week 24)	Visit 12 (Week 54)
Pooled Long-Term Safety Population:		
P010	10-Oct-2005	10-Jan-2006
P014	10-Oct-2005	10-Jan-2006
P020	12-Oct-2005	10-Jan-2006
P021	12-Oct-2005	10-Jan-2006
WAES reporting	18-Oct-2005	03-Mar-2006

From the applicant's Table 2.7.4:2, reference 2.7.4 Summary of Clinical Safety

Deaths

From the date cutoff of the original application (10/18/05) to the cutoff date for the SUR (3/3/06) 7 subjects died post-randomization:

Protocol	Therapy	Subject ID #	Gender	Age at entry	Relative day of death	Cause of death	Relevant Med. Hx
Phase 3							
P020	Sitagliptin 100mg qd	33058	Female	58	519	"Ruptured myocardium"	Death not assessed clinically, radiologically or by autopsy. Hx of CAD, obesity HTN, tachycardia. Mixed sleeping pills and alcohol and found unconscious
P021	Sitagliptin 200mg qd	30005	Male	63	273	Mesothelioma	Dx day 5, painful respiration since 2004, asbestos exposure
P021	Sitagliptin 100 qd	30984	Male	68	324	Lung adenocarcinoma	Ex-smoker, Hx asthma and repeated URI
P010	Sitagliptin 100 qd	3515	Male	48	449	Acute myocardial infarction	Hx CAD, prior inferior MI, hypercholesterolemia
Ongoing Studies							
P024	Blinded	41249	Male	65	191	Polytraumatism	Bicycle accident
P028	Sitagliptin 25 mg	40485	Male	56	141	Death	Asystole during hemodialysis, Hx CAD, ESRD
P036	Blinded	48140	Male	50	70	Sudden cardiac death	HTN, died in bed
P035	Blinded	50727	Male	67	230	Suicide by morphine OD	Suicide attempt 2 years earlier

From the Table above, no conclusion can be reached as to an effect of sitagliptin being associated with these events.

SAEs

Study P021

In Study P021, the cumulative incidence of SAEs over the 1 year period was 8.4 % (20 of 238) in the sitagliptin 100 mg and 6.4 % (16 of 250) in the sitagliptin 200 mg groups. Only considering the 30 weeks of observation in the SUR, the incidence of SAEs was similar

among the 4 groups, between 3 and 5 %. Two subjects had serious psychiatric events: one had suicidal ideation and the other made a suicidal attempt. Both were treated with sitagliptin 100 mg and both had history of depression and these SAEs were precipitated by acute events. No new laboratory SAEs were reported in the SUR for Study P021.

Study P020
The rate of SAEs was similar between the groups in Study P020, with 6 % in the sitagliptin 100 mg (28 of 464) and 5.5 % in the placebo/ glipizide group (13 of 237). No specific SAE was observed more frequently in the sitagliptin-treated group. No laboratory SAEs were reported in Study P020 for the 30 weeks of the SUR.

Long-Term Safety Population
Cumulative rates of SAEs in the Long-Term Safety Population were similar among the treatment groups and no specific class or event was clearly more prevalent in either sitagliptin group.

AEs that led to discontinuation of study therapy
No patterns of specific AEs or classes of AEs can be established from the Study P020, P021 and Long-Term Safety Population reports that were likely caused by treatment with sitagliptin.

Common AEs
From the original application common AEs (defined as occurring at an incidence greater than 3 % and incidence higher than in the non-exposed [placebo, glipizide or metformin] group) included diarrhea, nasopharyngitis, upper respiratory tract infection, urinary tract infection, arthralgia and headache. In the SUR, only Study P020 and the Long-Term Safety Population maintained a control arm, so comparative incidences of common AEs can be noted.
Study P020
In the SUR, the only study with a controlled group was P020, where subjects on placebo during Phase A were switched to glipizide during Phase B. In that Study, taking into analysis all 54 weeks of study the following AEs and their incidence is reported in the Table below

AE	% Incidence sitagliptin	% Incidence non-exposed
Arthralgia	4.3	2.5
Cough	3.2	2.5
Influenza	6.0	5.9
Nasopharyngitis	6.3	4.2

The pattern of occurrence of these AEs during Phase B was similar to that of Phase A, and no new AEs were noted as a result of more prolonged exposure to sitagliptin.
Long-Term Safety Population
Two specific AEs (nasopharyngitis and arthralgia) had incidences increased by ≥ 1 % relative to the non-exposed group in the SUR compared to the original application. The

numbers are very small however: 4 additional subjects in each group (1 % in sitagliptin and 2.6 % in non-exposed) had nasopharyngitis in the period of SUR. The difference in overall cumulative incidence decreased for the sitagliptin groups compared to the non-exposed groups, as follows: 44 of 429 (10.3%, from 9.3 % in the original application) in the sitagliptin 100 mg, 1 of 27 (3.7%, the same as in the original application) in the sitagliptin 200 mg and 12 of 154 (7.8%, from 5.2 % in the original application) in the non-exposed group. For the AE of arthralgia the difference in incidence between the groups remained similar as it was in the original application, with 6 new cases in the sitagliptin 100 mg group and 2 new cases in the non-exposed group.
Three additional pregnancies occurred during the SUR reporting period, one resulting in spontaneous abortion and the other 2 having outcomes unknown at the time of writing of the report. The treatment was blinded, but the spontaneous abortion occurred in study P035, an investigation of the effect of sitagliptin or placebo as add-on to glimepiride, a sulfonylurea medication not used during pregnancy.

Changes in serum creatinine (mg/dL) from baseline to weeks 24 and 54 in Study P020

Sitagliptin 100 mg	Change from baseline to week 24	Change from baseline to week 54
Mean	0.0194245	-0.01459
Std Dev	0.2261332	0.2314454
N	417	329

Placebo / Glipizide	Change from baseline to week 24	Change from baseline to week 54
Mean	0.0164931	-0.011806
Std Dev	0.1898224	0.2285548
N	192	144

Changes in serum creatinine (mg/dL) from baseline to weeks 24 and 54 in Study P021

Sitagliptin 100 mg	Change from baseline to week 24	Change from baseline to week 54
Mean	0.009	0.0052632
Std Dev	0.2233122	0.2428729
N	200	133

Sitagliptin 200 mg	Change from baseline to week 24	Change from baseline to week 54
Mean	0.0398936	-0.004202
Std Dev	0.2043746	0.2271395
N	188	119

Placebo / Sitagliptin 100 mg	Change from baseline to week 24	Change from baseline to week 54
Mean	0.0067416	0.0109091
Std Dev	0.2275351	0.2322776
N	89	55

Placebo / Sitagliptin 200 mg	Change from baseline to week 24	Change from baseline to week 54
Mean	0.0168539	0.0296296
Std Dev	0.1966977	0.2088871
N	89	54

The changes in serum creatinine from week 24 to week 54 in the 2 studies with findings in the 4-month SUR are reassuring for the lack of continued mean increase in creatinine

levels. However the same small mean increase in serum creatinine is seen when subjects initially randomized to placebo during Phase A of Study P021 were switched to sitagliptin treatment.
No data are available in the 4-month Safety Update Report on the serum creatinine changes that occurred in subjects participating in Study P028.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The applicant has created a "problem list" of adverse events designated to be specifically investigated in the Phase 3 development studies of sitagliptin.

- Hypoglycemia

Hypoglycemic AEs are common in patients with T2DM using insulin and/or insulin secretagogues. GLP1 is an insulin secretagogue, although insulin release occurs in a glucose-dependent fashion. Nevertheless, the clinical studies of exenatide, a GLP1 analog have demonstrated more hypoglycemic events in a dose-dependent manner, as compared to subjects randomized to placebo.
In the Pooled Phase 3 Population, the incidence of hypoglycemic AEs and the proportion of subjects with such events were similar among those subjects treated with 100 mg or 200 mg of sitagliptin daily, as compared to placebo.

Table 128. Incidence and proportion of hypoglycemic AEs among the treatment groups in the Pooled Phase 3 Population

Treatment (mg qd)	Subjects exposed	# subjects with ≥ 1 episode	# of episodes	Subject -years	Total episodes / 100 subject-years	Difference in Proportions vs. control (%) (95% CI)	p-Value
Sita 100	1082	13	29	453	6.41	0.2 (-0.8, 1.2)	0.7
Sita 200	456	4	6	174	3.45	0.4 (-0.7, 1.5)	0.6
Control	778	7	8	310	2.58		

Of all the perceived hypoglycemic AEs, only a small proportion had documented blood glucose levels less than 60 mg/dL.

- Gastrointestinal AEs

Due to the known effects of GLP1 on slowing gastric emptying and the finding of increased proportion of nausea, vomiting and diarrhea in studies of Exenatide, in a dose-dependent manner, the applicant has carefully collected and analyzed gastrointestinal AEs in the Phase 2 studies. In the Pooled Phase 3 Population only nausea had a greater incidence in the sitagliptin groups (1.4 % and 2.9% in the sitagliptin 100 mg and 200 mg, respectively, compared to 0.6 % in placebo). A statistical comparison of the proportion of nausea between sitagliptin 200 mg- and placebo-treated subjects demonstrates significance (p=0.02). Except for one subject who discontinued study participation due to nausea, all reported improvement with continued treatment. There was no association between nausea, and more severe events of vomiting or weight loss.
Constipation was not among the symptoms subject to more intense monitoring and statistical analysis, but was observed slightly more frequently in the sitagliptin-treated

subjects in the Pooled Phase 3 Studies.

- Neurologic and skeletal muscle AEs

These were subject to more scrutiny during Phase 2 studies, due to findings in animal toxicity studies, but did not reveal any concern and were not tracked as tier one symptoms during Phase 3 studies.

- Infections

DPP4, the target for sitagliptin inhibition, is identical to a cell membrane protein in T-lymphocytes, with a role in cellular immunity. The applicant classified AEs of infection as of special interest to verify effects on T-cell immunity. Immunosuppressants causing decrease in T-cell function can increase rates of certain infections, such as tuberculosis, deep fungal infections and certain viral infections and reactivation of past infections. In the combined Phase 2 and Phase 3 sitagliptin program, these types of infections were not seen. However, a slight increase in the proportion of upper respiratory infections, including nasopharyngitis, pharyngitis, and bronchitis occurred among sitagliptin-treated subjects, compared to placebo in the pooled Phase 3 Studies (5.7 % vs. 4.1 %). The rates of herpes simplex reactivations were reported in low and similar proportions among the groups. In the Pooled Long-Term Safety Population, bronchitis, nasopharyngitis, upper respiratory infection and urinary infection were noted more frequently in sitagliptin subjects compared to those non-exposed. The severity, duration and number of episodes of these infections were similar across treatment groups. The rate of AEs was constant over time of exposure to sitagliptin and there were no cases of worsened respiratory infection over time, such as pneumonia or respiratory failure reported in the Pooled Long-Term Safety Population.

- Urticaria, angioedema and skin lesions

Substance P and bradykinin are substrates for DPP4, and DPP4 is present in high concentrations in bronchial serosal submucosal glands. Therefore it would be reasonable to investigate effects of sitagliptin on the incidence of cough and angioedema (similar to what is noted with angiotensin converting enzyme inhibition). There was no increase in cough, angioedema or lower respiratory infections with sitagliptin treatment.

The toxicology studies of other DPP4 inhibitors conducted in monkeys with exposure of 6 months or longer revealed necrotic skin lesions in tail, digits, ears, nose and scrotum. There were no clinical cases that would be equivalent to these lesions or vasculitis. The applicant is currently conducting a toxicology study in monkeys.

- Laboratory findings

Although dose-dependent decreases in mean alkaline phosphatase and transaminases were noted in the sitagliptin groups compared to placebo, these were not clinically relevant. Mean transient increases in uric acid, white cell counts and numbers of neutrophils, not dose dependent, were seen in the sitagliptin groups, but these also lack clinical relevance. Mean serum hemoglobin was decreased slightly more often in subjects treated with sitagliptin than on placebo, but the changes were of small magnitude and unlikely to be of clinical relevance.

The only laboratory finding that possibly deserves to be in the problem list is the observed increase in mean serum creatinine that occurred with relatively rapid onset, and was dose dependent. The magnitude of increase was small and unlikely to be clinically relevant, but for the subset of diabetics with chronic renal insufficiency the mean increase in serum creatinine by 0.1 mg could represent a significant loss of glomerular filtration rate. This was noted despite dose correction according to the baseline estimated creatinine clearance.

For the majority of diabetics, this mild increase in creatinine, not accompanied by other laboratory markers of worsening glomerular filtration rate (BUN, uric acid, acid/base imbalance, and phosphate), will not represent any risk. But for those patients who would be treated with a combination of sitagliptin and metformin and have mild renal impairment, this could raise the risk of lactic acidosis. The concern must be tempered by the small frequency of these events and the small magnitude of increase in creatinine; in addition, this could represent an impairment of creatinine tubular secretion, rather than a negative effect on renal function as measured by the glomerular filtration rate.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

This clinical reviewer analyzed the safety of the Phase 3 studies by examining the overall data pooled from the four Phase 3 studies. These studies not only contributed the major proportion of the experience with sitagliptin at the dose proposed for marketing, but was adequately controlled by both a higher dose of sitagliptin and by placebo. The safety database in Pooled Phase 3 Population is comprised of the same subjects that participated in each of Studies P019, P020 (combination therapy), P021 and P023 (monotherapy). The studies were designed in a way that allows pooling the data for more robust analyses of safety. The particular benefit is the ability to compare incidences of common AEs, or AEs that occur more frequently in diabetics.

Some AEs cannot be adequately assessed by examination of exposure to 18 or 24 weeks of sitagliptin treatment. The applicant therefore proposed to look at issues of safety (SAEs, common AEs, laboratory abnormalities and trends, vital signs and ECG data) in a subset of subjects exposed to sitagliptin 100 mg qd for periods of one year or longer. The Long-Term Safety Population not only can provide evidence of durability of efficacy (an important outcome in the treatment of a chronic condition) but also shed light on AEs that cannot be expected to become manifest or distinct enough in studies of 6 months duration or less. There are important disadvantages in the review of safety in the Long-Term Safety Population. The groups compared are not randomly selected, but represent subjects that agreed to continue in studies possibly because they tolerated sitagliptin better, had less AEs or greater improvement in glycemia. The groups are therefore not adequately balanced, either in numbers of subjects or in their important characteristics. Nonetheless, this dataset provides important information.

In comparing data between the Pooled Phase 3 Population and the Pooled Long-Term Safety Population, it is important to note that substantial overlap exists, and these subjects in the 2 datasets are by no means unique subjects.

7.4.1.2 Combining data

Data were combined across studies in these pooled datasets according to treatment group. In some instances the safety data from all doses of sitagliptin were combined and compared to placebo (or non-exposed subjects) for particular analyses. The only data that were analyzed separately originated from Study P028, an investigation of the safety of sitagliptin use in subjects with mild, moderate or severe renal insufficiency. The risk factors for a multitude of morbid complications and mortality are somewhat higher in this population compared to diabetics with normal renal function so that pooling the safety data originated from both populations may inappropriately dilute the evidence of risks in diabetes with chronic renal insufficiency.

7.4.2 Explorations for Predictive Factors

The clinical reviewer explored for predictive factors among demographic variables, dose, and time to event.

7.4.2.1 Explorations for dose dependency for adverse findings

Two large Phase 2 studies randomized diabetic subjects to doses between 10 and 100 mg of sitagliptin daily. There was no dose dependency for AEs observed in those studies. In 2 of the Phase 3 studies, the applicant investigated the 100 mg daily dose against the 200 mg daily dose. Nausea appears to be more prevalent in the higher dose group. The mean rise in serum creatinine was also dose dependent, at least for the first 24 weeks of exposure to sitagliptin. This may not represent an AE (see discussion above, under the general heading 7.3). Other laboratory findings were also dose dependent, such as reduction in serum alkaline phosphatase, AST and ALT, but these are not considered AEs.

7.4.2.2 Explorations for time dependency for adverse findings

There was no time dependency for AEs in the clinical studies. In other DPP4 inhibitors under development, it appears that the necrotic skin lesions were observed in a dose and time dependent manner. A long-term sitagliptin toxicology study is being conducted in monkeys to specifically investigate effects on the skin

7.4.2.3 Explorations for drug-demographic interactions

Age categories
There were no differences in proportion of AEs and SAEs among the age categories of younger than 65 years or 65 years and older. There was a slight increase in the SAEs in the older subjects compared to the younger subjects, but the proportion was similar between sitagliptin-treated and placebo-treated subjects. Furthermore there was no dose response in the incidence of SAEs and AEs, between the 100 mg group and the 200 mg group. A slightly greater proportion of subjects older than 65 years in the sitagliptin 100 mg group discontinued study participation due to AEs and SAEs, compared to subjects in the same age category in the other groups, but the proportions of discontinuations in all groups was small.

Gender
Females had a slightly greater incidence of common AEs, compared to males, but the increase was similar across the treatment groups. There was no increase in SAEs or discontinuations in either gender.

Race
Although an increase in incidence of investigator-classified drug related AEs was noted in black subjects treated with sitagliptin 200 mg daily (5/23), this is a very small subset to allow any conclusions on the safety of sitagliptin among racial categories.

7.4.2.4 Explorations for drug-disease interactions

Diabetics with a variety of comorbidities were randomized and treated with sitagliptin during the clinical studies. Some comorbidities are usually encountered in T2DM, such as hypertension (58% of Phase 3 subjects), hyperlipidemia (53%), coronary artery disease, and other vascular problems, but a number of other diseases in all system organ classes were listed for the study participants. There was no apparent interaction between sitagliptin and a particular condition that would pose a safety risk.
The effect of sitagliptin on serum creatinine, although mild, raises concern of potential worsening of renal function in diabetic patients with mild or moderate renal insufficiency (see discussion above).

7.4.2.5 Explorations for drug-drug interactions

In Study P028 investigating the safety of sitagliptin in subjects with chronic renal insufficiency, 3 of 65 subjects in the sitagliptin group had hypoglycemia (2 of these 3 subjects were on insulin, among 7 subjects in this group who were on insulin), and one of 26 subjects in the placebo group had hypoglycemia (a subject on insulin, with an episode considered of marked severity; 2 subjects in this group were on insulin).
In the absence of safety studies in combination with insulin, [redacted]

Hypoglycemia: [redacted]

Overall, sitagliptin has a low propensity to be involved in drug-drug interactions and there are no anticipated precautions for drug interactions.

In vitro study findings
In vitro, sitagliptin is not an inhibitor of cytochrome P-450 (CYP) enzymes and is not an inducer of CYP3A4, nor an inhibitor of p-glycoprotein. At concentrations up to 100 μM, sitagliptin does not meaningfully inhibit (IC_{50} >100 μM) any of the following CYP activities: CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. Sitagliptin is not a time-dependent inhibitor of CYP3A4 nor is it an inducer of CYP 3A4 in primary hepatocyte cultures. Sitagliptin is not an inhibitor of human p-glycoprotein.

Clinical study findings
Sitagliptin is not expected to cause clinically meaningful interactions with co-administered medications:
Since sitagliptin does not alter the pharmacokinetics of simvastatin, a CYP 3A4 substrate, it does not appear to inhibit CYP 3A4, the primary enzyme involved in simvastatin metabolism.
As sitagliptin does not alter S-warfarin or glyburide pharmacokinetics, it is not a CYP2C9 inhibitor. Clinically meaningful interactions with other sulfonylureas (glipizide, tolbutamide, glimepiride) would also not be expected since they undergo metabolism predominantly by CYP 2C9. However, there is at least a theoretical potential for hypoglycemic events when combining sitagliptin with oral insulin secretagogues.
Sitagliptin does not alter the pharmacokinetics of rosiglitazone, indicating inability to inhibit CYP2C8 metabolism. Since pioglitazone is primarily metabolized by CYP2C8 and CYP3A4, a meaningful interaction would also not be expected between pioglitazone and sitagliptin.
Since sitagliptin does not inhibit R-warfarin pharmacokinetics, the data are also consistent with a lack of inhibitory effect by sitagliptin on CYP 3A4, CYP 1A2 and 2C.
Sitagliptin does not alter the pharmacokinetics of oral contraceptives (estrogen and progesterone-based)
Sitagliptin does not alter the pharmacokinetics of metformin, a substrate of the human organic cationic transporter (hOCT) and is therefore not an inhibitor of hOCT.
Sitagliptin has a small but not likely clinically relevant effect on the pharmacokinetics of digoxin. No dose adjustment for either sitagliptin or digoxin is recommended. Sitagliptin

100 mg doses increased the digoxin AUC by approximately 11% and C_{max} by approximately 18% (slightly higher effects were seen at 200 mg). Sitagliptin did not have a meaningful effect on the renal clearance of digoxin. The mechanism responsible for this modest effect is not understood, but since sitagliptin does not inhibit p-glycoprotein mediated transport in vitro up to a concentration of 500 μM, it is thought that the mechanism of this interaction is not explained by inhibition of p-glycoprotein.
Based on clinical data, sitagliptin is not expected to be vulnerable to clinically meaningful drug interactions caused by co-administered medications:
In evaluating the potential clinical significance of drug interactions, up to a 2-fold effect of co-administered drugs on sitagliptin AUC or C_{max} has been defined as not being clinically meaningful. Since sitagliptin is primarily renally eliminated (approximately 75 to 80% of the dose excreted unchanged in urine), alterations in the metabolic pathways of sitagliptin (approximately 16% of the dose metabolized) are not expected to meaningfully affect the exposure of sitagliptin.
Metformin, an OCT substrate which is also primarily renally eliminated, does not alter the pharmacokinetics of sitagliptin.
Supratherapeutic 600-mg doses of cyclosporine, a probe p-glycoprotein inhibitor, increased sitagliptin AUC by approximately 29% and C_{max} by approximately 68%. The renal clearance of sitagliptin was not meaningfully altered suggesting that effects may have been due to enhanced absorption via inhibition of intestinal p-glycoprotein. Considering that therapeutic doses of cyclosporine would be expected to have more modest effects, this interaction is not considered likely to be clinically meaningful. Other p-glycoprotein inhibitors, likely exhibiting less potent effects than cyclosporine A, would also not be expected to meaningfully alter the pharmacokinetics of sitagliptin.
In the population pharmacokinetic analysis from Phase 2B dose range finding studies in subjects with T2DM, there was no clinically meaningful effect of 83 different co-administered drugs on MK-0431 pharmacokinetics, 46 of which are reported to be cleared substantially via renal elimination (≥ 50% of the parent compound or its metabolites)
This clinical reviewer also looked at the effect of sitagliptin in subjects using anti-cholinergic medications for the treatment of urinary incontinence or intestinal spasms on a chronic basis. The question asked was whether blockade of the vagal stimulation of GLP1 release from the L-cells in the distal small intestine would affect the overall effect of GLP1 on insulin secretion proximally and glucose control more distally. The magnitude of HbA1c reduction was similar in these subjects compared to subjects not using anti-cholinergic medications.

7.4.3 Causality Determination

Determination of causality must take into account various factors to different extents: the relative frequency of an AE compared to the control group, the timing of the event and the likelihood that such event would be allowed to manifest itself in that period of exposure, the investigator opinion after analysis of confounding circumstances and the biologic plausibility based on the mechanism of action.
The most likely AE caused by sitagliptin in the clinical studies presented in this application

is nausea. This AE was elicited in a dose dependent fashion and was present in subjects treated with Exenatide as well.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

A dose response in efficacy variables has been established in the sitagliptin clinical studies. Progressively greater mean declines in HbA1c from baseline were observed in subjects participating in the Phase 2 studies P010 and P014, in doses ranging from 5 mg bid to 50 mg bid in Study P010 and from 25 mg qd to 100 mg qd or 50 mg bid) in Study P014. The applicant, based on the results of these studies and the PK studies, selected the 100 mg qd dose for a thorough evaluation of efficacy in the Phase 3 program. Because the 100 mg dose provided about 80 % DPP4 inhibition, the applicant also tested a sitagliptin dose of 200 mg daily in the Phase 3 Monotherapy studies. Study P021 data demonstrated a dose response between the 100 gm and 200 mg, albeit not remarkable. In Study P023, however, the magnitude of mean decline in serum HbA1c was greater with the 100 mg daily dose, compared with the 200 mg. Because of these conflicting data, the very small overall difference in efficacy between the 2 doses, and the slightly higher rate of nausea with the 200 mg daily dose of sitagliptin, the applicant elected to market the 100 mg dose as the only dose for the general population with T2DM and normal renal function.

8.2 Drug-Drug Interactions

In Study P028 investigating the safety of sitagliptin in subjects with chronic renal insufficiency, 3 of 65 subjects in the sitagliptin group had hypoglycemia (2 of these 3 subjects were on insulin, among 7 subjects in this group who were on insulin), and one of 26 subjects in the placebo group had hypoglycemia (a subject on insulin, with an episode considered of marked severity; 2 subjects in this group were on insulin).
In the absence of safety studies in combination with insulin, [redacted]

Hypoglycemia: [redacted]

Overall, sitagliptin has a low propensity to be involved in drug-drug interactions and there are no anticipated precautions for drug interactions.

In vitro study findings

In vitro, sitagliptin is not an inhibitor of cytochrome P-450 (CYP) enzymes and is not an inducer of CYP3A4, nor an inhibitor of p-glycoprotein. At concentrations up to 100 μM, sitagliptin does not meaningfully inhibit (IC_{50} >100 μM) any of the following CYP activities: CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. Sitagliptin is not a time-dependent inhibitor of CYP3A4 nor is it an inducer of CYP 3A4 in primary hepatocyte cultures. Sitagliptin is not an inhibitor of human p-glycoprotein.

Clinical study findings

Sitagliptin is not expected to cause clinically meaningful interactions with co-administered medications:

Since sitagliptin does not alter the pharmacokinetics of simvastatin, a CYP 3A4 substrate, it does not appear to inhibit CYP 3A4, the primary enzyme involved in simvastatin metabolism.

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Sitagliptin does not alter the pharmacokinetics of oral contraceptives (estrogen and progesterone-based)

Sitagliptin does not alter the pharmacokinetics of metformin, a substrate of the human organic cationic transporter (hOCT) and is therefore not an inhibitor of hOCT.

Sitagliptin has a small but not likely clinically relevant effect on the pharmacokinetics of digoxin. No dose adjustment for either sitagliptin or digoxin is recommended. Sitagliptin 100 mg doses increased the digoxin AUC by approximately 11% and C_{max} by approximately 18% (slightly higher effects were seen at 200 mg). Sitagliptin did not have a meaningful effect on the renal clearance of digoxin. The mechanism responsible for this modest effect is not understood, but since sitagliptin does not inhibit p-glycoprotein mediated transport in vitro up to a concentration of 500 μM, it is thought that the mechanism of this interaction is not explained by inhibition of p-glycoprotein.

Based on clinical data, sitagliptin is not expected to be vulnerable to clinically meaningful drug interactions caused by co-administered medications:

In evaluating the potential clinical significance of drug interactions, up to a 2-fold effect of co-administered drugs on sitagliptin AUC or C_{max} has been defined as not being clinically meaningful. Since sitagliptin is primarily renally eliminated (approximately 75 to 80% of the dose excreted unchanged in urine), alterations in the metabolic pathways of sitagliptin

(approximately 16% of the dose metabolized) are not expected to meaningfully affect the exposure of sitagliptin.
Metformin, an OCT substrate which is also primarily renally eliminated, does not alter the pharmacokinetics of sitagliptin.
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This clinical reviewer also looked at the effect of sitagliptin in subjects using anti-cholinergic medications for the treatment of urinary incontinence or intestinal spasms on a chronic basis. The question asked was whether blockade of the vagal stimulation of GLP1 release from the L-cells in the distal small intestine would affect the overall effect of GLP1 on insulin secretion proximally and glucose control more distally. The magnitude of HbA1c reduction was similar in these subjects compared to subjects not using anti-cholinergic medications.

8.3 Special Populations

The clinical studies are representative of the intended patient population, by age, gender, race and BMI. Of particular note:

- Elderly patients (≥65 years of age) comprised 17.7 % of all patients in the Pooled Phase 3 Population (P019, P020, P021, & P023). [Total population n=2316] and comprised 15.9 % of the patients in the Pooled Long-Term Safety Population. [Total population n=610]
- Approximately 50% of the patients were obese to morbidly obese, with mean BMI ranging from 18.9 to 44.7 kg/m^2 (mean 31.2, median 30.7) in the Pooled Phase 3 Population (P019, P020, P021, & P023). [n=2313] and mean BMI ranged from 20.2 to 48.5 kg/m^2 (mean 31.2, median 30.7) in the Pooled Long-Term Safety Population. [n=609].
- The proportion of African American subjects enrolled in clinical studies of sitagliptin (a little over 6% of the total number of subjects) is low compared to the proportion of patients with T2DM in the US Population who are African American. While in this sample of the population there is no evidence of particular safety issues (in quality or quantity) or different magnitude of HbA1c reduction derived from these studies, there is evidence form the review of Exenatide of faster clearance of this GLP1 analog,

which resulted in a somewhat blunted efficacy in black subjects in their glycemic control.

- In addition to the 100 mg dose, the applicant proposes to market a 50 mg daily dose of sitagliptin for patients with for moderate renal insufficiency and creatinine clearance between 30 and 50 mL/min, and a 25 mg daily dose of sitagliptin for patients with severe renal insufficiency (as determined by creatinine clearance of less than 30 mL/min or for patients on dialysis. These doses were developed based on modeling of renal clearance rates in non-diabetic subjects with mild, moderate or severe impairment of renal function treated with a single 50 mg sitagliptin dose (Study P008) and expected exposure effects on overall inhibition of DPP4. In subjects on hemodialysis, sitagliptin was only modestly removed into the dialysate (13.5 % at 4 hours compared to 3.5 % at 48 hours post-dialysis), suggesting that sitagliptin can be dosed in these patients without respect to the timing of hemodialysis. The single trial of these doses of sitagliptin in T2DM subjects, Study P028, was planned and conducted with the goal of assessment of sitagliptin safety in the population of diabetics with chronic renal insufficiency. The study was not powered or implemented to assess effects of sitagliptin on glycemic control. Nonetheless, the study does show modest efficacy in the 12 weeks of treatment with sitagliptin, compared to placebo, in improving HbA1c, fasting and postprandial glucose levels. The magnitude of reduction of HbA1c from baseline to week 12 is similar to that observed with the same doses in diabetics without chronic renal insufficiency in studies P010 and P014 at the same duration of treatment (Table 129). However, efficacy and safety of higher doses has not been tested in this population. Thus we have no basis to determine that these doses will be the most desirable in their risk to benefit profile. Since there is consistent evidence of benefit in improvement of glycemic control, derived from reductions of HbA1c, fasting and post-prandial plasma glucose compared to the control group (albeit with a smaller magnitude) and only a small mean increase in serum creatinine of unclear clinical relevance, the risk to benefit profile is still favorable for approval of the 25 mg and 50 mg doses for patients with T2DM and chronic renal insufficiency. However, the sitagliptin labeling must reflect these data to inform physicians on the expected benefits and risks in this subpopulation of diabetics.

Table 129. Change in mean HbA1c (SD) from baseline to week 12 in studies P010, P014, and P028

	Population / N	Control	Sita 25 mg	Sita 50
Study P010	N	119	122	120
	T2DM	0.3 (0.9)	-0.4 (0.7)	-0.4 (0.8)
Study P014	N	107	107	107
	T2DM	0.2 (0.6)	-0.2 (0.9)	-0.4 (0.7)
Study P028	N	25	24	34
	T2DM + CRI*	-0.2 (0.7)	-0.5 (0.7)	-0.4 (0.6)
*Chronic renal insufficiency				

No special dosing has been proposed for liver insufficiency. Sitagliptin is eliminated primarily through the kidneys, and a PK study in non-diabetic subjects with moderate hepatic insufficiency (category B, with a score of 7 to 9 on the Child-Pugh's scale) did not demonstrate any change in PK parameters as compared with subjects with normal liver function. There are no data on effects of sitagliptin in patients with severe liver

dysfunction.
There have not been any clinical studies evaluating sitagliptin in pregnant women, including women with gestational diabetes, or lactating women; therefore, the safety of sitagliptin in pregnant women is not known. Sitagliptin is not recommended for use in pregnancy.

8.4 Pediatrics

Sitagliptin has not been studied in pediatric subjects, and treatment of children and adolescents under the age of 18 years is not recommended. In the cover letter annexed to this application, the applicant requested a deferral of the pediatric data requirements for these indications until a safety database in adults has been developed that is adequate to support pediatric trials. As the safety profile of sitagliptin in adults has been characterized in this NDA, studies evaluating its efficacy and safety in the treatment of children and adolescents with T2DM should be conducted. Given the rise in the proportion of patients with T2DM under the age of 18 years in the US and in the rest of the world, these studies are essential.

8.5 Advisory Committee Meeting

The Division of Metabolic and Endocrine Products felt that consultation with the Endocrinologic and Metabolic Advisory Committee would not be necessary for the following reasons:

- Although sitagliptin is a new molecular entity, the sole mechanism of action to benefit patients with T2DM relies on enhancement of endogenous GLP1. A GLP1 analog, given in pharmacologic doses, has been recently approved for use in T2DM, and its safety and efficacy profiles have been well established in the intended population.
- The review of data from clinical studies did not raise specific questions on aspects of safety or efficacy for the population of diabetics as a whole or for specific subsets.

8.6 Literature Review

A literature review was conducted and relevant findings were summarized in Section 2.6 and in specific discussion of issues throughout this document.

8.7 Postmarketing Risk Management Plan

The applicant will continue to monitor the safety of sitagliptin in ongoing nonclinical studies, clinical trials and through routine pharmacovigilance.

Action Plan for Safety Concerns

Potential for sitagliptin to cause necrotic skin lesions in monkeys

Studies in monkeys are ongoing, but at least preliminary findings suggest that the necrotic skin lesions are not present in sitagliptin-treated monkeys and are present in less specific DPP4 inhibitors that have non-selective inhibition of DPP-8 and DPP-9.

AEs of special interest

The AEs of special interest, hypoglycemia and selected gastrointestinal events, and the selected laboratory findings, uric acid, alkaline phosphatase, and absolute neutrophil count, will be followed by routine post-marketing surveillance. Routine surveillance is appropriate for these laboratory findings because there were no recognized associated clinical sequelae in the clinical trials. Also, the applicant plans to monitor these AEs of special interest in ongoing and planned clinical trials. This clinical reviewer would strongly recommend continued monitoring of serum creatinine levels in ongoing and future studies of sitagliptin so that a better understanding of the mechanism involved in the elevation of creatinine is attained.

Exposure during pregnancy

Sitagliptin will be used in women of childbearing potential with the possibility of exposure to a developing fetus. In order to develop a better assessment of the safety profile of sitagliptin in pregnant women, the applicant proposes that pregnancy exposure to sitagliptin be followed through routine pharmacovigilance practices and via the establishment of a pregnancy registry for more intensified follow-up of pregnancy exposures.

A report summarizing the cumulative outcomes of pregnancy and congenital anomaly reports received by the applicant is written at product launch and updated annually. An outside expert in teratology is available to review data from the registry, as needed.

The pregnancy registry for sitagliptin will be operational in the United States. The data will be analyzed continually as it is received and will be compiled on an annual basis.

Unanticipated Safety Signals

Data from clinical trials cannot always predict rare AEs which may only become evident after being used in a larger number of patients with a greater range of co-morbid conditions. Unanticipated safety signals will be monitored through routine pharmacovigilance.

Ongoing and Planned Trials Yielding Additional Safety Information

A list of ongoing and planned clinical studies of sitagliptin is provided by the applicant. These studies are expected to involve [redacted] over the next few years.

No risk minimization plan is proposed, as no major issues related to safety were identified in the clinical studies; sitagliptin is not a drug with known psychotropic, mood-altering or analgesic properties; tablet properties (e.g., color, shape, size) were developed to minimize confusion with other commonly used oral diabetic agents and products in therapeutic classes of drugs routinely used by diabetic patients.

Risk minimization is primarily accomplished with the use of risk communication, through prescriber information for the health care professional and the patient package insert for the consumer.

8.8 Other Relevant Materials

Not applicable.

9. OVERALL ASSESSMENT

9.1 Conclusions

The pathogenesis of T2DM is based on 3 linked but separate disorders: insulin resistance, progressive beta cell failure and hepatic glucose overproduction. While multiple treatment modalities are now available for the treatment of this condition, many patients remain under poor glycemic control and are more prone to the chronic complications of diabetes. Incretins such as GLP1 and GIP are released during oral ingestion of glucose, but not after intravenous glucose infusion, and stimulate insulin release in a glucose-dependent fashion. These incretins also inhibit glucagon release and slow the rate of gastric emptying. The sum of these effects on insulin and glucagon release contributes to the limited rise in glucose after meals in non-diabetics. Patients with T2DM have decreased effects of incretins, with blunted GLP1 secretion and beta cell resistance to GIP. GLP1 has a very short plasma half life, being rapidly inactivated by the enzyme DPP4. Exenatide is a recently approved analog of GLP1, resistant to the effect of DPP4. Exenatide was shown to induce improvement in glycemic control in combination with other anti-diabetic agents. Sitagliptin is a potent and specific inhibitor of DPP4, and exerts its effect through enhancement of GLP1 (and GIP) activity.
The Phase 2 and Phase 3 clinical studies and their extensions conducted in subjects with T2DM provide substantial evidence of dose-dependent efficacy in improving glycemic control with durable benefit. Placebo-subtracted HbA1c reductions in the range of 0.6 to 0.8 % were observed in studies where sitagliptin at 100 mg daily was tested in monotherapy as well as in studies of subjects with poor glycemic control with metformin or pioglitazone. The reductions in HbA1c where more pronounced in subjects with higher baseline HbA1c. The efficacy of sitagliptin in reducing HbA1c and both fasting and 2-hour post-meal plasma glucose has been demonstrated in both indications sought by the applicant: use in monotherapy and use in combination with either metformin or a thiazolidinedione. The Phase 3 studies of sitagliptin use in monotherapy tested both a 100 mg and a 200 mg daily dose against placebo. In one of the studies the 200 mg dose appeared to be more effective but the other study had opposite results, with the 100 mg dose being more effective in reducing HbA1c, fasting and post-prandial glucose. Additional studies confirmed that improvement in glycemic control result from improved beta cell function, with glucose-dependent insulin release particularly effective in reducing post-prandial rises of plasma glucose. In contrast to the effect of sulfonylureas and insulin itself, sitagliptin does not cause hypoglycemia or weight gain. It is important to note that sitagliptin acts by stimulating endogenous release of insulin, and if used in combination with other insulin secretagogues, may cause hypoglycemia even in patients who may have not had this AE with the insulin secretagogue alone (a finding from the review of clinical studies with exenatide).

The safety of sitagliptin has been well characterized in these studies, as well as in pharmacokinetic studies conducted in special populations. Sitagliptin treatment may be associated with a small risk of upper respiratory infections and cough, arthralgia, nausea and urinary infections, but the proportion of subjects experiencing these AEs was only slightly higher than that of control subjects. Some clinical laboratory findings are noteworthy: mean serum alkaline phosphatase decreased in a dose dependent manner, without achieving mean stable levels at one year, and transient increases serum uric acid and in white blood cell counts. Mean serum creatinine also had transient, non-clinically significant and dose-dependent increases in the general population of subjects with T2DM, but was increased in some diabetic subjects with chronic renal insufficiency to a magnitude that could be associated with decreased renal function.

9.2 Recommendation on Regulatory Action

This clinical reviewer recommends the approval of sitagliptin at a dose of 100 mg daily for both indications sought by the applicant, and the reduced doses of 25 or 50 mg for diabetic patients with chronic renal insufficiency that are not using other anti-diabetic medications.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

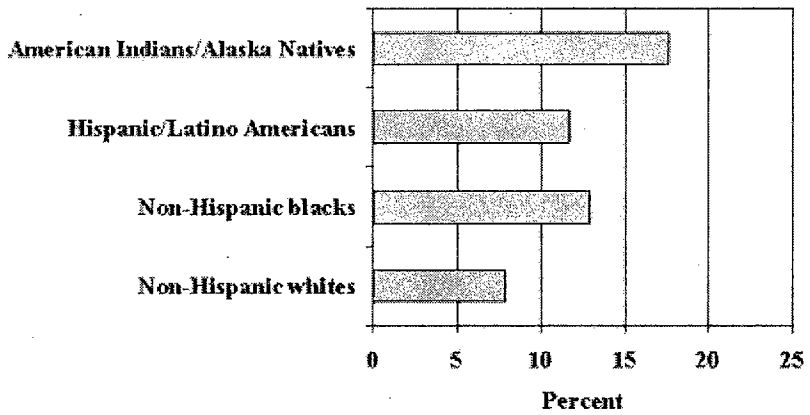
The applicant plans for both pharmacovigilance and the proposed pregnancy registry are adequate. The effect of sitagliptin on parameters of renal function, including assessment of serum creatinine levels and indicators of glomerular filtration, should be monitored in diabetic patients with moderate or severe renal insufficiency.

9.3.2 Required Phase 4 Commitments

1) Given the prevalence of patients treated with insulin or insulin secretagogues in the population of T2DM, the applicant will need to conduct clinical studies to determine both the efficacy and the safety of sitagliptin when added on to therapeutic regimens employing insulin and insulin secretagogues. If sitagliptin is to be used in patients already on insulin, insulin analogues or secretagogues (such as meglitinides or sulfonylureas) it is essential to determine the safety of the combination and in particular the risks of prolonged hypoglycemia resulting from the added sitagliptin-induced insulin secretion and suppression of endogenous glucagon secretion.
2) African-Americans were underrepresented in the clinical studies conducted and reviewed in this NDA. They constituted 6.2 % of 1538 subjects participating in Phase 3 studies (about 92 subjects, and even less exposed to the recommended dose of 100 mg

daily). The proportion of African-Americans with T2DM in the United States is far greater (see Figure 34). Therefore, in order to determine the safety and efficacy of sitagliptin in this racial group, an additional controlled study needs to be conducted.

Figure 34. Age-adjusted total prevalence of diabetes in people aged 20 years or older, by race/ethnicity -United States, 2002



Source: 1999–2001 National Health Interview Survey and 1999-2000 National Health and Nutrition Examination Survey estimates projected to year 2002. 2002 outpatient database of the Indian Health Service.

3) The recent rise in the proportion of children and adolescents with T2DM requires demonstration of the safety of sitagliptin in this population, particularly in its effects on linear growth. In the cover letter annexed to this application, the applicant requested a deferral of the pediatric data requirements for these indications until a safety database in adults has been developed that is adequate to support pediatric trials.

9.3.3 Other Phase 4 Requests

1. There is evidence of increased serum creatinine that occurs during treatment with sitagliptin. The increase is slight and very likely not associated with any clinical implications for patients with normal renal function. The magnitude of increase in serum creatinine was larger in a small study of sitagliptin in subjects with both T2DM and varying degrees of chronic renal insufficiency, but not associated with other parameters (clinical or laboratorial) indicating worsening of renal function. The applicant interprets these results as possibly related to effects of sitagliptin in reducing creatinine tubular secretion. Better characterization of sitagliptin effects on serum creatinine and glomerular function would be desirable and clinically relevant: this request could be satisfied by a pharmacokinetic dose-response study to investigate whether the increase in serum creatinine found in clinical studies is related to inhibition of active tubular secretion or to a decrease in glomerular filtration rate, the latter with clinical consequences.
2. Clinical studies also indicated a trend in decreasing mean serum alkaline phosphatase levels over time, without evidence of stabilization or reversal of this trend. The changes were related to both components (bone and liver) of alkaline phosphatase. Continuous

monitoring of serum levels of alkaline phosphatase in ongoing and future studies may determine whether alkaline phosphatase becomes stable or continues to decrease. If the latter is true after a period of one or two years of treatment, a pre-clinical study with serial bone biopsies or a clinical study that could assess for adynamic bone disease in a non-invasive fashion would be needed.

9.4 Labeling Review

The Division of Medication Errors and Technical Support (DMETS) has reviewed the proposed trade name Januvia and considered the name unacceptable. This conclusion was based on a potential for confusion with the trade name Tarceva (erlotinib), when scripted. The two medications also share a common dose of 100 mg daily administered orally, and the possibility of administration without food (sitagliptin can be given with or without food). This reviewer considers the trade name Januvia acceptable.
The Office of Surveillance and Epidemiology also reviewed the Patient Package Information and had proposed some minor revisions, mostly related to standard language and consistency with the Patient Counseling Information section in the PI.
This reviewer recommends adding to the label information regarding the small increase in mean serum creatinine among subjects treated with sitagliptin, particularly among those diabetics with chronic renal insufficiency, and the advice to monitor serum creatinine in order to adjust the sitagliptin dose, if needed. For additional proposed changes in labeling, please refer to the line-by-line review in the Appendix (Section 10.2).

9.5 Comments to Applicant

None.

10. APPENDICES

10.1 Review of Individual Study Reports

The four Phase 3 studies investigating the use of sitagliptin as monotherapy or in combination with other anti-diabetic agents were extensively reviewed and presented in Sections 6 and 7 of this document. Study P028, investigating the use of lower doses of sitagliptin in subjects with chronic renal insufficiency, was also reviewed and had the efficacy and safety data presented in Sections 6 and 7, respectively. The Phase 2 studies P010, P014, P015 and RC431A201 were reviewed and only a summary of their pertinent

data were presented as comparison to the Phase 3 data for efficacy. These Phase 2 studies and their extensions beyond the original double-blind, placebo-controlled 12-week studies, also provided important safety information that was presented as the Pooled Long-Term Safety Population in Section 7 of this document.
Therefore only Phase 2 studies P010 and its extension, P014 and its extension, P015 and RC431A201 will be briefly summarized here.

10.1.1 Study P010

Study Design
This is a multicenter, randomized, placebo- and active-controlled, dose-ranging study of sitagliptin in subjects with inadequate control of T2DM. The study enrolled 743 subjects (of 2186 screened) in 83 centers in the United States and 46 centers internationally. The randomized, placebo-controlled phase of the study was 12 weeks long and started on July 18th 2003 and ended on August 25th, 2004. The primary objective of the study was to evaluate the effect of doses of sitagliptin ranging from 5 mg bid to 50 mg bid on parameters of glycemic control, as compared to placebo or to glipizide. Safety and tolerability, incidence of hypoglycemia and effects on weight were other goals of the study. To be eligible, a patient with T2DM must had been between 21 and 75 years of age, and had a HbA1c $\geq$ 6.5 and < 10 % either at their first visit or after wash out of other anti-diabetic medications. Prior to randomization, each subject underwent a diet and placebo run in period of up to 10 weeks. Subjects deemed eligible were randomized in a 1:1:1:1:1:1 ratio to receive either placebo, sitagliptin 5 mg bid, sitagliptin 12.5 mg bid, sitagliptin 25 mg bid, sitagliptin 50 mg bid or glipizide. Those randomized to glipizide were started on 5 mg qd and their dose was uptitrated to 10 mg bid, as necessary to control glycemia. For a figure of study design, please refer to the left part of Figure 35, labeled as "Base Study". The primary endpoint was the change in HbA1c from baseline to week 12. Secondary endpoints included FPG, fructosamine, average capillary glucose from a 7-point self blood glucose monitoring (SBGM), post-MTT (in a subset of subjects undergoing meal tolerance test), and body weight. There were multiple exploratory endpoints related to parameters of insulin secretion and sensitivity, appetite/satiety (measured by questionnaire to subjects) and changes in lipids and free fatty acids. The primary analysis method for the change in HbA1c was an ANCOVA model with terms for treatment, prior anti-diabetic medication stratum (on or off medications at screening), and baseline value as covariate.

Subject disposition
Please refer to Table 82 in this review document.

Efficacy Results
Reduction in mean HbA1c occurred in all active treatment groups. Among the sitagliptin groups, there was a dose proportional response, except for the absence of a step up between 12.5 mg bid and 25 mg bid (Table 130).

Table 130. HbA1c changes in Study P010

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	7.9 (1.0)	8.1 (1.2)	0.3 (0.9)	0.2	(0.1, 0.4)	<0.001
Sita 5 mg bid	122	7.9 (0.9)	7.8 (1.2)	-0.1 (0.8)	-0.1	(-0.3, 0.0)	0.031
Sita 12.5 mg bid	122	7.8 (0.9)	7.5 (1.0)	-0.4 (0.7)	-0.4	(-0.6, -0.3)	<0.001
Sita 25 mg bid	120	7.9 (0.9)	7.5 (1.1)	-0.4 (0.8)	-0.4	(-0.6, -0.3)	<0.001
Sita 50 mg bid	121	7.8 (1.0)	7.3 (1.0)	-0.5 (0.7)	-0.5	(-0.7, -0.4)	<0.001
Glipizide	119	7.8 (1.0)	7.1 (0.9)	-0.7 (0.8)	-0.8	(-0.9, -0.6)	<0.001

The best dose of sitagliptin from this study was the 50 mg bid, with a placebo-subtracted HbA1c reduction (95% CI) of -0.77 % (-0.96, -0.58). Glipizide was superior to sitagliptin in reducing HbA1c ($p < 0.03$). In reference to the secondary endpoints, sitagliptin achieved statistically significant reductions in fasting plasma glucose, fructosamine and the average 7-point assessments from the SBGM, compared to placebo. The sitagliptin effect on body weight was neutral.

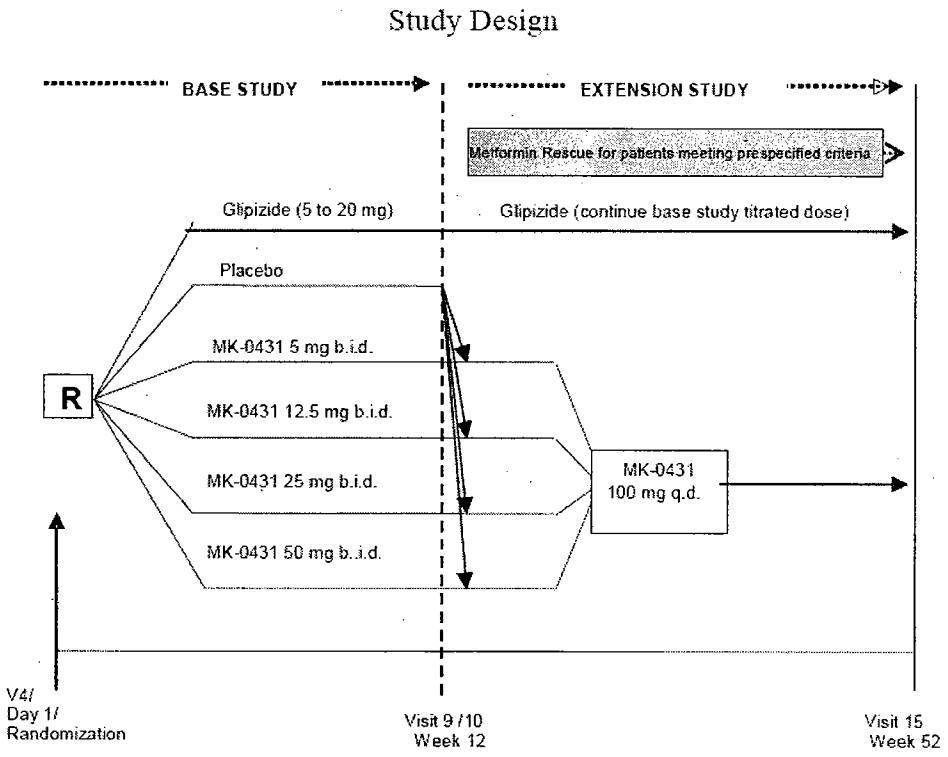
Safety

No deaths, drug-related SAEs or serious laboratory drug-related AEs occurred. Hypoglycemia was the most common drug-related AE, observed in the glipizide group with incidence of 14.6%, compared to 2% in placebo and between 0 and 3 % in the sitagliptin dose groups. Three subjects on glipizide discontinued due to SAEs, deemed not drug-related by the investigators. The profile of AEs and SAEs in this study was similar to the profile described in the Phase 3 studies, under Section 7 of this review document.

10.1.2 Study P010X1

This study is the 40-week extension to study P010. The study was conducted from October 30th, 2003 until May 30th, 2005 in 59 centers in the US and 39 centers outside the US. All subjects completing Visit 9 of the base study at week 12 were offered participation in the extension study. The primary goal of the study was to evaluate the long-term (52 weeks) safety and efficacy of sitagliptin. Subjects who had been randomized to sitagliptin at one of the 4 doses (5 mg bid, 12.5 mg bid, 25 mg bid or 50 mg bid) in the base study were to continue on the same dose during Study P010X1. Subjects randomized to placebo that elected to continue participation in the extension were re-randomized to one of the 4 doses of sitagliptin, while subjects randomized to glipizide in the base study were to continue treatment with glipizide. After review of results in the base study, the applicant modified Study P010X1, so that all subjects being treated with sitagliptin at any dose would be switched to 100 mg qd (termed by the applicant "dose collapse"). Subjects on glipizide were to receive a matching placebo to sitagliptin to maintain blinding. The "dose collapse" occurred usually at the subject's next scheduled extension study visit to the center or at an unscheduled visit, if considered appropriate by the investigator. For a schema of the study design, please refer to Figure 35.

Figure 35. Design of Study P010 and its extension P010X1



From the 743 subjects in study P010, 509 continued in the extension study. Subjects discontinued participation in Study P010X1 at similar proportions among the treatment groups. Of the 509 who entered the extension study 362 subjects are currently continuing on a second extension study (Study P010X2), which is ongoing. The study, being not randomized, had no hypothesis being tested, but the study endpoints continue to be HbA1c and other parameters of glycemic control. Coefficient of durability is an endpoint defined by the applicant as the slope of change in HbA1c from week 25 to week 52 in the 2 treatment groups.

Results

Treatment groups including sitagliptin 5 mg bid, 12.5 mg bid and 25 mg bid had mean reductions in HbA1 after their dose was switched to sitagliptin 100 mg qd. The sitagliptin 50 mg bid / 100 mg qd group had maximal effect on HbA1c at week 8 (-0.53 % reduction). After week 16, mean HbA1c rose, with maintenance of 72 % of the maximal treatment effect by week 52. The glipizide group achieved maximal mean HbA1c reduction at week 16 (-1 %) with subsequent rise. At week 52, 66% of the maximal mean effect of glipizide on HbA1c had been maintained. The calculated coefficients of durability of sitagliptin and glipizide were 0.005% per week and 0.009 % / week, respectively. When these analyses were conducted among completers (subjects with a week 52 measurement), the change in HbA1c from week 12 to week 52 was smaller (-0.65 % from baseline to -0.61% from baseline) in the sitagliptin group, and the coefficient of durability was -0.002 % / week. In contrast, the completers in the glipizide group showed a faster rate of deterioration in

glycemic control from week 16 (mean -1.06 % from baseline) to week 52 (-0.79 % from baseline), with a calculated coefficient of durability of 0.003% / week.
Safety of sitagliptin treatment for 52 weeks has been extensively described in Section 7, as part of the Long-Term Safety Population.

10.1.3 Study P014

Study Design
This is the other significant Phase 2, multicenter, randomized, placebo-controlled, parallel-group, dose-range finding study of sitagliptin in subjects with T2DM. The study enrolled 555 subjects (out of 1322 screened) in 59 centers in the United States and 65 centers internationally. The placebo-controlled, randomized phase of the study was 12 weeks long. The study started on September 23, 2003 and ended on July 21, 2004. The objectives of the study were to assess the effects of sitagliptin given once daily on parameters of glycemic control and to compare the effects of sitagliptin 50 mg bid to sitagliptin 100 mg qd dosing on these parameters. Other objectives include the assessment of sitagliptin safety and tolerability, changes in body weight, and leukocyte gene expression in microarray patterns, with more detailed genetic analyses in Icelandic diabetic subjects. To be eligible, male and female diabetics between the ages of 21 and 75 years would need to have HbA1c $\geq$ 6.5 % and < 10 % at screening (if on no other therapy) or at the randomization visit (after careful wash out of their prior therapy and a period of diet and exercise enforcement). All subjects had a 2-week, single-blind, placebo run-in period preceding the randomization and the 12-week double-blind, placebo-controlled phase. Eligible subjects were randomized 1:1:1:1:1 to receive either placebo or one of four doses of sitagliptin (25 mg qd, 50 mg qd, 100 mg qd or 50 mg bid). For a figure of study design, please refer to the left part of Figure 36, labeled as "Base Study". The primary endpoint was the change in HbA1c from baseline to week 12. Secondary endpoint included FPG, fructosamine, average capillary glucose from a 7-point self blood glucose monitoring (SBGM), and body weight. The primary analysis method for the change in HbA1c was an ANCOVA model with terms for treatment, prior anti-diabetic medication stratum (on or off medications at screening), and baseline value as covariate.

Subject disposition
Please refer to Table 84 in this review document.

Efficacy Results
Reduction in HbA1c compared to placebo occurred in all active treatment groups.

Table 131. HbA1c changes in Study P014

		Mean		Change from baseline			
Treatment	N	Baseline (SD)	Week 12 (SD)	Mean (SD)	LS Mean	95% CI for LS Mean	Within-Group p-Value
Placebo	107	7.6 (0.9)	7.8 (1.1)	0.2 (0.6)	0.1	(0, 0.3)	0.102
Sitagliptin 25 mg qd	107	7.7 (0.9)	7.5 (1.3)	-0.2 (0.9)	-0.3	(-0.4, -0.1)	<0.001
Sitagliptin 50 mg qd	107	7.6 (0.9)	7.2 (1.0)	-0.4 (0.7)	-0.4	(-0.6, -0.3)	<0.001
Sitagliptin 100 mg qd	106	7.8 (0.9)	7.4 (1.1)	-0.4 (0.8)	-0.4	(-0.6, -0.3)	<0.001
Sitagliptin 50 mg bid	108	7.8 (0.8)	7.4 (1.1)	-0.4 (0.8)	-0.4	(-0.6, -0.3)	<0.001

Adapted from the applicant's Table 7-1, reference P014

In this study the differences in effect among doses were less clear, particularly among the cohorts of 50 mg and 100 mg overall daily doses in the ITT analysis. The step ups of the mean estimates among doses were slightly clearer among completers. Nonetheless, the applicant demonstrated that, consistent with expected PK/PD findings, there were no differences in effect in dosing 100 mg of sitagliptin once daily or twice daily. Compared to placebo, statistically significant reductions in fasting plasma glucose, fructosamine, and average 7-point assessments from the SBGM were observed in the data analyses of both ITT population and completers populations. The effect of sitagliptin on body weight was neutral.

Safety

There were no deaths in this study. Two SAEs were reported in the placebo group (1.8%): squamous cell carcinoma and small intestinal obstruction. One SAE was reported in the 25 mg sitagliptin: atrial fibrillation. Three SAEs were reported in the 50 mg group: one myocardial infarction, and two accidental overdoses. Three subjects has SAEs in the sitagliptin 100 mg group: one drug abuser and suicide attempt, one with pancreatitis and ileus (on days 37 and 50, respectively) diagnosed with colon cancer on day 67, and one with acute renal failure on day 59. Three subjects reported SAEs in the sitagliptin 50 mg bid group: intermittent claudication (day 85), acute cholecystitis (day 80) and psoriasis (day 25). AEs of hypoglycemia were reported in 2 subjects in the 100 mg dose group, and 1 subject in each of the other sitagliptin groups, and none in the placebo group. Overall the AE profile of sitagliptin in this study reflects the profile described in the Phase 3 studies, under Section 7 of this review document.

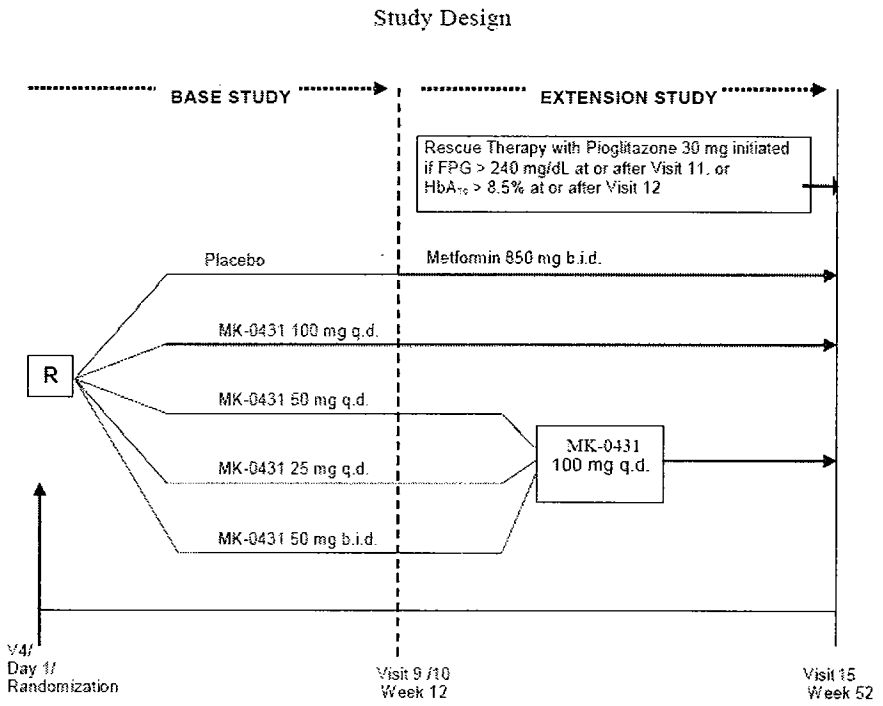
10.1.4 Study P014X1

Study design

This study is the 40-week extension to study P010. The study was conducted from December 23rd, 2003 until May 9th, 2005 in 41 centers in the US and 31 centers outside the US. All subjects completing Visit 9 of the base study at week 12 were offered participation in the extension study. The primary goal of the study was to evaluate the long-term (52 weeks) safety and efficacy of sitagliptin. Subjects who had been randomized to sitagliptin at one of the 4 doses (25 mg qd, 50 mg qd, 100 mg qd or 50 mg bid) in the base study were to continue on the same dose during Study P014X1. All these subjects were later switched to sitagliptin 100 mg qd, after review of the base study data and approval of the "dose collapse". Subjects randomized to placebo in the base study were switched to metformin

850 mg qd, uptitrated to 850 mg bid. These subjects, in addition to receiving metformin, also received placebo to sitagliptin in order to maintain blinding. From the 555 subjects in the base study, 338 entered the extension study. For a schema of the study design, please refer to Figure 36.

Figure 36. Design of Study P014 and its extension P014X1



Subjects discontinued participation in Study P014X1 at similar proportions among the treatment groups. Of the 338 who entered the extension study 274 subjects completed the 40 weeks of study and 225 are currently continuing on a second extension study (Study P014X2), which is ongoing. The study, being not randomized, had no hypothesis being tested, but the study endpoints continue to be HbA1c and other parameters of glycemic control. Coefficients of durability and their 95 % CI are calculated, similarly to P010X1.

Results

Changes in HbA1c from baseline of Study P014 until week 52 of the extension Study P014X1 are shown in Table 132. The table shows the changes reported in HbA1c with and without imputation of missing data by LOCF, only in the 2 sitagliptin groups with a 100 mg total daily dose (50 mg bid /100 mg qd and 100 mg qd / 100 mg qd), and the placebo group which started metformin therapy at week 12, for 40 weeks.

Table 132. LS Means changes in HbA1c from baseline in Study P014 to week 52 in the extension Study P014X1 with and without imputation of missing data by LOCF

	With LOCF imputation		Without LOCF imputation	
Treatment	N	LS mean change from baseline (SE)	N	LS mean change from baseline (SE)
Sita 100 mg qd/100 mg qd	65	-0.3 (0.1)	43	-0.4 (0.1)
Sita 50 mg bid/100 mg qd	69	-0.1 (0.1)	44	-0.5 (0.1)
Placebo/metformin	62	-0.4 (0.1)	44	-0.5 (0.1)

Adapted from the applicant's Table 11-4, reference P014X1

The differences noted between the analytical methods are remarkable, in part due to the small overall numbers and in part due to the absence of data from a substantial number of subjects with missing data or who had to receive glycemic rescue therapy.

There was a dose proportional reduction in HbA1c and fasting plasma glucose from week 12 until week 25, the last time point for all subjects before the doses of sitagliptin in the 25 mg qd, 50 mg qd and 50 mg bid groups were collapsed to 100 mg qd.

The coefficients of durability of the effect (slope of HbA1c from week 25 to week 52 are 0.006 %/ week for the 100 mg qd / 100 mg qd group and 0.008% / week for the 50 mg bid / 100 mg qd group., with their positivity indicating arise of HbA1c levels and a loss of the maximal effect on HbA1c. The control group treated with metformin during the extension study had a mean reduction in HbA1c after 13 to 22 weeks of treatment (weeks 25 and 34 in the overall study) with a loss of effect at a rate similar to the sitagliptin groups thereafter until week 52.

There were no deaths during the extension study. SAEs were reported with similar frequencies across all dose groups and placebo/metformin, before and after all sitagliptin groups were collapsed to 100 mg qd.

Similar to the overall safety profile for the Pooled Phase 3 population, there were more frequent reports of upper respiratory infections and nasopharyngitis in the sitagliptin groups, which were mild to moderate, did not lead to discontinuation and did not increase in frequency over time.

10.1.5 Study P015

Study Design

This study was originally designed and conducted as a Phase 2, double-blind, placebo-controlled, crossover trial to examine the effects on glycemic control of adding sitagliptin 50 mg bid or placebo to a regimen of metformin at doses ≥ 1500 mg qd. The study duration was planned to be of 13 weeks, including a 5-week screening / diet run-in period (with a single-blind, 2-week, placebo run-in period) and an 8-week double-blind treatment period, consisting of two 4-week treatment periods. Since all subjects were supposed to be in stable glycemic control at the start of the double-blind period 1, no additional, confounding effect from metformin treatment was expected. In addition, the crossover design potentially had a greater power to detect changes in glycemic control and greater precision on the magnitude of effect, compared to a parallel group study design. The 2 potential risks of confounding in the crossover design are the "period" effect and the "carryover" effect. The 4-week interval in Period 1 was clearly insufficient time for natural history of T2DM to change substantially, and therefore was not a confounder. On the other hand, the 4-week interval unexpectedly had a "carryover" effect, as mean glycemic control at the end of

Period 1 for sitagliptin subjects did not return to baseline after 4 weeks of placebo in Period 2. Therefore, the study results after Period 1 were analyzed as a randomized, placebo-controlled, 4-week parallel arm study after Period 1. The study enrolled 28 subjects with T2DM who had inadequate glycemic control (HbA1c ≥ 6.5 % and < 10 %) while treated with ≥ 1500 mg of metformin daily. The study was conducted in 6 centers in the US, from December 10th, 2003 to June 19th, 2004.
The primary endpoint was the change in 24-hour weighted mean glucose (WMG) between the 2 groups, tested with an ANOVA model for a 2-period crossover design. The model included fixed terms for period and treatment. The 24-hour WMG was based upon collection of 7 blood samples pre- and post-meals and overnight and was calculated as the area under the 24-hour glucose curve (AUC [0-24 hr]) divided by 24; the 24-hour glucose profile was formed by 7 plasma glucose measurements collected at the site.

Subject disposition
Thirteen of the 28 subjects were randomized to the Sequence (Period 1 / 2) placebo / sitagliptin, and 15 subjects were randomized to the Sequence sitagliptin / placebo. One subject in each group withdrew consent, and 12 subjects in sequence 1 and 14 subjects in sequence 2 completed the study.

Efficacy Results
The LS mean difference (95% CI) between sitagliptin 50 mg bid and placebo in the primary endpoint (24 hour WMG) at week 4 was -32.8 mg.h/dL (-49.7, -16.0) ($p<0.001$).
Between-group differences in the changes from baseline to week 4 in the secondary efficacy endpoints were as follows:
Fructosamine: -33.7 μmol/ L (-54.5, -12.9) ($p=0.003$)
Fasting plasma glucose: -20.3 mg/dL (-31.1., -9.6) ($p<0.001$).
Please refer to Figure 28 for a profile plot of the 24-hour mean glucose excursions after 4 weeks of treatment in Study P015.

Safety
There were no SAEs or deaths reported in Study P015. There were 2 drug related AEs reported:
One subject had chest pain, abdominal pain and vomiting, with onset at the first standard meal on Visit 6 (after 4 weeks of sitagliptin treatment). The symptoms lasted less than 1 hour, but the subject requested blood sampling to stop. The investigator considered this subject discontinuation as due to withdrawal of consent, rather than due to AE.
One subject had nausea (self-limiting) on day 4, and continued for 28 days on sitagliptin without recurrence of the symptom. The laboratory AEs were similar to the profile described in the Safety section of this review document.

10.1.6 Study RC431A20

Study Design
This Phase 2 study was sponsored by Banyu Pharmaceutical Company, Ltd. (partner with the applicant) and

[redacted]. The study was conducted in 40 centers in Japan, from June 16, 2004 until April 25, 2005. This was a Phase 2 multicenter, randomized, placebo-controlled, double-blind, parallel-group study. After a 2-week, single-blind, placebo run-in period, 151 subjects were randomized 1:1 to receive placebo or sitagliptin 100 mg daily for 12 weeks. To be eligible, subjects (both genders, between the ages of 20 and 70 years) had to have T2DM with HbA1c ≥ 6.5% and < 10% and FPG ≥ 126 and ≤ 240 mg/dL at the randomization visit. A subject receiving another treatment for T2DM in monotherapy would be eligible if HbA1c fell in the range 6 to 9% and met the HbA1c at the randomization visit after washout of up to 8 weeks. The primary study endpoint was the change in HbA1c between the 2 treatment groups. Secondary endpoints were the change in fasting plasma glucose and in glycosylated albumin, as well as change in body weight.

Subject disposition
Of the 151 subjects randomized, 140 completed the study. Nine of the eleven subjects who discontinued prematurely were in the placebo group. None in the sitagliptin group was discontinued due to safety issues or AEs.

Efficacy Results
The LS mean difference (95% CI) between groups in the change in HbA1c from baseline to week 12 was -1.05 % (-1.27, -0.84) ($p < 0.001$). For the changes in FPG, the LS mean difference between groups was -31.9 mg/dL (-39.7, -24.1) and for changes in glycosylated albumin, the LS mean difference was -3.9 % (-4.6, -3.1). Both secondary endpoints had statistically significant reductions with sitagliptin treatment ($p < 0.001$).

Safety
No deaths were reported in this study. Five SAEs were reported, in 3 subjects on placebo and in 1 subject on sitagliptin (overdose, without any untoward clinical consequence). No AEs of hypoglycemia were reported. Incidences of various AEs reported were similar between the 2 groups.

10.2 Line-by-Line Labeling Review

The changes we propose have not been discussed with the applicant at the time of this review, so they must be considered preliminary.

[redacted]

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 3

Other Pertinent Information

Not applicable.

REFERENCES

All references used, in addition to the applicant's NDA submission, are mentioned in relevant sections of the review document.

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/s/

Ilan Irony
8/30/2006 04:31:24 PM
MEDICAL OFFICER

Mary Parks
8/31/2006 07:56:45 AM
MEDICAL OFFICER