CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202343Orig1s000

MEDICAL REVIEW(S)

Division Director's Memo

NDA	202-343
Drug Product	Sitagliptin-Simvastatin Fixed-Dosed Combination Tablets
Company	Merck
Date of Submission	December 6, 2010
PDUFA Goal Date	October 7, 2011

This NDA is for the fixed-dose combination (FDC) of sitagliptin and simvastatin. Both of these drug products are approved for use as described in the clinical reviews of Drs. Pratt and Irony. The pivotal studies supporting approval were bioequivalence studies to determine if the pharmacokinetics of the individual components in the FDC differed from when they are individually co-administered. These studies have been reviewed by Drs. Chung and Vaidyanathan and the Office of Clinical Pharmacology has recommended approval. The FDC will be available in the following sitagliptin/simvastatin dosage strengths: 100 mg/10 mg, 100 mg/20 mg, and 100 mg/40 mg. I concur with the medical and clinical pharmacology reviewers that this application can be approved and my memo will only note selected issues in the NDA which need to be highlighted.

Dosage Strengths
Sitagliptin is available in 25, 50, and 100 mg strengths. The 50 mg dose is recommended for patients with moderate renal impairment and the 25 mg dose is recommended for patients with severe renal impairment or with endstage renal disease. Simvastatin is available in 5, 10, 20, 40 and 80 mg strengths. Drug utilization data for both drug products revealed minimal use of the lowest dosage strengths; therefore, the company was not required to develop a FDC containing sitagliptin 25 mg and simvastatin 5 mg. However, extensive discussions were held with the company regarding the availability of dosage strengths of sitagliptin 50 mg and simvastatin 80 mg.

For sitagliptin 50 mg, it was felt that the population of patients with T2DM and moderate renal impairment was not an insignificant number. Not making available a FDC with sitagliptin 50 mg might result in such patients taking a higher dose than recommended. Labeling against its use was not appropriate given the sizeable patient population. The company proposed to develop and manufacture a FDC containing sitagliptin 50 mg and requested submission of data to support approval of sitagliptin/simvastatin 50/10, 50/20, and 50/40 as an efficacy supplement after approval of the FDC tablets containing sitagliptin 100 mg. This was deemed acceptable as the applicant provided a letter committing to submit this supplement to FDA by November 30, 2011, which did not signify an unreasonable delay to market. In the meanwhile, the label will include a "Limitations of Use" stating that patients with moderate and severe renal impairment should not take the FDC product due to unavailability of the 50 and 25-mg dosage strengths of sitagliptin.

Prior to submission of this efficacy supplement, the Division was evaluating data from the SEARCH trial and assessing the risk of muscle toxicity associated with simvastatin 80 mg. Plans were underway to restrict the use of this dose to only those patients who were already on simvastatin 80 mg and tolerating

the drug without evidence of muscle symptoms. The Division did not feel that it would be appropriate to consider approval of a FDC that would include the simvastatin 80 mg dose strength as it might further encourage the inappropriate use of this dose, especially as a new initiation only for the purpose of convenience dosing. (b) (4) The applicant acknowledged the Division's position on the matter and did not pursue marketing of the simvastatin 80 mg dosage strength; however, bioequivalence data including the sita/simva 10/80 fixed-dose combination tablet were accepted for review with biowaiver consideration for the lower dosage strengths intended for marketing.

Statins and Diabetes

Recently, two published meta-analyses of several randomized statin trials revealed an increased risk of developing diabetes associated with statin use, notably atorvastatin, rosuvastatin, and simvastatin.[1,2] This was also observed by FDA in its review of rosuvastatin's JUPITER trial and such an association has been included in rosuvastatin's label (Warnings and Precautions and Adverse Reactions).

The significance of this finding, particularly with a FDC to be used in the diabetic population was considered. As summarized by the authors of one meta-analysis, the risk of developing diabetes in absolute terms was low in comparison to the benefits of statins in lowering a patient's risk for future cardiovascular events. Reassuring for simvastatin is that analyses of large outcomes trial did not exclude the benefits of CV risk reduction from patients with T2DM. However, labeling to describe this observation is appropriate such that healthcare providers and patients are aware of the potential for worsening glycemic control and adjust diabetic medications accordingly.

The applicant has proposed to conduct a randomized, double-blind, active-controlled trial to study the effect of the FDC versus sitagliptin on glycemic control in T2DM patients on background metformin therapy as a postmarketing trial to prospectively evaluate the effects of simvastatin on glycemic control. This is an important trial that will inform prescribers and patients on the risk and benefits of this FDC product and will therefore be a required trial under FDAAA.

Labeling

The applicant is proposing that the FDC be indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate. Although FDA reviews and the applicant's rationale for development of this product suggest a benefit with convenience dosing, the label should not include language which may be promotional to this effect. The applicant has not provided any data to support an assertion that the administration of one pill instead of two improves compliance or leads to better clinical outcomes. Although not a consideration in the approval process, one could argue from a health economics standpoint that a new FDC product might cost more than co-administration of the individual components, especially given that simvastatin is available as a generic. More importantly, the 'convenience' of the FDC should not encourage prescribing practice that runs contrary to the safe use of the individual components. To this end, the recent labeling changes recommended for simvastatin must be incorporated into the FDC label prior to approval.

(b) (4)

[1] Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *The Lancet*. 2010; 375:735-742.

[2] Rajpathak S et al. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care*. 2009; 32:1924-1929.

(b) (4) Although this labeling request was made to the (b) (4) the changes are important to the safe use of any drug product containing simvastatin and therefore the FDC of sitagliptin and simvastatin should include these changes prior to approval.

Recommendations
Pending agreed-upon labeling, this application can be approved.

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/s/

MARY H PARKS
10/06/2011
Division Director's memo

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-343
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Submit Date(s)	12-6-10
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Division / Office	DMEP/ODEII/OND
Reviewer Name(s)	Valerie S. W. Pratt, M.D.
Review Completion Date	09-01-11
Established Name	Sitagliptin/simvastatin FDC
(Proposed) Trade Name	(b) (4)
Therapeutic Class	DPP-4 inhibitor/Statin
Applicant	Merck
Formulation(s)	100/10, 100/20, & 100/40 mg tablets
Dosing Regimen	Once daily
Indication(s)	Diabetes/hyperlipidemia
Intended Population(s)	Adult diabetics with hyperlipidemia

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of sitagliptin/simvastatin fixed dose combination (FDC) new drug application (NDA) 202-343 for use in patients for whom treatment with both sitagliptin and simvastatin is appropriate.

1.2 Risk Benefit Assessment

Sitagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, has been approved for treatment of type 2 diabetes mellitus (T2DM) in the United States (US) since October 2006 under NDA 21-995. The recommended dose is 100 mg daily for subjects with normal renal function, 50 mg daily for subjects with moderate renal impairment, and 25 mg daily for subjects with severe and end stage renal disease (ESRD).

Simvastatin, a hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin), was approved in December 1991 and currently has five cardiovascular (CV) indications.

As T2DM patients are at high risk for macrovascular complications and compliance with medications decreases as the number of required medications increases, the applicant proposes sitagliptin/simvastatin FDC for use in patients for whom treatment with both sitagliptin and simvastatin is appropriate. Prior to submitting NDA 202-343, teleconferences were held with the applicant regarding the proposed doses of sitagliptin/simvastatin FDC and which doses were required for filing. On September 30, 2010, the following agreements were made:

- (b) (4)
- Submission of a NDA without the 50 mg sitagliptin dose for use in subjects with moderate renal insufficiency is both a review and safety issue.
- If not contained in the original NDA, the development of the 50 mg sitagliptin doses may be a post-marketing requirement (PMR).

Thus, the current NDA 202-343 proposes sitagliptin/simvastatin 100/10, 100/20, and 100/40 mg FDC tablets, as previously agreed. The applicant is now developing 50/10, 50/20, and 50/40 mg FDC doses and plans to submit a supplemental NDA (sNDA) for them by November 2011.

The registration of sitagliptin/simvastatin FDC is based on the demonstration of bioequivalence (BE) between the FDC tablets and co-administration of corresponding doses of sitagliptin and simvastatin. Although no phase 3 clinical studies were conducted with the sitagliptin/simvastatin FDC or with the co-administration of sitagliptin and simvastatin, seven clinical pharmacology studies support registration of the FDC.

There are published reports of statins altering glycemic control.[1,2] However, the applicant demonstrated that the risks of the concomitant administration of sitaglitpin and simvastatin do not outweigh its benefits. We will require a postmarketing clinical study to conclusively demonstrate the safety of this convenience product.

- Using subgroup analyses, the applicant demonstrated that there was no clinically significant difference in the change in glycemic control (HbA1c) in T2DM subjects randomized to simvastatin compared to placebo in the simvastatin clinical development program.
    - Heart Protection Study (HPS): In a random sample of T2DM subjects, there was no significant difference (-0.03 ± 0.13) between treatment groups in the change in HbA1c.
    - In study MK-0733-P187, there was no significant difference between the simvastatin 40 mg and placebo groups in the change in HbA1c at week 24 (95% confidence interval [CI] -0.1, 0.4).
- The HbA1c-lowering efficacy of sitagliptin versus comparator was analyzed in 19 pooled sitagliptin clinical trials in the following subgroups: simvastatin users, statin users, and non-statin users. The results were generally similar between the groups, although few subjects were on simvastatin or any statin in some studies, which resulted in wide 95% CI intervals. (See section 6.1.4Analysis of Primary Endpoint(s) for full details.)
- Review of the change from baseline HbA1c in patients who initiated simvastatin/statin during the treatment period in the sitagliptin clinical development program did not suggest a clinically significant effect on the initiation of simvastatin or another statin on glycemic control.

As no phase 3 studies were conducted with the sitagliptin/simvastatin FDC, the applicant analyzed the safety of the FDC using sitagliptin and simvastatin co-administration data from the following 19 sitagliptin studies which were included in the Summary of Clinical Safety (SCS):

- Phase 1 protocol 061
- Phase 2 protocols 010 and 014
- Phase 3 protocols 019, 020, 021, 023, 024, 035, 036, 040, 047, 049, 051, 052, 053, 064, 079, and 801

1 Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJM. Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. Lancet 2010;375:735-42.
2 Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. NEJM 2008:359:2195-207.

Exposure to sitagliptin in combination with simvastatin did not increase one's risk of death, serious adverse events (SAEs), or discontinuation compared to use of sitagliptin alone or with all statins combined.

Due to the risk of myopathy and liver enzyme abnormalities with simvastatin, the safety database was reviewed for events of blood creatinine phosphokinase (CPK) increased and serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) consecutive elevations ≥3x upper limit of normal (ULN).

- The effect of the co-administration of sitagliptin and simvastatin on myositis was analyzed using six prespecified terms. The rate at which blood CPK increased occurred was not significantly different between treatment groups (see Table 19) nor was there a dose-related effect of simvastatin (see Table 20). There were no blood CPK elevations ≥10x ULN in the simvastatin population.
- The incidence of consecutive ALT and/or AST elevations ≥3x ULN were not statistically significantly different between the sitagliptin and non-exposed groups in the simvastatin, all statins, and other statin populations (see Table 22).

Although the sitagliptin label warns about the risks of pancreatitis, hypoglycemia (when used with insulin or an insulin secretagogue), hypersensitivity, and renal impairment (recently added), the concomitant use of simvastatin does not increase these risks.

The incidence of adverse events (AEs) in the simvastatin and all statins populations in the controlled portions of pooled studies, excluding data after initiation of glycemic rescue, was similar between the sitagliptin and non-exposed groups (62.8-65.1%). The 95% CI between-group difference included zero in both populations, although AEs were reported most frequently in the following three system organ classes (SOCs) for the simvastatin and all statins populations: infections and infestations, gastrointestinal disorders, and musculoskeletal and connective tissue disorders.

Limited chemistry and hematology values were analyzed in the SCS by mean changes from baseline over time and the incidence of measurements meeting predefined limits of change (PDLC), as agreed at the pre-NDA meeting. No clinically meaningful differences were observed between treatment groups in the simvastatin and all statins populations.

No dose-, time-, or demographic-dependent effect on adverse events was observed. The available postmarketing data do not suggest safety concern with the co-administration of sitagliptin and simvastatin.

With regards to vital signs and electrocardiograms (ECGs), the changes from baseline to week 104/106 in blood pressure and heart rate were small and likely not clinically meaningful in both the simvastatin and all statins population (see Table 37). A thorough QT (tQT) study of the sitagliptin/simvastatin FDC was not required. However, the

applicant has initiated TECOS, a randomized, placebo controlled clinical trial to evaluate CV outcomes after treatment with sitagliptin in patients with T2DM and inadequate glycemic control on mono- or dual combination oral antihyperglycemic therapy. This study will include subjects on sitagliptin and simvastatin. Its planned completion date is December 2014.

In summary, the applicant has demonstrated that the benefits of the concomitant administration of sitaglitpin and simvastatin outweigh its risks. In addition, as T2DM patients are at high risk for macrovascular complications, sitagliptin and simvastatin are already commonly co-prescribed (see April 26, 2011 IND 103,183 submission), and the applicant asserts that compliance with medications decreases as the number of required medications increases, the FDC offers the benefit of convenience and may increase compliance.

However, as discussed at the May 24, 2010 teleconference, (b) (4) of the sitagliptin prescriptions in the US are for 50 mg. Given the increasing prevalence of T2DM and the associated co-morbidity of renal impairment, the applicant should manufacture 50/10, 50/20, and 50/40 mg dose strengths of the FDC. The applicant proposes to submit a sNDA for these doses in November 2011, such that the 50 mg doses could be available within one year of approval of the 100 mg doses.

As I concluded that the benefits of the sitagliptin/simvastatin FDC outweigh its risks and the proposed timeline for the development of the sitagliptin 50 mg doses is not excessive and can be enforced with a post-marketing requirement, I recommend approval of sitagliptin/simvastatin FDC NDA 202-343.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

On March 25, 2011, the applicant submitted a proposed Risk Evaluation and Mitigation Strategy (REMS) for the sitagliptin/simvastatin FDC. It contained a Medication Guide (MG) and timetable for submission of assessments, similar to that currently approved for sitagliptin (Januvia NDA 21-995) and sitagliptin/metformin FDC (Janumet NDA 22-044).

However, the draft guidance for industry entitled *Medication Guides: Distribution Requirements and Inclusion of Medication Guides in Risk Evaluation and Mitigation Strategies* was recently issued. This guidance addresses when a MG is required as part of a REMS. Following the guidance, on April 14, 2011, the Division communicated to the applicant that a REMS was no longer necessary to ensure the benefits of sitagliptin outweigh it risks, although a MG will continue to be part of the approved labeling. As my review of the sitagliptin/simvastatin FDC did not reveal a new safety issue requiring other elements of REMS (Elements to Assure Safe Use [ETASU] or a Communication Plan), a REMS should not be required for NDA 202-343.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend the following PMRs:

- Submission of a sNDA for sitagliptin/simvastatin FDC dose strengths 50/10, 50/20, and 50/40 mg by December 31, 2011 as discussed with the applicant prior to NDA-filing and as consistent with the applicant's own development plan so as to not restrict use of the FDC in subjects with renal impairment.
- A clinical study in ≥ 200 T2DM subjects per group on metformin randomized to sitagliptin/simvastatin FDC or the component monotherapies for ≥16 weeks to conclusively demonstrate the safety of co-administration for this convenience product.

A CV outcomes study of sitagliptin/simvastatin FDC is not required because the guidance for industry recommends evaluating CV risk in new antidiabetic therapies, and sitagliptin and simvastatin are both currently approved. Furthermore, TECOS, a CV outcomes study of sitagliptin, is ongoing with the planned completion date of December 2014. It will include subjects on sitagliptin and simvastatin.

2 Introduction and Regulatory Background

2.1 Product Information

Merck submitted this 505(b)(1) NDA for the use of sitagliptin/simvastatin FDC (MK-0431D, proposed trade name (b) (4) in patients for whom treatment with both sitagliptin and simvastatin is appropriate.

Sitagliptin, a DPP-4 inhibitor, prevents the degradation of incretin hormones like glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). It has been approved for treatment of T2DM in the US since October 2006 under NDA 21-995. The recommended dose is 100 mg daily for subjects with normal renal function, 50 mg daily for subjects with moderate renal impairment, and 25 mg daily for subjects with severe and end stage renal disease.

Simvastatin is a HMG-CoA reductase inhibitor (statin), that is available in 5, 10, 20, 40, and 80 mg once daily tablets. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. Simvastatin was approved in December 1991 and is currently indicated as follows:

- Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction (MI), stroke, and the need for revascularization procedures in patients at high risk for coronary events.

- Reduce elevated total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
- Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbeta-lipoproteinemia.
- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia.
- Reduce elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy.

As T2DM patients are at high risk for macrovascular complications and the applicant asserts that compliance with medications decreases as the number of required medications increases, the applicant proposes a sitagliptin/simvastatin FDC in 100/10, 100/20, and 100/40 mg tablet strengths.

Prior to submitting NDA 202-343, several teleconferences were held with the applicant regarding the proposed dose strengths of sitagliptin/simvastatin FDC and which strengths were required for filing (see section 2.5 Summary of Presubmission Regulatory Activity Related to Submission). The goal was to maximize availability of the product for consumers, including subjects with renal failure, but to avoid confusion for physicians and patients.

- The development of FDC doses containing simvastatin 80 mg was not recommended due to safety issues (see section 2.3).
- The development of FDC doses containing sitagliptin 25 mg or simvastatin 5 mg is not required due to the low usage rate (2.2% and 0.6%, respectively).
- The development of the FDC with sitagliptin 50 mg doses is required.

In the Four-Month Safety Update, the applicant proposed the following timeline (see Table 1) for developing the sitagliptin 50 mg doses, with registration planned in November 2011. As the Prescription Drug User Fee Act (PDUFA) goal date for NDA 202-343 is October 7, 2011 and an NDA supplement for the sitagliptin 50 mg doses would be reviewed under a 10-month time clock, the additional sitagliptin 50 mg doses could be available within one year of approval of the 100 mg doses. This is acceptable because the risk/benefit assessment of the proposed sitagliptin/metformin XR NDA with 100 mg sitagliptin is favorable. However, as previously mentioned, I believe submission of a supplemental NDA (sNDA) for the sitagliptin 50 mg doses should be a PMR with the due date of December 31, 2011 to ensure that subjects with moderate renal insufficiency have the appropriate doses available for use.

Table 1. Timeline for the development of sitagliptin/simvastatin FDC tablets containing 50 mg sitagliptin

* accelerated from previous estimated timeline

Source: Four-Month Safety Update

2.2 Tables of Currently Available Treatments for Proposed Indications

Medications currently approved for the treatment of type 2 diabetes mellitus include the following:

- Insulin
- Sulfonylureas
  - Tolazamide (Tolinase)
  - Chlopropramide (Diabinese)
  - Glyburide (Micronase)
  - Glipizide (Glucotrol and Glucotrol XL)
  - Glimepiride (Amaryl)
- Meglitinide analogs: Repaglinide (Prandin)
- D-Phenylalanine: Nateglinide (Starlix)
- Biguanides: Metformin (e.g., Glucophage and Glucophage XR)

- Thiazolidinediones (TZDs)
  - Rosigitazone (Avandia)
  - Pioglitazone (Actos)
- α-Glucosidase inhibitors
  - Acarbose (Precose)
  - Miglitol (Glyset)
- Incretin-mimetics
  - Exenatide (Byetta)
  - Liraglutide (Victoza)
- Amylinomimetics
  - Pramlintide (Symlin)
- Dipeptidyl peptidase 4 inhibitors
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
  - Linagliptin (Tradjenta)
- Bile acid sequestrants
  - Colesevelam (WelChol)
- Dopamine receptor agonists
  - Bromocriptine mesylate (Cycloset)

Currently approved statins:

- Lovastatin (Mevacor)
- Pravastatin (Pravachol)
- Simvastatin (Zocor)
- Fluvastatin (Lescol)
- Atorvastatin (Lipitor)
- Rosuvastatin (Crestor)
- Pitavastatin (Livalo)

2.3 Availability of Proposed Active Ingredient in the United States

Sitagliptin (NDA 21-995) has been approved for the treatment of T2DM in the US since October 2006 in 25, 50, and 100 mg daily doses.

Simvastatin (NDA 19-766) has been approved since December 1991. Five, 10, 20, 40, and 80 mg tablets are available. However, the SEARCH CV outcomes trial, which evaluated patients post-MI treated with simvastatin 80 mg or 20 mg, found no improvement in the incidence of MACE events with the higher dose, and there were more cases of severe myopathy with 80 mg than 20 mg (11 of the patients on 80 mg developed rhabdomyolysis compared to no patients on 20 mg). Therefore, on September 30, 2010, the applicant was informed that due to the safety issues associated with simvastatin 80 mg, a FDC including simvastatin 80 mg was not approvable.

2.4 Important Safety Issues With Consideration to Related Drugs

Labeled safety concerns with sitagliptin include the following:

- Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis
- Dose adjustment in patients with moderate, severe, and end stage renal disease and the need to assess renal function prior to and during sitagliptin use
- Risk of hypoglycemia when used with an insulin secretagogue (e.g. sulfonylurea [SU]) or insulin
- Serious allergic and hypersensitivity reactions, including anaphylaxis, angioedema, and exfoliative skin conditions

Labeled safety concerns with simvastatin include the following:

- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, and renal impairment.
- Patients should be advised to report promptly any symptoms of myopathy. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected.
- Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic aminotransferases can occur. Monitor liver enzymes before and during treatment.

Note, a revised simvastatin label was approved in June 2011. The applicant should revise the proposed prescribing information (PI) and MG to include these recent changes.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On August 19, 2008, the applicant requested a pre-IND meeting but did not submit draft questions. On September 16, 2008, the applicant resubmitted the type B (pre-phase 3) meeting request. The meeting request was denied on October 15, 2008. The applicant was encouraged to include any questions in the IND submission.

The sitagliptin/simvastatin FDC IND 103,183 was opened on December 8, 2008. FDA conveyed comments regarding the proposed doses and the development plan at that time. On September 2, 2009, the applicant was informed of the agency's new requirement to develop FDC doses for use by patients with renal insufficiency.

(b) (4)

on April 12, 2010, the applicant was asked to submit drug utilization information for sitagliptin and simvastatin as well as a justification for the FDC dose strengths it does not plan to

manufacture. A teleconference was held March 4, 2010 to discuss the need for a dedicated pharmacodynamic (PD) study, in light of a recent meta-analysis which suggested that statin therapy is associated with a slightly increased risk of developing diabetes.[1]

On May 24, 2010, a pre-NDA teleconference was held with the applicant. The following points were conveyed:

- A biowaiver request for the 100/40 and 100/20 mg strengths should be submitted based on the following:
  - BE data on the highest (100/80 mg) and lowest (100/10 mg) dose strengths
  - Dissolution profile comparison data for the middle strengths 100/40 and 100/20 mg in three media using the same dissolution testing conditions
  - Similarity F2 values, which are calculated based on the two formulations' dissolution profiles, using both the highest and lowest strengths as the reference
- A clinical efficacy study in ≥200 T2DM subjects per group on metformin randomized to sitagliptin/simvastatin FDC or the component monotherapies for ≥16 weeks may be required as a PMR. The protocol need not be submitted with the NDA.
- The applicant will be required to develop the 50/10, 50/20, and 50/40 mg tablets in addition to the 100/10, 100/20, and 100/40 mg tablets. This will offer the advantages of the FDC to as many patients as possible, yet will lessen the chance of inappropriate dosing that could result if dose strengths of sitagliptin aimed to treat diabetics with moderate impaired renal function were not available in the FDC.
- The applicant should analyze the safety and tolerability of co-administration of sitagliptin 100 mg with simvastatin and the co-administration of sitagliptin 100 mg with any statin excluding simvastatin in the Integrated Summary of Safety (ISS).
- The applicant will analyze safety using the full analysis set (FAS) for all protocols. For efficacy, the applicant should submit an analysis using the FAS for all protocols in addition to an analysis using FAS for all protocols but studies 024 and 049, which were non-inferiority studies, using the per protocol (PP) population.
- The applicant agreed to submit narratives of glycemic control for the 5-10 subjects who initiated a statin in the pooled database.
- The applicant was asked to address the Pediatric Research Equity Act (PREA) in the NDA.

On July 12, 2010, another teleconference was held to discuss the filing of the renal doses. The following agreements were made:

- The applicant will develop a FDC or copackaging plan with both sitagliptin 100 and 50 mg.
- It will file a NDA with the sitagliptin 100 mg dose and then submit a supplement for the 50 mg doses. However, submitting the NDA without the 50 mg sitagliptin dose will make this a review issue.
- The agency expressed concern for medication error if the applicant pursued a sitagliptin 100 mg FDC and 50 mg copackaging plan.
- The agency will accept 6 month formal stability study data for the FDC product with 50 mg sitagliptin.
- The applicant plans to bridge the 100 and 50 mg formulations using in vitro dissolution studies. The acceptability of the bridging studies should be confirmed by the ONDQA-Biopharm group.
- The applicant agreed to update the agency on the development of the 50 mg doses when the NDA for the sitagliptin 100 mg doses is filed.

On September 30, 2010, another teleconference was held to discuss the proposed timing for the development of the 50/10, 50/20, and 50/40 mg tablets and to discuss whether doses containing 50 or 25 mg sitagliptin would be required for filing. The applicant was informed that, because of safety issues associated with the 80 mg simvastatin dose, the 100/80 mg tablet is not approvable. However, the applicant could use data from the BE studies for the 100/80 and 100/10 mg doses to obtain a biowaiver for the 100/20 and 100/40 mg dose strengths and to bridge to the 50/40, 50/20, and 50/10 mg doses. The agency clarified that submission of an NDA without the 50 mg sitagliptin dose is both a review and safety issue. If not contained in the original NDA, the development of the 50 mg sitagliptin doses may be a PMR.

2.6 Other Relevant Background Information

On February 16, 2011, the applicant responded to an information request, clarifying the MedDRA version used in the pooled analysis and details regarding study P801.

On March 25, 2011, the applicant submitted a proposed REMS for NDA 202-343. The REMS consisted of a MG and timetable for submission of assessments.

On April 5, 2011, the applicant submitted the Four-Month Safety Update which contained information about the development of the FDC containing sitagliptin 50 mg.

On August 31, 2011, the applicant clarified by email what was meant by “Merck prior environment” and “Merck current environment” in parts 1 and 2, respectively, of the financial disclosure information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic submission was of appropriate quality and was well organized. All trials were conducted following Good Clinical Practice standards.

3.2 Compliance with Good Clinical Practices

As the registration of sitagliptin/simvastatin FDC is based on the demonstration of BE between the FDC tablets and co-administration of corresponding doses of sitagliptin and simvastatin, seven clinical pharmacology studies support registration of the FDC.

OSI was consulted to investigate clinical study site ICON Development Solutions' (San Antonio, TX) and analytical site (b) (4) participation in the definitive BE studies P255 and P153. At the time of review finalization, the OSI consult was still pending. However, as no phase 3 clinical studies were conducted with the sitagliptin/simvastatin FDC or with randomization to the co-administration of sitagliptin and simvastatin, OSI was not asked to investigate clinical trial study sites.

3.3 Financial Disclosures

The applicant submitted financial disclosure information in two parts:

- Part 1: Data collected in Merck prior environment (i.e. a search of Merck's internal financial databases for Significant Payments of Other Sorts in excess of $25,000.00 made to the investigator, investigator's spouse, dependent children or an institution on behalf of the investigator during the time the study was ongoing and through one year following completion of the study)
- Part 2: Data collected in Merck current environment (i.e. the investigator was directly requested to provide Significant Payments of Other Sorts in excess of $25,000.00 made to him/herself on behalf of Merck the applicant; this request also included the investigator's spouse, dependent children or an institution on behalf of the investigator during the time the study was ongoing and through one year following completion of the study)

The applicant did not enter into any financial arrangement with clinical investigators whereby the value of the investigator's compensation could be affected by the outcome of the study. The applicant conducted an internal search for all payments that met the definition of "significant payments of other sorts" and reported the information as appropriate. "Significant payments of other sorts" are calculated cumulatively when an investigator is involved in more than one protocol in a submission.

In part 1, the applicant stated it would not provide financial disclosure information from sitagliptin NDA 21-995 for the base studies previously submitted and approved, i.e. the following:

- Protocols 010, 014, 020, 021, and 023: Approved October 2006
- Protocols 024 and 035: Approved October 2007
- Protocol 036: Approved October 2007

However, data for these studies' extension periods was provided.

In part 1, the grand total number of all investigators/subinvestigators was 2,959. A total of 2,866 were certified regarding the absence of financial interests and arrangements. A total of 47 were not certified (i.e. no longer at site or did not return requested information). A total of 46 investigators/subinvestigators held financial interests or had arrangements requiring disclosure (44 significant payments of other sorts [up to $79,213], 2 equity interest [up to $65,593]).

In part 2, the applicant stated it would not provide financial disclosure information from sitagliptin NDA 21-995 base study 064, which was previously submitted and approved in February 2010. However, the following clinical studies were covered: 1) sitagliptin/simvastatin FDC studies protocols: 153, 154, 155, 168, 169, 255 and 2) sitagliptin study protocols: 040, 047, 049, 053, 061, 064, and 079. In part 2's covered studies, there were 1,601 investigators/subinvestigators. A total of 1,528 were certified regarding the absence of financial interests and arrangements; 64 were not certified; and 9 held financial interests or arrangements requiring disclosure (6 significant payments of other sorts [up to $43,536], 3 equity interest [up to $100,000]).

Although some investigators/subinvestigators were not certified or held financial interests or arrangements with the applicant requiring disclosure, this occurred infrequently. The blinded, multicenter-design of most trials further minimized potential bias.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The final market image (FMI) of the sitagliptin/simvastatin FDC is a film coated bilayer tablet consisting of one layer of a sitagliptin (b) (4) and another layer of a simvastatin (b) (4)

Multimedia in vitro dissolution testing demonstrated similar dissolution profiles for the sitagliptin and simvastatin components of all four FDC tablet strengths.

The final market composition (FMC) sitagliptin/simvastatin FDC tablets used in the BE studies were identical to the FMI tablets, except for a minor change in the film coating color, which should not affect in vivo performance.

On August 3, 2011, CMC recommended approval pending outstanding facility inspections. Please refer to Drs. Su Tran and John Hill's CMC reviews for full details.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Sitagliptin and simvastatin are commonly coadministered in clinical practice. According to the ICH Guidance M3(R2) approved in January 2010, "For most combinations which involve two late stage entities for which there is adequate clinical experience with co-administration, combination toxicity studies would generally not be recommended to support clinical studies or marketing unless there is significant toxicological concern (e.g., similar target organ toxicity)." However, due to the rhabdomyolysis sometimes seen clinically with high doses of simvastatin and the slight skeletal muscle degeneration previously noted histomorphologically in preclinical studies in dogs treated with a high dose of sitagliptin, an additional 3-month nonclinical study in rats with co-administration of sitagliptin and simvastatin was conducted to rule out possible interactions on the skeletal muscle or other potential interactions.

Sitagliptin/simvastatin dose levels of 0/30, 0/60, 180/0, 180/30, and 180/60 mg/kg/day were investigated. All animals survived to study termination. Comparing the antemortem changes in the 0/60, 180/0, and 180/60 mg/kg/day dose groups, there were slightly more changes or changes of slightly greater severity in the 180/60 mg/kg/day dose group. However, these differences were limited in nature and were known effects of simvastatin in rats seen in previous studies. Therefore, treatment of rats with sitagliptin at 180 mg/kg/day in combination with simvastatin at 60 mg/kg/day was considered not to substantially influence simvastatin-associated changes.

Please also refer to Dr. Patricia Brundage's nonclinical review and section 13 Nonclinical Toxicology of the Januvia and Zocor labels.

4.4 Clinical Pharmacology

The goal of the clinical pharmacology program was to demonstrate BE between sitagliptin/simvastatin FDC and coadministration of corresponding doses of sitagliptin (Januvia) and simvastatin (Zocor).

Table 2. Clinical pharmacology studies

Study Type	Protocol Number
Biopharmaceutics Studies	
MK-0431D Tablet Probe Formulation Study	P154
MK-0431D Tablet Definitive Bioequivalence Study	P153
MK-0431D Tablet Food Effect Study	P155
MK-0431D Tablet Definitive Bioequivalence Study	P255
Pharmacokinetic Studies	
Simvastatin Interaction Study†	P025
Sitagliptin Interaction Study	P168
Digoxin Interaction Study	P169
† Component of original sitagliptin filing Dec-2005.	

Two probe formulations (D1 and D2) were initially developed and tested in probe biocomparison study P154. The D1 and D2 formulations contained the same sitagliptin layer formulation but differed in the simvastatin layer composition. The simvastatin formulation used in D1 was based on that for Vytorin, while the D2 simvastatin formulation was based on that for Zocor. Study P154 demonstrated that the AUC and Cmax of simvastatin and simvastatin acid in the D1 and D2 formulations were modestly increased compared to generic simvastatin. These results were unexpected but could potentially be explained by lower exposure of the generic simvastatin, so the D2 formulation was retested in biocomparison study P153 Part 1 at the 100/80 mg strength and compared to coadministration of Januvia 100 mg and Zocor 80 mg. Study P153 Part 1 demonstrated PK similarity and assisted in determining the sample size and power for the definitive BE study P153 Part 2.

Although an 100/80 mg tablet strength was originally considered, the applicant did not propose its registration. However, the dose was used in some studies to support registration of the 100/10, 100/20, and 100/40 mg doses (e.g. in high-dose BE study P153).

Low-dose BE study, P255, was also conducted to establish BE between the 100/10 mg FDC tablets and coadministration of the corresponding doses of sitagliptin and simvastatin.

In study P155, a high-fat breakfast did not affect the PK of sitagliptin after administration of the FMC FDC tablet at the 100/80 mg dose. The AUC0-last decreased by 24% for simvastatin and increased by 37% for simvastatin acid. The high-fat meal increased the Cmax for simvastatin and simvastatin acid by 20% and 116%, respectively. Based on these results, the applicant does not recommend dose adjustment when the sitagliptin/simvastatin FDC is administered with food.

Three PK studies (P025, P168, and P169) were also conducted.

- P025 examined the effect of sitagliptin on simvastatin PK as part of the sitagliptin development program and was previously submitted.
- P168 was a multiple dose, one-way drug interaction study that assessed the potential for simvastatin to effect sitagliptin PK in healthy males and females.
- P169 was a multiple dose, PK interaction study to assess the effect of simvastatin and sitagliptin coadministration on the PK of coadministered digoxin relative to digoxin administration alone.

Please refer to Dr. Sang Chung's clinical pharmacology review and Dr. Sandra Suarez's biopharmaceutical review for full details.

4.4.1 Mechanism of Action

Sitagliptin/simvastatin FDC contains two active product ingredients, sitagliptin and simvastatin.

Sitagliptin, a DPP-4 inhibitor, is believed to slow the inactivation of incretin hormones, such as GLP-1 and GIP. Incretins are involved in the regulation of glucose. When blood glucose is normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By selectively inactivating the enzyme DPP-4 and increasing and prolonging active incretin levels, sitagliptin increases insulin and decreases glucagon in a glucose-dependent manner.

Simvastatin is a prodrug that is hydrolyzed to its active β-hydroxyacid form, simvastatin acid, after administration. Simvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

4.4.2 Pharmacodynamics

Please refer to section 12.2 Pharmacodynamics of the sitagliptin and simvastatin labels.

4.4.3 Pharmacokinetics

Study 153 part II demonstrated bioequivalence between sitagliptin/simvastatin FDC 100/80 mg and co-administration of the corresponding tablets. Thus, study 153 part II supports approval of NDA 202-343.

Table 3. Bioequivalence study results

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

Source: Clinical pharmacology August 30, 2011 wrap up meeting handout
GMR = Geometric mean ratio (FDC / (Simvastatin + Sitagliptin)) (n=99)

Please also refer to section 12.3 Pharmacokinetics of the sitagliptin and simvastatin labels for details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4. Studies included in the pooled analysis for safety by exposure to sitagliptin and statins, including controlled portions and excluding data after initiation of glycemic rescue therapy.

Note: Studies were also used to evaluate the HbA1c-lowering efficacy of sitagliptin in the sitagliptin development program by statin use

Study: Design	Sitagliptin		Non-exposed		Total
	Randomized Group	n	Randomized Group	n	N
P061: Phase 1, combination factorial study with pioglitazone HbA1c Analysis: Week 12 FAS	Simvastatin: Sita 100 QD Sita 100 QD + pio 30 QD	 8 9	Simvastatin: Pio 30 QD Plb	 8 8	33
	All statins: Sita 100 QD Sita 100 QD + pio 30 QD	 17 22	All statins: Pio 30 QD Plb	 22 15	76
P010: Phase 2b, BID dose-range finding HbA1c Analysis: Week 12 FAS	Simvastatin: Sita 50 BID → 100 QD	 25	Simvastatin: Glipizide	 25	50
	All statins: Sita 50 BID → 100 QD	 47	All statins: Glipizide	 45	92
P014: Phase 2b, QD dose-range finding HbA1c Analysis: Week 12 FAS	Simvastatin: Sita 100 QD Sita 50 BID → 100 QD	 15 12	Simvastatin: Plb → Met	 10	37
	All statins: Sita 100 QD Sita 50 BID → 100 QD	 33 40	All statins: Plb → Met	 32	105
P019: Phase 3, add-on to pioglitazone HbA1c Analysis: Week 24 FAS	Simvastatin: Sita 100 QD	 13	Simvastatin: Plb	 24	37
	All statins: Sita 100 QD	 73	All statins: Plb	 70	143
P020: Phase 3, add-on to metformin HbA1c Analysis: Week 24 FAS	Simvastatin: Sita 100 QD	 94	Simvastatin: Plb → glipizide	 57	151
	All statins: Sita 100 QD	 198	All statins: Plb → glipizide	 106	304
P021: Phase 3, monotherapy HbA1c Analysis: Week 24 FAS	Simvastatin: Sita 100 QD (Phase A)	 17	Simvastatin: Plb (Phase A then → sita	 31	48

Study: Design	Sitagliptin		Non-exposed		Total
			100/200 in Phase B)		
	All statins: Sita 100 QD (Phase A)	79	All statins: Plb (Phase A then → sita 100/200 in Phase B)	99	178
P023: Phase 3, monotherapy HbA1c Analysis: Week 18 FAS	Simvastatin: Sita 100 QD	32	Simvastatin: Plb → Pio 30	17	49
	All statins: Sita 100 QD	76	All statins: Plb → Pio 30	43	119
P024: Phase 3, SU non-inferiority add-on to metformin HbA1c Analysis: Week 52 PP	Simvastatin: Sita 100 QD	135	Simvastatin: Glipizide	125	260
	All statins: Sita 100 QD	301	All statins: Glipizide	287	588
P035: Phase 3, add-on to SU (with/without metformin) HbA1c Analysis: Week 24 FAS	Simvastatin: Sita 100	46	Simvastatin: Plb (→ Pio 30 at week 24)	39	85
	All statins: Sita 100	107	All statins: Plb (→ Pio 30 at week 24)	91	198
P036: Phase 3, combination therapy factorial study with metformin HbA1c Analysis: Week 24 FAS	Simvastatin: Sita 100 QD (Sita 50 + Met 500) BID (Sita 50 + Met 1000) BID	27 31 24	Simvastatin: Plb (→ Met 1000 BID at week 24) Met 500 BID Met 1000 BID	27 19 35	163
	All statins: Sita 100 QD (Sita 50 + Met 500) BID (Sita 50 + Met 1000) BID	58 65 62	All statins: Plb (→ Met 1000 BID at week 24) Met 500 BID Met 1000 BID	60 53 67	365
P040: Phase 3, monotherapy study in India, Korea, & China HbA1c Analysis: Week 18 FAS	Simvastatin: Sita 100 QD	5	Simvastatin: Plb	1	6
	All statins: Sita 100 QD	27	All statins: Plb	19	46
P047: Phase 3, monotherapy study in elderly HbA1c Analysis: Week 24 FAS	Simvastatin: 100 mg QD (CrCl ≥50 ml/min)	24	Simvastatin: Plb (CrCl ≥50 ml/min)	14	38
	All statins: 100 mg QD (CrCl ≥50 ml/min)	53	All statins: Plb (CrCl ≥50 ml/min)	53	106

Study: Design	Sitagliptin		Non-exposed		Total
P049: Phase 3, metformin non-inferiority monotherapy HbA1c Analysis: Week 24 PP	Simvastatin: Sita 100 QD	94	Simvastatin: Met 2000 QD	85	179
	All statins: Sita 100 QD	169	All statins: Met 2000 QD	163	332
P051: Phase 3, add-on to insulin (with/without metformin) study HbA1c Analysis: Week 24 FAS	Simvastatin: Sita 100	81	Simvastatin: Plb	73	154
	All statins: Sita 100	171	All statins: Plb	162	333
P052: Phase 3, add-on to metformin and rosiglitazone HbA1c Analysis: Week 18 FAS	Simvastatin: Sita 100	29	Simvastatin: Plb	16	45
	All statins: Sita 100	88	All statins: Plb	50	138
P053: Phase 3, add-on to metformin HbA1c Analysis: Week 18 FAS	Simvastatin: Sita 100 QD	16	Simvastatin: Plb	15	31
	All statins: Sita 100 QD	34	All statins: Plb	28	62
P064: Phase 3, combination therapy with pioglitazone HbA1c Analysis: Week 24 FAS	Simvastatin: Sita 100 QD + Pio 30 QD (→ 45 during extension)	18	Simvastatin: Pio 30 QD (→ 45 during extension)	21	39
	All statins: Sita 100 QD + Pio 30 QD (→ 45 during extension)	44	All statins: Pio 30 QD (→ 45 during extension)	45	89
P079: Phase 3, active-comparator, combination therapy study with metformin HbA1c Analysis: Week 18 FAS	Simvastatin: (Sita 50 + Met 1000) BID	58	Simvastatin: Met 1000 BID	67	125
	All statins: (Sita 50 + Met 1000) BID	146	All statins: Met 1000 BID	152	298
P801: Phase 3, add-on to metformin HbA1c Analysis: Week 18 FAS	Simvastatin: Sita 100 QD	14	Simvastatin: Rosi 4 BID Plb	16 22	52
	All statins: Sita 100 QD	29	All statins: Rosi 4 BID Plb	31 33	93
Total	**Simvastatin:**	**827**	**Simvastatin:**	**755**	**1582**

Study: Design	Sitagliptin		Non-exposed		Total
	All statins:	**1939**	**All statins:**	**1726**	**3665**

Key: FAS = full analysis set; PP = per protocol; Sita = sitagliptin; Pio = pioglitazone; Rosi = rosiglitazone; Plb = placebo; Met = metformin; SU = sulfonylurea; → = "switched to"; All doses are in mg.
Source: SCS Tables 2.7.4: 2 and 2.7.4: 3; SCE Table 2.7.3: 6

5.2 Review Strategy

No phase 3 studies were conducted with the sitagliptin/simvastatin FDC. However, on May 24, 2010, the applicant was informed that a clinical efficacy study in ≥200 T2DM subjects per group on metformin randomized to sitagliptin/simvastatin FDC or the component monotherapies for ≥16 weeks may be required as a PMR.

Thus, the efficacy of the FDC was evaluated as follows:

- Assessment of the glycemic effect on simvastatin subjects with T2DM in simvastatin studies
- Assessment of the glycemic efficacy of sitagliptin in subgroups of subjects treated with or without statins in sitagliptin studies
- A description of HbA1c changes in subjects who initiated a statin during the treatment period in the sitagliptin program

The safety assessment focused on data from subjects in sitagliptin studies who were coadministered sitagliptin and simvastatin. Subjects treated with simvastatin and placebo or an active-comparator were the control. To explore potential class effects of statins when coadministered with sitagliptin, safety was also assessed in patients who were coadministered sitagliptin and other statins in a pool of sitagliptin studies.

5.3 Discussion of Individual Studies/Clinical Trials

No phase 3 studies were conducted with the sitagliptin/simvastatin FDC. Please refer to Table 4 above for a summary of the phase 2/3 clinical trials in which sitagliptin was coadministered with simvastatin.

6 Review of Efficacy

Efficacy Summary

The applicant submitted this NDA for the use of sitagliptin/simvastatin FDC in patients for whom both sitagliptin and simvastatin is appropriate.

Although clinical pharmacology studies were conducted to bridge the efficacy of sitagliptin and simvastatin to the sitagliptin/simvastatin FDC, no phase 3 studies were conducted with the sitagliptin/simvastatin FDC. However, due to concerns about published reports of statins altering glycemic control (see section 1.2), the applicant was asked to analyze the effect of simvastatin and statins on glycemic control in completed studies, as agreed upon at the pre-NDA meeting.

- The applicant demonstrated that there was no clinically significant difference in the change in glycemic control (HbA1c) in T2DM subjects randomized to

simvastatin compared to placebo in the simvastatin clinical development program.
    - Heart Protection Study: In a random sample of T2DM subjects, there was no significant difference (-0.03 ± 0.13) between treatment groups in the change in HbA1c.
    - In study MK-0733-P187, there was no significant difference between the simvastatin 40 mg and placebo groups in the change in HbA1c at week 24 (95% CI -0.1, 0.4).
- The HbA1c-lowering efficacy of sitagliptin versus comparator was analyzed in the following subgroups in the 19 sitagliptin clinical trials (the same 19 sitagliptin studies that were included in the SCS): simvastatin users, statin users, and non-statin users. The results were generally similar between the groups, although few subjects were on simvastatin or any statin in some studies. This resulted in wide 95% CI intervals.
- Review of the change from baseline HbA1c in patients who initiated simvastatin/statin during the treatment period in the sitagliptin clinical development program did not suggest a clinically significant effect on the initiation of simvastatin or another statin on glycemic control.

Thus, the applicant demonstrated that the risks of the concomitant administration of sitaglitpin and simvastatin do not out weigh its benefits, although we will require a postmarketing clinical study to conclusively demonstrate the safety of this convenience product.

6.1 Indication

The applicant submitted this NDA for the use of sitagliptin/simvastatin FDC in patients for whom both sitagliptin and simvastatin is appropriate. Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM. Simvastatin is indicated as an adjunctive therapy to diet to:

- Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal MI, stroke, and the need for revascularization procedures in patients at high risk for coronary events.
- Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
- Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbeta-lipoproteinemia.
- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia.
- Reduce elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy.

6.1.1 Methods

No phase 3 studies were conducted with the sitagliptin/simvastatin FDC. In addition to the clinical pharmacology studies that were conducted to bridge the efficacy of sitagliptin and simvastatin to the sitagliptin/simvastatin FDC, data from simvastatin and sitagliptin studies were analyzed to demonstrate effects of simvastatin and statins on glycemic control in T2DM subjects, as follows:

- Change in glycemic control (HbA1c) in T2DM subjects randomized to simvastatin and placebo in the simvastatin clinical development program.
- Analyses of the HbA1c-lowering efficacy of sitagliptin versus comparator in the following subgroups in the sitagliptin program: simvastatin users, statin users, and non-statin users
- Description of HbA1c in patients who initiated simvastatin/statin during the treatment period in the sitagliptin clinical development program

6.1.2 Demographics

See also section 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.

6.1.3 Subject Disposition

Not applicable.

6.1.4 Analysis of Primary Endpoint(s)

As described in section 6.1.1 Methods, data from simvastatin and sitagliptin studies were analyzed to demonstrate effects of simvastatin and statins on glycemic control in T2DM subjects. Glycemic control (i.e. change in HbA1c) was the primary endpoint in these analyses.

- Change in glycemic control (HbA1c) in T2DM subjects randomized to simvastatin and placebo in simvastatin studies
- Analyses of the HbA1c-lowering efficacy of sitagliptin versus comparator in the following subgroups in the sitagliptin program: simvastatin users, statin users, and non-statin users
- Description of changes in HbA1c in patients who initiated simvastatin/statin during the treatment period in the sitagliptin clinical development program

<u>Change in glycemic control (HbA1c) in T2DM subjects randomized to simvastatin and placebo in simvastatin studies</u>

In the Summary of Clinical Efficacy, the applicant assessed the change in glycemic control in T2DM subjects in the Heart Protection Study (HPS) and study MK-0733-P187. The HPS enrolled adults (40 – 80 years) who were at high risk of coronary heart

disease (CHD) due to a history of MI or other CHD, occlusive disease of the non-coronary arteries, diabetes mellitus, or treated HTN and had non-fasting serum total cholesterol levels ≥135 mg/dl. A total of 5,963 T2DM adults and 14,573 non-diabetic adults were randomly assigned to receive placebo, antioxidant vitamins, simvastatin 40 mg daily, or vitamins + simvastatin 40 mg for 5 years in the United Kingdom. Endpoints included the first major coronary and vascular events. Study MK-0733-P187 compared the efficacy and tolerability of simvastatin 40 mg daily versus placebo over 24 weeks in 253 T2DM subjects with LDL-C >100 mg/dl and HbA1c ≤9% on a stable TZD dose (rosiglitazone or pioglitazone). The primary endpoint was the effect on LDL-C concentration.

Approximately 29% of HPS subjects had T2DM at baseline (5,963 of 20,536). A random sample of 1,087 T2DM had HbA1c measurements at initial screening and after 4.6 years of follow up. There was no significant difference between the treatment groups in the change in HbA1c. There were also no meaningful differences in the reporting rate of hospital admissions for unstable diabetes (3.1% simvastatin vs. 3.2% placebo) or laser treatment for retinopathy (1.4% simvastatin vs. 1.2% placebo). For the 4,867 T2DM subjects for whom antihyperglycemic agent (AHA) information was available at baseline and follow up, there were no meaningful differences between the simvastatin and placebo groups in the number (%) of subjects who initiated or stopped AHAs.

Reviewer comment: However, the HPS was not powered to detect the subtle differences published in the meta-analysis.

Table 5. HPS: Change from baseline in HbA1c in a random sample of T2DM subjects at the end of follow up in HPS

Measure A1C (%)	Simvastatin Comparison	
	Active (n=562)	Placebo (n=525)
Baseline	6.99 ± 0.11†	7.06 ± 0.10
Follow-up	7.14 ± 0.06	7.17 ± 0.06
Change	0.15 ± 0.09	0.12 ± 0.09
Difference	-0.03 ± 0.13	

† Mean ± SD.

Source: Summary of Clinical Efficacy (SCE), Table 2.7.3: 2.

Table 6. HPS: Number (%) of T2DM subjects on AHA at baseline and change in AHA at final follow up visit

	Simvastatin 40 mg N=2470	Placebo N=2397
Baseline use		
Insulin	814 (33%)	801 (33%)
Oral antihyperglycemic agent	1212 (49%)	1151 (48%)
Any antihyperglycemic agent	1992 (81%)	1923 (80%)
Not on antihyperglycemic agent	478 (19%)	474 (20%)
Started treatment not recorded at entry		
Insulin	428 (17%)	388 (16%)
Oral antihyperglycemic agent	356 (14%)	360 (15%)
Any antihyperglycemic agent†	310 (65%)†	313 (66%)†
Stopped treatment recorded at entry		
Insulin	61 (2%)	68 (3%)
Oral antihyperglycemic agent	278 (11%)	239 (10%)
Any antihyperglycemic agent	96 (4%)	93 (4%)
† Among patients not on an antihyperglycemic agent at baseline.		

Source: SCE, Table 2.7.3: 3.

Study MK-0733-P187 compared the efficacy and tolerability of simvastatin 40 mg daily versus placebo over 24 weeks in 253 T2DM subjects with HbA1c ≤9% on a stable TZD dose (rosiglitazone or pioglitazone). Although the primary efficacy endpoint was LDL-C, the study also evaluated HbA1c at baseline and week 24. There was no significant difference between groups in the change in HbA1c at week 24, although the trial was not powered to detect small differences such as those reported in the meta-analysis.

Table 7. MK-0733-P187: Change from baseline in HbA1c in T2DM subjects at week 24

Treatment	N	Pre-Mean	Post-Mean	LS Mean Change	p-Value
Simvastatin 40 mg	103	7.2%	7.4%	0.1	0.367
Placebo	114	7.2%	7.2%	-0.1	0.429
Between-group		p-Value	LS Mean	95% CI	
Simvastatin vs. Placebo		0.139	0.2	-0.1, 0.4	

Source: SCE, Table 2.7.3: 5.

Analyses of the HbA1c-lowering efficacy of sitagliptin versus comparator in the following subgroups in the sitagliptin program: simvastatin users, statin users, and non-statin users

The applicant conducted a subgroup analysis of the change in HbA1c using the same 19 sitagliptin studies that were included in the SCS. (See 7.1.1 Studies/Clinical Trials Used to Evaluate Safety more details.)

The goal of the subgroup analysis was to evaluate the glycemic effects (i.e. change in HbA1c) of sitagliptin with and without simvastatin/statins in the sitagliptin development program. As subjects were not stratified by statin use in the 19 studies, the applicant calculated estimated treatment differences and 95% CIs. The subgroups were as follows:

- Simvastatin users: Subjects who took any dose of simvastatin from the start of the treatment period to the analysis time point.
- Statin users: Subjects who took any statin from the start of the treatment period to the analysis time point.
- Non-statin users: Subjects who did not take any statin from the start of the treatment period to the analysis time point.

As proposed in the pre-NDA briefing document and discussed at the May 24, 2010 meeting, the applicant used the FAS population for the 17 studies other than non-inferiority protocols 024 and 049, for which the PP population was used. The applicant used PP analysis for studies 024 and 049 because it is recommended by ICH Guidance for Industry *E9 Statistical Principals for Clinical Trials*. In addition, a secondary analysis of the FAS in studies 024 and 049 was consistent with the PP analysis (see Table 8). The analysis treated data after the initiation of glycemic rescue as missing. The last observation carried forward (LOCF) method was used for missing values in the FAS population.

Reviewer comment: Treating the data after the initiation of glycemic rescue as missing tends to favor statin users whose glycemic control deteriorated but HbA1c does not rise (because the data are missing).

The results of the change in HbA1c analysis were generally similar between the simvastatin, statin, and non-statin groups and are shown in the figures below. Few subjects were on simvastatin or any statin in some studies, which resulted in wide 95% CI.

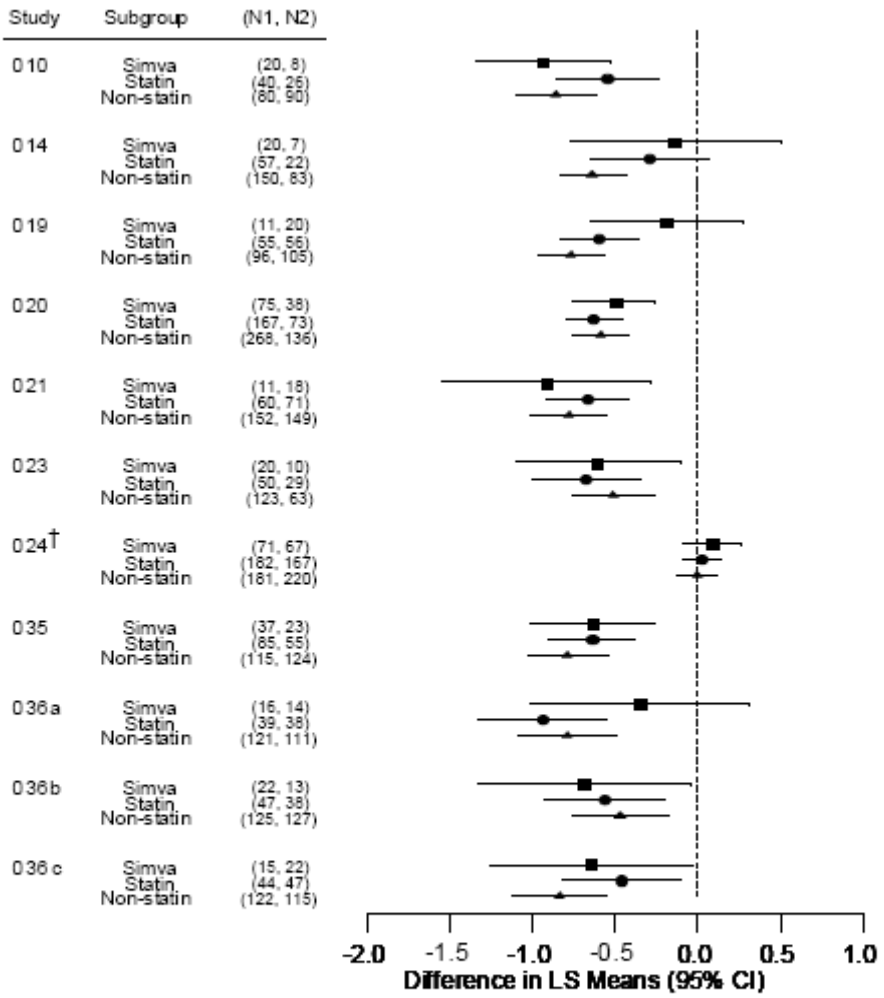
Table 8. Analysis of change from baseline in HbA1c by simvastatin/statin use (FAS unless specified)

Study Number: Description	Subgroup	N1, N2	Diff in LS Mean (95% CI)
010: Sita 50 BID vs Plb	Simva	20, 8	-0.94 (-1.35, -0.53)

	Statin	40, 26	-0.55 (-0.86, -0.23)
	Non-statin	80. 90	-0.86 (-1.11, -0.62)
014: Sita 100 vs Plb	Simva	20, 7	-0.14 (-0.78, -0.50)
	Statin	57, 22	-0.29 (-0.65, -0.06)
	Non-statin	150, 83	-0.64 (-0.83, -0.44)
019: Sita 100 vs Plb	Simva	11, 20	-0.19 (-0.65, 0.28)
	Statin	55, 56	-0.60 (-0.83, -0.36)
	Non-statin	96, 105	-0.77 (-0.97, -0.56)
020: Sita 100 vs Plb	Simva	75, 38	-0.50 (-0.75, -0.25)
	Statin	167, 73	-0.63 (-0.80, -0.46)
	Non-statin	268, 136	-0.59 (-0.76, -0.43)
021: Sita 100 vs Plb	Simva	11, 18	-0.92 (-1.55, -0.29)
	Statin	60, 71	-0.67 (-0.91, -0.43)
	Non-statin	152, 149	-0.78 (-1.01, -0.55)
023: Sita 100 vs Plb	Simva	20, 10	-0.61 (-1.11, -0.11)
	Statin	50, 29	-0.68 (-1.00, -0.35)
	Non-statin	123, 63	-0.51 (-0.77, -0.25)
024 (FAS): Sita 100 vs Glipizide	Simva	106, 92	0.03 (-0.15, 0.20)
	Statin	261, 232	0.04 (-0.08, 0.16)
	Non-statin	287, 296	0.07 (-0.06, 0.19)
024 (PP): Sita 100 vs Glipizide	Simva	71, 67	0.09 (-0.09, -0.27)
	Statin	182, 167	0.02 (-0.09, 0.14)
	Non-statin	181, 220	-0.00 (-0.13, 0.12)
035: Sita 100 vs Plb	Simva	37, 23	-0.63 (-1.01, -0.26)
	Statin	85, 55	-0.64 (-0.90, -0.38)
	Non-statin	115, 124	-0.79 (-1.03, -0.54)
036: Sita 100 vs Plb	Simva	16, 14	-0.35 (-1.02, 0.31)
	Statin	39, 38	-0.94 (-1.33, -0.55)
	Non-statin	121, 111	-0.79 (-1.09, -0.49)
036: Sita 50 BID + Met 500 BID vs Met 500 BID	Simva	22, 13	-0.69 (-1.33, -0.04)
	Statin	47, 38	-0.57 (-0.94, -0.20)
	Non-statin	125, 127	-0.47 (-0.75, -0.18)
036: Sita 50 BID + Met 1000 BID vs Met 1000 BID	Simva	15, 22	-0.65 (-1.26, -0.03)
	Statin	44, 47	-0.46 (-0.82, -0.11)
	Non-statin	122, 115	-0.84 (-1.13, -0.55)
040: Sita 100 vs Plb	Simva	5, 1	-0.32 (-21.00, 20.36)
	Statin	20, 16	-1.10 (-1.98, -0.21)
	Non-statin	314, 151	-1.01 (-1.22, -0.80)
047: Sita 100 vs Plb	Simva	22, 11	-0.62 (-1.19, -0.06)
	Statin	50, 48	-0.65 (-0.91, -0.39)
	Non-statin	38, 32	-0.83 (-1.33, -0.33)
049 (FAS): Sita 100 vs Met	Simva	86, 76	0.20 (0.03, 0.37)
	Statin	151, 145	0.17 (0.06, 0.29)
	Non-statin	349, 343	0.19 (0.09, 0.29)
049 (PP): Sita 100 vs Met	Simva	78, 71	0.15 (0.01, 0.29)
	Statin	139, 128	0.15 (0.04, 0.25)
	Non-statin	306, 304	0.14 (0.04, 0.24)
051: Sita 100 vs Plb	Simva	75, 69	-0.54 (-0.80, -0.29)
	Statin	153, 150	-0.55 (-0.73, -0.38)
	Non-statin	142, 153	-0.53 (-0.74, -0.31)
052: Sita 100 vs Plb	Simva	22, 13	-1.14 (-1.77, -0.51)

	Statin	73, 42	-0.91 (-1.22, -0.60)
	Non-statin	85, 41	-0.58 (-0.94, -0.22)
053: Sita 100 vs Plb	Simva	12, 13	-0.71 (-1.62, 0.20)
	Statin	25, 23	-0.76 (-1.37, -0.15)
	Non-statin	64, 64	-1.15 (-1.58, -0.72)
061: Sita 100 vs Plb	Simva	7, 8	-0.88 (-1.82, 0.07)
	Statin	15, 12	-0.73 (-1.34, -0.12)
	Non-statin	31, 35	-0.81 (-1.39, -0.23)
061: Sita 100 + Pio 30 vs Pio 30	Simva	9, 8	-0.96 (-1.79, -0.13)
	Statin	20, 22	-0.86 (-1.34, -0.38)
	Non-statin	27, 30	-0.34 (-0.95, 0.28)
064: Sita 100 vs Plb	Simva	10, 12	-0.14 (-0.82, 0.55)
	Statin	33, 29	-0.51 (-0.99, -0.03)
	Non-statin	211, 212	-0.92 (-1.19, -0.65)
079: Sita 50 BID + Met 1000 BID vs Met 1000 BID	Simva	46, 40	-0.57 (-1.05, -0.09)
	Statin	103, 101	-0.33 (-0.64, -0.02)
	Non-statin	428, 429	-0.64 (-0.84, -0.43)
801: Sita 100 vs Plb	Simva	13, 20	-0.24 (-0.68, 0.20)
	Statin	28, 31	-0.31 (-0.61, -0.01)
	Non-statin	62, 56	-0.64 (-0.91, -0.38)

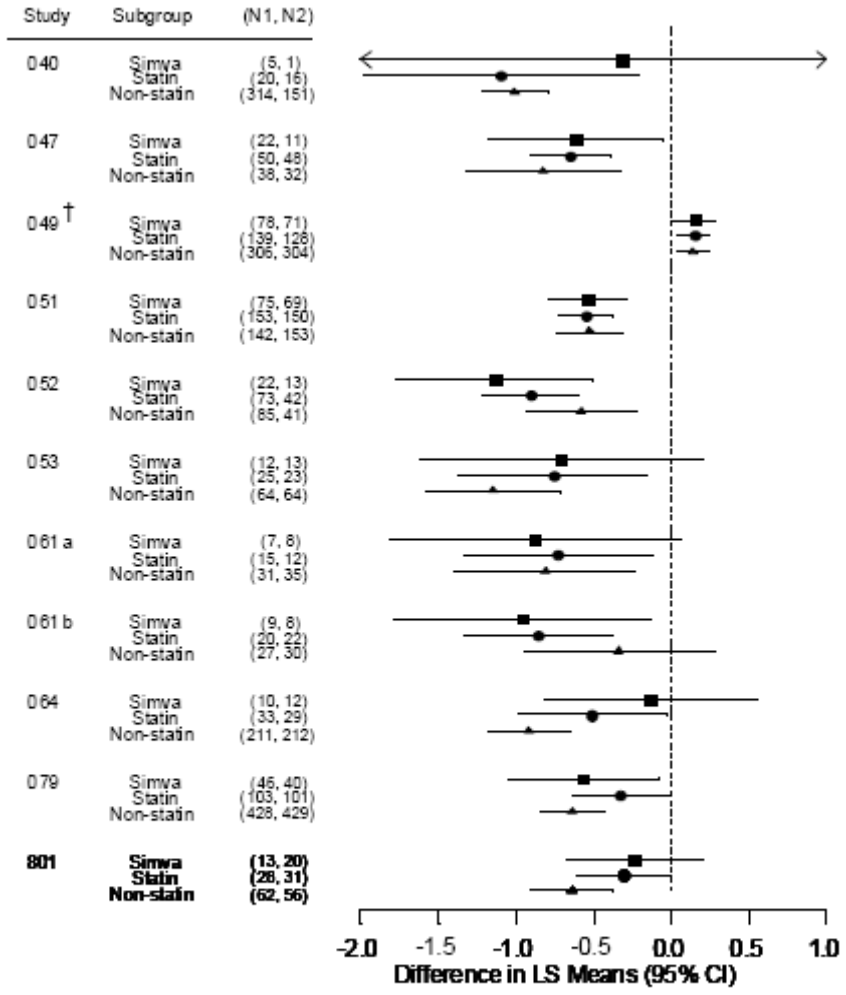
Key: FAS = full analysis set; PP = per protocol; N1, N2 = number for sitagliptin and non-exposed respectively; Sita = sitagliptin; Pio = pioglitazone; Rosi = rosiglitazone; Plb = placebo; Met = metformin; SU = sulfonylurea; All doses are in mg.
Source: SCE Appendices 2.7.3:1 – 2.7.3: 21



Simva = Simvastatin users; Statin = Statin users; Non-statin = Non-statin users
(N1, N2) = Number in the analysis for sitagliptin and non-exposed, respectively
036a = Protocol 036 comparison of sitagliptin vs. placebo
036b = Protocol 036 comparison of (sitagliptin 50 mg + metformin 500 mg) bid vs. metformin 500 mg bid
036c = Protocol 036 comparison of (sitagliptin 50 mg + metformin 1000 mg) bid vs. metformin 1000 mg bid
†Comparison of sitagliptin vs. glipizide (non-inferiority)

Figure 1. Analysis of change from baseline in HbA1c (%) by simvastatin/statin use (Protocols 010 – 036)

Source: SCE Figure 2.7.3: 1



Simva = Simvastatin users; Statin = Statin users; Non-statin = Non-statin users
(N1, N2) = Number in the analysis for sitagliptin and non-exposed, respectively
061a = Protocol 061 comparison of sitagliptin vs. placebo
061b = Protocol 061 comparison of sitagliptin + pioglitazone vs. pioglitazone
†Comparison of sitagliptin vs. metformin (non-inferiority)

Figure 2. Analysis of change from baseline in HbA1c (%) by simvastatin/statin use (Protocols 040 – 801)

Source: SCE Figure 2.7.3: 2

Description of HbA1c in patients who initiated simvastatin/statin during the treatment period in the sitagliptin clinical development program

Only a small number of subjects initiated simvastatin (n=95) or another statin (n=177) in sitagliptin studies. Note, the addition of simvastatin/statins occurred at different times after randomization and changes in HbA1c are strongly associated with the effects of study medication (i.e. sitagliptin, active comparator, or placebo). My review of the data submitted in the Summary of Clinical Efficacy's (SCE's) Appendices 2.7.3: 22 and

2.7.3:23 did not suggest a clinically significant effect on the initiation of simvastatin or another statin on glycemic control.

6.1.5 Analysis of Secondary Endpoints(s)

As no phase 3 trials were conducted with the FDC, there was no analysis of secondary endpoints. Please refer to section 6.1.4 above.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant proposes that the FDC be administered once daily in the evening, as this is consistent with sitagliptin and simvastatin's PK/PD properties and product labels. Dosing simvastatin in the evening was previously shown to be more effective than morning dosing. The sitagliptin product label recommends it be administered once daily without regard to food. PK data from twice daily sitagliptin suggests that the dosing time will not affect its PK profile.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

Prior to submitting NDA 202-343, teleconferences were held with the applicant regarding the proposed doses of sitagliptin/simvastatin FDC and which doses were required for filing. On September 30, 2010, the following agreements were made:

- The 100/80 mg tablet is not approvable because of safety issues (i.e. rhabdomyolysis) associated with the 80 mg simvastatin dose. The SEARCH CV

outcomes trial evaluated patients post-MI treated with simvastatin 80 mg or 20 mg and found no improvement in the incidence of MACE events with the higher dose, although there were more cases of severe myopathy with 80 mg than 20 mg (11 of the 80 mg patients developed rhabdomyolysis compared to zero 20 mg patients).

- Submission of a NDA without the 50 mg sitagliptin dose for use in subjects with moderate renal insufficiency is both a review and safety issue.
- If not contained in the NDA, the development of the 50 mg sitagliptin doses may be a PMR.

Thus, the current NDA 202-343 proposes sitagliptin/simvastatin 100/10, 100/20, and 100/40 mg FDC tablets, as previously agreed. The development of FDC doses containing sitagliptin 25 mg or simvastatin 5 mg is not required due to the low usage rate (2.2% and 0.6%, respectively). The development of FDC doses containing simvastatin 80 mg was not recommended due to safety issues (see section 2.3).

As no phase 3 studies were conducted with the sitagliptin/simvastatin FDC, the applicant analyzed sitagliptin and simvastatin co-administration data from the following 19 sitagliptin studies which were included in the SCS:

- Phase 1 protocol 061
- Phase 2 protocols 010 and 014
- Phase 3 protocols 019, 020, 021, 023, 024, 035, 036, 040, 047, 049, 051, 052, 053, 064, 079, and 801

Although the applicant assessed safety and tolerability "in patients who were co-administered sitagliptin and simvastatin in a pool of sitagliptin studies," it did not clearly state why the above studies were chosen for inclusion in the SCS. As shown in Table 9, most studies were previously submitted to NDAs 21-995 and 22-044 (sitagliptin and sitagliptin/metformin FDC, respectively).

The exposure to sitagliptin in combination with simvastatin or any statin in this population was acceptable (n=827 and n=1,938, respectively). The mean duration of exposure was ~280 days, although it ranged from <14 to ≥720 days. The majority of subjects, who received simvastatin, received 20 or 40 mg.

Exposure to sitagliptin in combination with simvastatin did not increase one's risk of death, SAEs, or discontinuation compared to non-exposed subjects.

- Thirteen of the 3,691 subjects included in the all statins pooled analysis died (6 sitagliptin, 7 non-exposed). Seven of these subjects had been exposed to simvastatin (2 sitagliptin, 5 non-exposed).
- The incidence of nonfatal SAEs in the simvastatin population in the controlled portions of pooled studies was similar between the sitagliptin and non-exposed groups (7.0% vs. 7.2%, respectively).

- The rate of discontinuations due to AEs was similar between treatment groups in both the simvastatin and all statin analyses (range 3.3 - 4.2%), despite an increase in the gastrointestinal SOC that was more prevalent in the non-exposed (i.e. simvastatin population: sitagliptin 0.2% vs. non-exposed 1.3%).

Due to the risk of myopathy and liver enzyme abnormalities with simvastatin, the safety database was reviewed for events of blood CPK increased and serum ALT or AST consecutive elevations ≥3x ULN.

- The effect of the co-administration of sitagliptin and simvastatin on myositis was analyzed using six prespecified terms. The rate at which blood CPK increased occurred was not significantly different between treatment groups (see Table 19) nor was there a dose-related effect of simvastatin (see Table 20). There were no blood CPK elevations ≥10x ULN in the simvastatin population.
- The incidence of consecutive ALT and/or AST elevations ≥3x ULN were not statistically significantly different between the sitagliptin and non-exposed groups in the simvastatin, all statins, and other statin populations (see Table 22).

Although the sitagliptin label warns about the risks of pancreatitis, hypoglycemia (when used with an insulin secretagogue), hypersensitivity, and renal impairment (recently added), the concomitant use of simvastatin does not increase these risks.

The incidence of AEs in the simvastatin and all statins populations in the controlled portions of pooled studies, excluding data after initiation of glycemic rescue, was similar between the sitagliptin and non-exposed groups (62.8-65.1%). The 95% CI between-group difference included zero in both populations. AEs were reported most frequently in the following three SOCs for the simvastatin and all statins populations: infections and infestations, gastrointestinal disorders, and musculoskeletal and connective tissue disorders.

The SCS analyzed limited chemistry and hematology values by mean changes from baseline over time and the incidence of measurements meeting PDLC, as agreed at the pre-NDA meeting. No clinically meaningful differences were observed between treatment groups in the simvastatin and all statins populations.

No dose-, time-, or demographic-dependent effect on adverse events was observed. The available postmarketing data do not suggest a safety concern with the co-administration of sitagliptin and simvastatin.

With regards to vital signs and ECGs, the changes from baseline to week 104/106 in blood pressure and heart rate were small and likely not clinically meaningful in both the simvastatin and all statins population (see Table 37). A tQT study of the sitagliptin/simvastatin FDC was not required because 1) a tQT study of sitagliptin was previously conducted and was found to be negative, 2) there is approximately 20 years' clinical experience with simvastatin without clinical evidence of QT prolongation, and 3)

there is a recent precedent for approving a simvastatin FDC without a tQT study. However, the applicant has initiated TECOS, a randomized, placebo controlled clinical trial to evaluate CV outcomes after treatment with sitagliptin in patients with T2DM and inadequate glycemic control on mono- or dual combination oral antihyperglycemic therapy. This study will include subjects on sitagliptin and simvastatin. Its planned completion date is December 2014.

Although sitagliptin is pregnancy category B, simvastatin is pregnancy category X. The applicant proposes pregnancy category X for sitagliptin/simvastatin FDC, which is acceptable.

The applicant requested a waiver from required pediatric studies "because it does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients". On August 17, 2011, the Pediatric Review Committee (PeRC) recommended a full waiver. I concur with this decision.

As the PDUFA goal date for NDA 202-343 is October 7, 2011 and an NDA supplement for the sitagliptin 50 mg doses would be reviewed under a 10-month time clock, the additional sitagliptin 50 mg doses could be available within one year of approval of the 100 mg doses, based on the applicant's plan to submit a sNDA for those doses in November 2011. This is acceptable because the risk/benefit assessment of the proposed sitagliptin/metformin XR NDA is favorable. However, I believe submission of a supplemental NDA for the sitagliptin 50 mg doses should be a PMR with the due date of December 31, 2011 to ensure that patients with moderate renal insufficiency have the appropriate doses available for use.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As no phase 3 studies were conducted with the sitagliptin/simvastatin FDC, the applicant analyzed sitagliptin and simvastatin co-administration data from 19 sitagliptin studies in the SCS:

- Phase 1 protocol 061
- Phase 2 protocols 010 and 014
- Phase 3 protocols 019, 020, 021, 023, 024, 035, 036, 040, 047, 049, 051, 052, 053, 064, 079, and 801

The majority of these studies were previously submitted and reviewed as shown in Table 9. Studies that were not previously reviewed include extension and long term studies, populations not reflective of the general American population (e.g. international)

a phase 1 study, and an active comparator study (see Table 4). This is acceptable because the applicant only proposes the following two labeling sentences in section 6.1 Clinical Trials Experience based on the pooled analysis, *In a pooled subgroup analysis of 19 controlled clinical studies of sitagliptin involving 1582 patients whose background therapy included simvastatin, incidences of adverse reactions for patients treated with sitagliptin and simvastatin (n=827) were similar to those for patients treated with control therapy (placebo or active comparator) and simvastatin (n=755). Among these patients 3.3% of the sitagliptin-treated group and 4.2% of the controls discontinued due to adverse reactions.*

Table 9. Submission timeline of studies included in SCS

Studies in SCS	When Submitted
P010 (incl. Extension 1), P014 (incl. Extension 1), P019, P028, P020 (Part A), P021 (Part A), and P023 (Part A)	Sitagliptin NDA
P020 (Part A)	Sitagliptin/metformin FDC NDA
P051, P052, P024 (Part A), P035 (Part A), P036 (Part A), and P064 (Part A)	Sitagliptin supplements (S-002, S-011, S-012) and sitagliptin/metformin supplements (S-003, S-004, S-012)
P040, P047, P049, P053, P061, P079, P801, P010 (Extension 2), P014 (Extension 2), P036 (Extension), P064 (Extension), and long term data (Parts A and B from P020, P021, P023, P024, P035, and P036)	Not previously submitted

7.1.2 Categorization of Adverse Events

The applicant's coding and categorization of AEs was adequate. MedDRA version 12.0 was used to create the pooled analysis. This version was also used for the last completed study included in the pool, although other versions were used for earlier clinical study reports.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See section 7.1.1 Studies/Clinical Trials Used to Evaluate Safety.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The exposure to sitagliptin in combination with simvastatin or any statin was acceptable (n=827 and n=1,938, respectively). The mean duration of exposure was ~280 days, although it ranged from <14 to ≥720 days. The majority of subjects, who received simvastatin, received 24 or 40 mg.

Table 10. Exposure to sitagliptin and simvastatin in controlled portion of pooled studies, excluding data after initiation of glycemic rescue

Treatment	<84 days	84 to <180 days	180 to <360 days	360 to <540 days	540 to <720 days	≥720 days	Total Patients	Mean duration (days)
Sita 100	78	325	181	107	56	80	827	289.0
Non-exposed	123	325	144	71	41	47	751	240.7

Source: SCS Table 2.7.4: 4

Table 11. Exposure to sitagliptin and simvastatin in controlled portion of pooled studies, excluding data after initiation of glycemic rescue

Treatment	<84 days	84 to <180 days	180 to <360 days	360 to <540 days	540 to <720 days	≥720 days	Total Patients	Mean duration (days)
Simva <20								
Sita 100	11	35	16	19	6	15	102	318.5
Non-exposed	18	45	23	6	1	2	95	190.2
Simva 20								
Sita 100	28	152	69	57	25	28	359	284.6
Non-exposed	52	139	51	28	23	20	313	244.1
Simva 40								
Sita 100	28	90	56	21	15	27	237	284.5
Non-exposed	38	92	38	22	12	17	219	247.5
Simva 80								
Sita 100	2	12	10	1	2	3	30	284.3
Non-exposed	7	5	6	3	0	4	25	274.5
Mixed dose								
Sita 100	0	4	9	6	4	7	30	440.3
Non-exposed	3	13	9	7	5	3	40	325.4
Unknown dose								
Sita 100	9	32	21	3	4	0	69	219.5
Non-exposed	5	31	17	5	0	1	59	206.8

Source: SCS Table 2.7.4: 5

Table 12. Exposure to sitagliptin and any statin in controlled portion of pooled studies, excluding data after initiation of glycemic rescue

Treatment	<84	84 to	180 to	360 to	540 to	≥720	Total	Mean

	days	<180 days	<360 days	<540 days	<720 days	days	Patients	duration (days)
Sita 100	216	756	395	252	142	177	1938	284.7
Non-exposed	276	759	313	168	103	103	1722	242.6

Source: SCS Table 2.7.4: 6

Of the subjects who used simvastatin or any statin in combination with sitagliptin during the controlled portions of the pooled studies, the majority (87.7-92.1%) of subjects were on the statin prior to the start of the treatment period. The majority (82.6-87.5%) of subjects were also on the statin for the entire treatment period.

Table 13. Summary of simvastatin and any statin use in controlled portions of pooled studies, excluding data after initiation of glycemic rescue

Simva/Statin use	Simvastatin		Any statin	
	Sita 100 n=827	Non-exposed n=755	Sita 100 n=1939	Non-exposed n=1726
On simva/statin at start of treatment (n [%])	725 (87.7)	659 (87.3)	1786 (92.1)	1571 (91.0)
Started during treatment (n [%])	102 (12.3)	96 (12.7)	153 (7.9)	155 (9.0)
On for entire treatment (n [%])	683 (82.6)	623 (82.5)	1697 (87.5)	1496 (86.7)
Stopped prior to end of treatment (n [%])	43 (5.2)	38 (5.0)	83 (4.3)	59 (3.4)
Gap >14 days during treatment (n [%])	8 (1.0)	12 (1.6)	33 (1.7)	39 (2.3)
Percentage of treatment period on simva/statin (mean [SD])	92.0 (21.1)	90.7 (23.7)	94.3 (18.5)	94.0 (18.7)
Days on simva/sita prior to treatment	818 (1011)	828 (1054)	788 (996)	836 (1009)

Source: SCS Tables 2.7.4: 7 and 2.7.4: 8

In the 19 studies included in the pooled safety analysis, the mean subject age was ~58 years. Slightly more than half of subjects were male. The majority were white (74.0-79.9%); approximately 10% of subjects were Asian. The mean duration of T2DM and mean HbA1c were ~6 years and 8%, respectively. The mean BMI of subjects was 31. Few subjects had liver disease (5.7-7.0%), but the majority had dyslipidemia (88.1-91.4%) with a mean LDL-C of 93 mg/dl. (See Table 14.)

Table 14. Demographics of controlled portions of pooled studies, excluding data after initiation of glycemic rescue therapy

Characteristic	Simvastatin		All statins	
	Sitagliptin (n=827)	Non-exposed (n=755)	Sitagliptin (n=)	Non-exposed (n=)
Age (mean years [SD])	58.0 (9.0)	57.7 (9.4)	57.3 (9.3)	57.4 (9.5)
Gender (male n [%])	477 (57.7)	435 (57.6)	1068 (55.1)	966 (56.0)
Race (n [%])				
White	656 (79.3)	603 (79.9)	1415 (73.0)	1278 (74.0)
Black	34 (4.1)	28 (3.7)	103 (5.3)	109 (6.3)
Am. Indian or Alaskan native	1 (0.1)	3 (0.4)	4 (0.2)	8 (0.5)
Asian	82 (9.9)	76 (10.1)	207 (10.7)	181 (10.5)

Multi-racial	16 (1.9)	11 (1.5)	48 (2.5)	35 (2.0)
Native Hawaiian or Pac. Islander	7 (0.8)	9 (1.2)	8 (0.4)	11 (0.6)
Unknown	31 (3.7)	25 (3.3)	154 (7.9)	104 (6.0)
BMI (mean [SD])	31.2 (5.5)	31.3 (5.5)	31.2 (5.5)	31.4 (5.4)
Baseline HbA1c (mean % [SD])	8.1 (1.1)	8.1 (1.1)	8.2 (1.2)	8.2 (1.1)
Duration of DM (mean years [SD])	6.0 (6.1)	5.7 (5.8)	6.0 (6.0)	5.8 (5.7)
CPK (IU/L [SD])	65.9 (32.8)	64.6 (35.7)	69.9 (43.6)	66.5 (36.0)
History of liver disease (yes n [%])	47 (5.7)	49 (6.5)	135 (7.0)	100 (5.8)
History of dyslipidemia (yes n [%])	741 (89.6)	665 (88.1)	1772 (91.4)	1555 (90.1)
LDL-C (mg/dl mean [SD])	94 (36)	93 (36)	94 (36)	94 (36)
Triglycerides (mg/dl mean [SD])	167 (97)	184 (142)	182 (143)	187 (151)
HDL-C (mg/dl mean [SD])	46 (11)	45 (11)	45 (11)	45 (11)
Non-HDL-C (mg/dl mean [SD])	126 (42)	129 (44)	129 (45)	130 (44)
Tot. cholesterol (mg/dl mean [SD])	172 (43)	175 (43)	175 (45)	175 (44)

Source: SCS Tables 2.7.4: 9 – 2.7.4: 13 and 2.7.4:15 – 2.7.4: 19

7.2.2 Explorations for Dose Response

Not applicable. Please refer to the appropriate sections of the sitagliptin NDA 21-995 and simvastatin NDA 19-766 labels.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to section 4.3 Preclinical Pharmacology/Toxicology for a discussion of the relevant animal data with sitagliptin/simvastatin.

7.2.4 Routine Clinical Testing

Not applicable, as no clinical trials were conducted to support the NDA.

7.2.5 Metabolic, Clearance, and Interaction Workup

Clinical pharmacology study P025, a simvastatin interaction study, was submitted and reviewed under the original sitagliptin NDA in 2005. Study P168 was a multiple dose, crossover drug interaction study that assessed the potential for simvastatin to effect sitagliptin PK in 10 healthy males and females. In part A, subjects received a single dose of sitagliptin 100 mg. In part B, subjects received simvastatin 80 mg daily for seven days and sitagliptin 100 mg on day 5. Multiple dose administration of simvastatin had no clinically significant effect on the single dose PK of sitagliptin. Please refer to Dr. Sang Chung's clinical pharmacology review and the product labels of NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

In the SCE, the applicant addressed the potential concern that statin therapy is associated with a slightly increased risk of worsening glycemic control. See section 6 Review of Efficacy for full details.

The structure of the integrated summary of safety was discussed at the pre-NDA meeting. In the SCS, the applicant analyzed myopathy and transaminitis as adverse events of special interest. I also reviewed the SCS for special adverse events of interest, including pancreatitis, hypoglycemia, hypersensitivity, and renal impairment.

7.3 Major Safety Results

7.3.1 Deaths

Thirteen of the 3,691 subjects included in the all statins pooled analysis died (6 sitagliptin, 7 non-exposed). Seven of these subjects had been exposed to simvastatin (2 sitagliptin, 5 non-exposed). Simvastatin subject 33583 in study P020 died of both hepatic and renal failure. Subject 50865 in study P035 died of a fall and drowning.

Causes of death in the all statins analysis which occurred in the sitagliptin treatment group but not the non-exposed group were as follows: death (n=2), drowning (n=1), multiple injuries (n=1), astrocytoma malignant (n=1), and interstitial lung disease (n=1). The two sitagliptin subjects who received a statin other than simvastatin and whose cause of death was “death” are as follows:

- Subject 33058: 60 year old female with T2DM, hypertension (HTN), hyperlipidemia, tachycardia, obesity, depression, atopic dermatitis, degenerative joint disease, and sleep apnea. On day 456, she had a syncope after consuming sleeping pills with alcohol. This was not considered a suicide attempt. On Day 519, she was found dead. The immediate cause of death on the death certificate was “ruptured myocardium” although an autopsy was not done.
- Subject 33561: Male with T2DM, HTN, and hypercholesterolemia who was found dead. No autopsy was conducted. Prior to the event, he had flu symptoms, decreased appetite, vomiting, dyspnea, and hyperglycemia. The subject was to follow up at an appointment that evening but never arrived.

Exposure to sitagliptin or sitagliptin in combination with simvastatin does not increase one’s risk of death.

Table 15. Deaths in the controlled portions of pooled studies, including data after the initiation of glycemic rescue

Preferred Term (n [%])	Simvastatin		All Statins	
	Sitagliptin (n=834)	Non-exposed (n=760)	Sitagliptin (n=1950)	Non-exposed (n=1741)
Total number (%) who died	2 (0.2)	5 (0.7)	6 (0.3%)	7 (0.4)
Myocardial infarction	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)
Death	-	-	2 (0.1)	0 (0.0)
Drowning	-	-	1 (0.1)	0 (0.0)
Sudden cardiac death	-	-	0 (0.0)	1 (0.1)
Hepatic failure	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Fall	-	-	1 (0.1)	0 (0.0)
Multiple injuries	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Astrocytoma malignant	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Hepatic neoplasm non-resectable	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Oesophageal cancer metastatic	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Completed suicide	-	-	0 (0.0)	1 (0.1)
Renal failure	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Interstitial lung disease	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)

Source: SCS Tables 2.7.4: 30 and 2.7.4: 31

7.3.2 Nonfatal Serious Adverse Events

The incidence of nonfatal SAEs in the simvastatin population in the controlled portions of pooled studies was similar between the sitagliptin and non-exposed groups (7.0% vs. 7.2%, respectively). The incidence of SAEs by SOC was also similar between treatment groups with the following notable exceptions:

- Occurred more commonly in the sitagliptin group:
  - Musculoskeletal disorders (0.6% vs. 0.1%): The incidence was primarily due to 3 cases of osteoarthritis in the sitagliptin group. All other events were single events.
  - Neoplasms (1.2% vs. 0.8%): All events in the sitagliptin group were single events, except for prostate cancer (n=2).
  - Renal and urinary disorders (0.4% vs. 0.0%): There was one event of nocturia and two events of renal colic in the sitagliptin group.
- Occurred more commonly in the non-exposed group:
  - Cardiac disorders (2.3% vs. 1.3%): The difference was primarily due to six events of coronary artery disease, three events each of MI and angina pectoris, and two events each of angina unstable and atrial flutter in the non-exposed group.
  - Nervous system disorders (0.9% vs. 0.5%): There were three events of syncope in the non-exposed group but only one in the sitagliptin group.

Sitagliptin, when used in combination with simvastatin, does not appear to increase SAEs.

Table 16. Nonfatal SAEs in the simvastatin population in controlled portions of pooled studies, excluding data after initiation of glycemic rescue

	Sitagliptin 100 mg		Non-Exposed	
	n	(%)	n	(%)
Patients in population	827		755	
with one or more non fatal serious adverse events	58	(7.0)	54	(7.2)
with no non fatal serious adverse events	769	(93.0)	701	(92.8)
Blood and lymphatic system disorders	**1**	**(0.1)**	**0**	**(0.0)**
Anaemia	1	(0.1)	0	(0.0)
Cardiac disorders	**11**	**(1.3)**	**17**	**(2.3)**
Acute coronary syndrome	1	(0.1)	0	(0.0)
Acute myocardial infarction	1	(0.1)	0	(0.0)
Angina pectoris	1	(0.1)	3	(0.4)
Angina unstable	2	(0.2)	2	(0.3)
Atrial flutter	0	(0.0)	2	(0.3)
Atrioventricular block	1	(0.1)	0	(0.0)
Cardiac failure congestive	1	(0.1)	1	(0.1)
Coronary artery disease	1	(0.1)	6	(0.8)
Coronary artery stenosis	1	(0.1)	0	(0.0)
Myocardial infarction	1	(0.1)	3	(0.4)
Myocardial ischaemia	0	(0.0)	1	(0.1)
Sick sinus syndrome	0	(0.0)	1	(0.1)
Sinus bradycardia	1	(0.1)	0	(0.0)
Supraventricular tachycardia	1	(0.1)	0	(0.0)
Eye disorders	**1**	**(0.1)**	**0**	**(0.0)**
Cataract	1	(0.1)	0	(0.0)
Gastrointestinal disorders	**4**	**(0.5)**	**3**	**(0.4)**
Gastritis	1	(0.1)	0	(0.0)
Inguinal hernia	1	(0.1)	2	(0.3)
Intestinal obstruction	0	(0.0)	1	(0.1)
Melaena	1	(0.1)	0	(0.0)
Reflux oesophagitis	1	(0.1)	0	(0.0)
Umbilical hernia	1	(0.1)	0	(0.0)
General disorders and administration site conditions	**4**	**(0.5)**	**4**	**(0.5)**
Adverse drug reaction	0	(0.0)	1	(0.1)
Chest pain	0	(0.0)	1	(0.1)
Fatigue	1	(0.1)	0	(0.0)
Non-cardiac chest pain	2	(0.2)	2	(0.3)
Oedema peripheral	1	(0.1)	0	(0.0)
Hepatobiliary disorders	**2**	**(0.2)**	**2**	**(0.3)**
Cholecystitis	0	(0.0)	1	(0.1)
Cholelithiasis	2	(0.2)	1	(0.1)
Infections and infestations	**5**	**(0.6)**	**6**	**(0.8)**
Anal abscess	0	(0.0)	1	(0.1)
Arthritis bacterial	1	(0.1)	0	(0.0)
Dengue fever	0	(0.0)	1	(0.1)
Gastroenteritis	1	(0.1)	0	(0.0)
Helicobacter infection	0	(0.0)	1	(0.1)

	Sitagliptin 100 mg		Non-Exposed	
	n	(%)	n	(%)
Infections and infestations	**5**	**(0.6)**	**6**	**(0.8)**
Liver abscess	0	(0.0)	1	(0.1)
Lower respiratory tract infection	0	(0.0)	1	(0.1)
Pneumonia	0	(0.0)	1	(0.1)
Pneumonia streptococcal	0	(0.0)	1	(0.1)
Postoperative wound infection	1	(0.1)	0	(0.0)
Pyelonephritis chronic	1	(0.1)	0	(0.0)
Sinusitis	1	(0.1)	0	(0.0)
Injury, poisoning and procedural complications	**9**	**(1.1)**	**7**	**(0.9)**
Ankle fracture	0	(0.0)	1	(0.1)
Head injury	0	(0.0)	1	(0.1)
Incisional hernia	0	(0.0)	1	(0.1)
Medical device complication	1	(0.1)	0	(0.0)
Meniscus lesion	1	(0.1)	0	(0.0)
Multiple injuries	1	(0.1)	0	(0.0)
Overdose	1	(0.1)	1	(0.1)
Pneumothorax traumatic	1	(0.1)	0	(0.0)
Postoperative thoracic procedure complication	0	(0.0)	1	(0.1)
Postoperative thrombosis	0	(0.0)	1	(0.1)
Procedural complication	1	(0.1)	0	(0.0)
Rib fracture	0	(0.0)	1	(0.1)
Skin laceration	1	(0.1)	0	(0.0)
Tendon injury	1	(0.1)	0	(0.0)
Traumatic ulcer	1	(0.1)	0	(0.0)
Musculoskeletal and connective tissue disorders	**5**	**(0.6)**	**1**	**(0.1)**
Arthritis	1	(0.1)	1	(0.1)
Musculoskeletal pain	1	(0.1)	0	(0.0)
Osteoarthritis	3	(0.4)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**10**	**(1.2)**	**6**	**(0.8)**
B-cell lymphoma	1	(0.1)	0	(0.0)
Basal cell carcinoma	1	(0.1)	2	(0.3)
Bladder cancer	1	(0.1)	0	(0.0)
Colon cancer	1	(0.1)	0	(0.0)
Diffuse large B-cell lymphoma	1	(0.1)	0	(0.0)
Malignant melanoma	1	(0.1)	1	(0.1)
Prostate cancer	2	(0.2)	3	(0.4)
Renal cell carcinoma	1	(0.1)	0	(0.0)
Small cell lung cancer stage unspecified	1	(0.1)	0	(0.0)
Nervous system disorders	**4**	**(0.5)**	**7**	**(0.9)**
Carotid artery disease	0	(0.0)	1	(0.1)
Carotid artery stenosis	1	(0.1)	1	(0.1)
Cerebrovascular accident	1	(0.1)	1	(0.1)
Guillain-Barre syndrome	0	(0.0)	1	(0.1)
Presyncope	1	(0.1)	0	(0.0)
Syncope	1	(0.1)	3	(0.4)

	Sitagliptin 100 mg		Non-Exposed	
	n	(%)	n	(%)
Psychiatric disorders	**0**	**(0.0)**	**3**	**(0.4)**
Depression	0	(0.0)	1	(0.1)
Hallucination	0	(0.0)	1	(0.1)
Suicidal ideation	0	(0.0)	1	(0.1)
Renal and urinary disorders	**3**	**(0.4)**	**0**	**(0.0)**
Nocturia	1	(0.1)	0	(0.0)
Renal colic	2	(0.2)	0	(0.0)
Reproductive system and breast disorders	**1**	**(0.1)**	**2**	**(0.3)**
Endometriosis	0	(0.0)	1	(0.1)
Hydrometra	0	(0.0)	1	(0.1)
Ovarian cyst	1	(0.1)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**2**	**(0.2)**	**1**	**(0.1)**
Acute pulmonary oedema	1	(0.1)	0	(0.0)
Asthma	0	(0.0)	1	(0.1)
Pulmonary embolism	1	(0.1)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(0.1)**	**0**	**(0.0)**
Skin ulcer	1	(0.1)	0	(0.0)
Surgical and medical procedures	**1**	**(0.1)**	**0**	**(0.0)**
Finger amputation	1	(0.1)	0	(0.0)
Vascular disorders	**5**	**(0.6)**	**3**	**(0.4)**
Aneurysm	0	(0.0)	1	(0.1)
Aortic aneurysm	0	(0.0)	1	(0.1)
Aortic stenosis	1	(0.1)	0	(0.0)
Arteriosclerosis	1	(0.1)	0	(0.0)
Deep vein thrombosis	1	(0.1)	0	(0.0)
Leriche syndrome	1	(0.1)	0	(0.0)
Peripheral arterial occlusive disease	2	(0.2)	0	(0.0)
Peripheral ischaemia	0	(0.0)	1	(0.1)

Every patient is counted a single time for each applicable specific adverse event. A patient with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Source: SCS Table 2.7.4: 32

In the all statins population of pooled studies, slightly more SAEs occurred in the sitagliptin group when compared to the non-exposed group (7.0% vs. 6.4%). The incidence of SAEs by SOC and treatment group was similar but for the following:

- Cardiac disorders occurred more commonly in the non-exposed group (1.7% vs. 1.4%).
- Neoplasms occurred more commonly in the sitagliptin group (1.4% vs. 0.7%). Cancers which occurred in more than one subject in the sitagliptin group were basal cell carcinoma (n=5), breast (n=3), prostate (n=3), and squamous cell carcinoma of the skin (n=2). All of those cancers but squamous cell carcinoma of the skin also occurred in the non-exposed group.

The use of sitagliptin with statins does not appear to increase the risk of SAEs.

Table 17. Nonfatal SAEs in the all statins population in the controlled portions of pooled studies, excluding data after initiation of glycemic rescue

System Organ Class (n [%])	Sitagliptin (n=1939)	Non-exposed (n=1726)

Total nonfatal SAEs	136 (7.0)	110 (6.4)
Blood & lymphatic	1 (0.1)	1 (0.1)
Cardiac	28 (1.4)	30 (1.7)
Congenital, familial, & genetic	1 (0.1)	0 (0.0)
Ear & labyrinth	1 (0.1)	0 (0.0)
Eye	1 (0.1)	1 (0.1)
Gastrointestinal	12 (0.6)	8 (0.5)
General & administrative site	5 (0.3)	9 (0.5)
Hepatobiliary	3 (0.2)	3 (0.2)
Infections & infestations	13 (0.7)	9 (0.5)
Injury, poisoning, & procedural	16 (0.8)	15 (0.9)
Investigations	2 (0.1)	1 (0.1)
Metabolism & nutrition	2 (0.1)	2 (0.1)
Musculoskeletal & connective tissue	8 (0.4)	4 (0.2)
Neoplasms	27 (1.4)	12 (0.7)
Nervous	7 (0.4)	11 (0.6)
Psychiatric	2 (0.1)	5 (0.3)
Renal & urinary	6 (0.3)	2 (0.1)
Reproductive & breast	2 (0.1)	2 (0.1)
Respiratory, thoracic, & mediastinal	5 (0.3)	4 (0.2)
Skin & subcutaneous tissue	1 (0.1)	1 (0.1)
Surgical & medical procedures	1 (0.1)	0 (0.0)
Vascular	8 (0.4)	5 (0.3)

Source: Reference 2409

7.3.3 Dropouts and/or Discontinuations

The rate of discontinuations due to adverse events was similar between treatment groups in both the simvastatin and all statin analyses (range 3.3 - 4.2%). A notable difference in discontinuation rates (sitagliptin 0.2% vs. non-exposed 1.3%) was seen in the gastrointestinal SOC of the simvastatin population. This was mainly due to six events of diarrhea and two events of abdominal pain in the non-exposed group. This difference persisted in the all statins pool (0.6% vs. 1.2%). The discontinuation rates in the other SOCs were similar between treatment groups.

Use of sitagliptin with simvastatin did not increase the discontinuation rate.

Table 18. Subjects with adverse events which resulted in discontinuation in controlled portions of pooled studies, excluding data after initiation of glycemic rescue

System Organ Class	Simvastatin		All Statins	
	Sitagliptin (n=827)	Non-exposed (n=755)	Sitagliptin (n=1939)	Non-exposed (n=1726)
Patients discontinued (n [%])	27 (3.3)	32 (4.2)	77 (4.0)	68 (3.9)
Blood & lymphatic	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Cardiac	4 (0.5)	4 (0.5)	8 (0.4)	8 (0.5)
Endocrine	-	-	1 (0.1)	0 (0.0)

Eye	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)
Gastrointestinal	2 (0.2)	10 (1.3)	12 (0.6)	20 (1.2)
General & administrative site	-	-	2 (0.1)	1 (0.1)
Hepatobiliary	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)
Infections & infestations	2 (0.2)	0 (0.0)	5 (0.3)	2 (0.1)
Injury, poisoning, & procedural	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)
Investigations	3 (0.4)	4 (0.5)	16 (0.8)	13 (0.8)
Metabolism & nutrition	1 (0.1)	2 (0.3)	5 (0.3)	4 (0.2)
Musculoskeletal & connective tissue	-	-	1 (0.1)	2 (0.1)
Neoplasms	5 (0.6)	6 (0.8)	9 (0.5)	7 (0.4)
Nervous	3 (0.4)	2 (0.3)	4 (0.2)	2 (0.1)
Psychiatric	1 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)
Renal & urinary	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)
Respiratory, thoracic, & mediastinal	2 (0.2)	0 (0.0)	3 (0.2)	1 (0.1)
Skin & subcutaneous tissue	2 (0.2)	1 (0.1)	5 (0.3)	2 (0.1)

Source: SCS Table 2.7.4: 33 and 2.7.4: 34

7.3.4 Significant Adverse Events

Due to the risk of myopathy and liver enzyme abnormalities with simvastatin, the safety database was reviewed for events of blood CPK increased and serum ALT or AST consecutive elevations ≥3x ULN.

Blood CPK increased:
As skeletal muscle effects (e.g. myopathy and rhabdomyolysis) are labeled, potential adverse effects of statins, the applicant analyzed the effect of the co-administration of sitagliptin and simvastatin on these events using the following prespecified terms: myopathy, myositis, blood CPK increased, myoglobinemia, myoglobinuria, and rhabdomyolysis. Of these terms, only blood CPK increased occurred in the simvastatin, all statin, and other statin analyses (sitagliptin 8 vs. non-exposed 4). The incidence of blood CPK increased was numerically less in the simvastatin group when compared to the other statins group. The rate at which blood CPK increased occurred was not significantly different between treatment groups (see Table 19) nor was there a dose-related effect of simvastatin (see Table 20).

Table 19. Subjects with muscle events in controlled portions of pooled studies, excluding data after initiation of glycemic rescue

Treatment	**N, %**	**Difference in % vs. Non-exposed**	
		Estimate (95% CI)	**p-value**
Simvastatin population			
Sitagliptin 100 mg	827		
Non-exposed	755		
Muscle events (All increased CPK)			
Sitagliptin 100 mg	2 (0.2)	0.2 (-0.3, 0.9)	0.242
Non-exposed	0 (0.0)		
All statins population			

Sitagliptin 100 mg	1939		
Non-exposed	1726		
Muscle events (All increased CPK)			
Sitagliptin 100 mg	8 (0.4)	0.2 (-0.2, 0.7)	0.275
Non-exposed	4 (0.2)		
Other statins population			
Sitagliptin 100 mg	1112		
Non-exposed	971		
Muscle events (All increased CPK)			
Sitagliptin 100 mg	6 (0.5)	0.3 (-0.4, 1.0)	0.372
Non-exposed	3 (0.3)		

Source: SCS Table 2.7.4: 36, 2.7.4: 44, and 2.7.4.58

Table 20. Summary of subjects with blood CPK increased by statin and sitagliptin use, excluding data after initiation of glycemic rescue

Statin	Sitagliptin		Difference in % vs Non-exposed	
	Exposed	Non-exposed	Estimate (95% CI)	p-value
Simvastatin				
10 mg	1 (1.0%)		1.0 (-2.9, 5.4)	0.332
20 mg	1 (0.3%)		0.3 (-0.9, 1.6)	0.348
Atorvastatin				
10 mg	1	2		
20 mg	1	1		
40 mg	2			
Lovastatin 20 mg		1		
Pravastatin 40 mg	1			
Rosuvastatin 10 mg	1			
Total	**8**	**4**		

Note: Dose represents highest statin dose used concomitantly with sitagliptin.
Source: Reference 2290

The applicant reported the following narratives for the eight subjects with increased CPK (see also Table 20 and Table 21:

- Subject 38514 (simvastatin 20 mg, sitagliptin 100 mg): 55 year old male experienced blood CPK increased (295 mIU/ml) on day 86, which resolved by day 92. Baseline CPK was elevated (124 mIU/ml). He experienced non-serious muscle spasms on Day 12, which resolved on day 20. He completed the study on day 386, when CPK was less than baseline (81 mIU/ml) and muscle spasms recurred.
- Subject 50178 (simvastatin 10 mg, sitagliptin 100 mg): 70 year old male experienced blood CPK increased on days 31-32 (320 and 516 mIU/ml). He was hospitalized due to decreased sodium on day 31 (110 mEq/l). Study drug was discontinued on day 32. Chest CT on day 43 was consistent with small cell lung carcinoma.
- Subject 3356 (all statins [atorvastatin 20 mg], sitagliptin 100 mg): 44 year old male experienced blood CPK increased (10,520 mIU/ml), ALT increased (46

mIU/ml), and AST increased (174 mIU/ml) on day 15. On day 17, CPK was 48,300 IU/ml. Study drug and atorvastatin were discontinued on day 18. On day 19, CPK, ALT, and AST were 10300, 174, and 302, respectively. He had increased his exercise routine on days 13-15 (1 hour swimming, 1 hour walking with weights). Study drug was restarted on day 46, when CPK, ALT, and AST were 117, 15, and 14. He took the last dose of study drug on day 299 and was lost to follow up.

- Subject 33098 (all statins [atorvastatin 40 mg], sitagliptin 100 mg): 62 year old female with T2DM, back pain, fibromyalgia, intervertebral disc degeneration, and mitral regurgitation experienced myalgia on day 697, coronary artery disease (CAD) on day 698, blood CPK increased on day 700 (851 IU/l), and postoperative hemorrhage after percutaneous transluminal coronary angioplasty (PTCA) and vessel stenting on day 701. The ECG on day 174 indicated an ST-T segment abnormality. The patient received three stents on days 417 and 428. Study drug was discontinued on day 698, when she experienced unstable angina. Atorvastatin was discontinued on day 700 due to myalgia, which improved but did not resolve. After her postoperative hemorrhage and extended hospital stay, CPK was 3,442 IU/l on day 702. At the time of discharge on day 705, CPK was 965 IU/l. On days 713 and 718, CPK was 79 and 65 IU/l.
- Subject 30211 (all statins [rosuvastatin 10 mg], sitagliptin 100 mg): 57 year old male experienced blood CPK increased (244 mIU/ml) on day 43. His baseline CPK was elevated (146 mIU/ml). He withdrew consent to participate on day 254, when CPK was 110 mIU/ml.
- Subject 30643 (all statins [atorvastatin 10 mg], sitagliptin 100 mg): 49 year old male with spondylosis experienced blood CPK increased (205 mIU/ml) on day 168. His screening CPK was elevated (170 mIU/ml). He completed the study on day 729.
- Subject 30776 (all statins [atorvastatin 20-40 mg], sitagliptin 100 mg): 58 year old male with arthritis experienced blood CPK increased on day 1 and 131. On day 1, he experienced an event of coordination abnormal when CPK was 354 mIU/ml; this resolved on day 8. On day 11, the atorvastatin dose was decreased to 20 mg. On day 131, CPK was 179 mIU/ml. He completed the study on day 771 when CPK was 41 mIU/ml.
- Subject 38789 (all statins [pravastatin 40 mg], sitagliptin 100 mg): 45 year old male with plantar fasciitis and extremity pain experienced CPK increased (484 mIU/ml) on day 45. At screening, CPK was 160 mIU/ml. On day 45, the investigator recommended stopping pravastatin. ON day 87, CPK was 152 mIU/ml. He withdrew consent on day 132.
- Subject 2216 (all statins [lovastatin 20 mg], non-exposed): 57 year old male experienced blood CPK increased (172 mIU/ml) on day 35. His screening CPK was elevated (342 mIU/ml). It improved on day -49 (113 mIU/ml) but increased at baseline (day 1, 177 mIUm/l). He completed the study on day 757,
- Subject 30212 (all statins [atorvastatin 10 mg], non-exposed): 49 year old female with myofascial pain syndrome, osteoarthritis, and facet joint syndrome

experienced blood CPK increased on days 22 (310 mIU/ml) and 182 (393 mIU/ml). She had an elevated baseline CPK of 136 mIU/ml. He withdrew consent on day 218, when CPK was 120 mIU/ml.

- Subject 30594 (all statins [atorvastatin 10 mg], non-exposed): 67 year old male with spinal osteoarthritis experienced blood CPK increased (263 mIU/ml) on day 85. He discontinued the study on day 687, after meeting the glycemic discontinuation criteria.
- Subject 30674 (all statins [atorvastatin 20 mg], non-exposed): 74 year old male with spinal osteoarthritis experienced blood CPK increased on days 122 and 164 (216 and 243 mIU/ml, respectively). The CPK values remained slightly above normal throughout the study.

Table 21. CPK values for subjects with blood CPK (mIU/ml) increased, excluding data after initiation of glycemic rescue

Day	Subject											
	38514	**50178**	**3356**	**33098**	**30211**	**30643**	**30776**	**38789**	**2216**	**30212**	**30594**	**30674**
-90 to -76								160				
-75 to -61	116				148				342			98
-60 to -46			124						113			
-45 to -31							73					
-30 to -16					125	170				108	59	
-15 to -1			154						115			
1 to 15	124		135, 10520		146	113	354	125	177, 113	136	64	84
16 to 30	161		48300, 10300, 571, 146			126	174		328	310	72	137
31 to 45	73	320, 516			244	156		486, 484	172			121
46 to 60			117, 132, 147, 140				163		99	136		
61			152									190

to 75												
76 to 90	295		117		187	123		152	324	194	263	113
91 to 105	92						54		106		131	
106 to 120									112			
121 to 135	100		183		110	94	179	136		211	128	216
136 to 150	153											154
151 to 165	63, 80		170									243
166 to 180					146	205	69		127		118	188, 130
181 to 195									153	393		
196 to 210												203
211 to 225	80									120		
226 to 240			225						134			
241 to 255					110							
256 to 270						189					106	138
271 to 285							29					
286 to 315												
316 to 330						172						
331 to												

360												
361 to 375							45		246		94	106
376 to 390	81					195						
391 to 405												
406 to 420									89			
421 to 435				34		135						
436 to 480												
481 to 495						159	155				72	137
496 to 540												
541 to 555									165			
556 to 570						166						
571 to 630												
631 to 645											201, 144	
646 to 660						157					83	
661 to 675							53					
676 to 690											104	
691 to 705				851, 2950, 3442, 2333, 1730, 965								

706 to 720				79, 65								
721 to 735				128								135
736 to 765												
766 to 780							46					

Source: SCS Section 2.7.4.2.5.2

There were no blood CPK elevations ≥10x ULN in the simvastatin population. Only one sitagliptin subject in both the all statins and other statins populations had an elevation ≥10x ULN (subject 3356 described above). This was not a significant difference when compared to the non-exposed group (all statins 95% CI -0.7, 1.2; other statins 95% CI -1.3, 2.2).

In summary, the cases above describe subjects with elevated baseline CPK, concomitant diagnoses that may explain the elevated CPK, and improved (or stabilized) CPK with prolonged use, such that the use of sitagliptin/simvastatin FDC does not appear to elevate CPK in a clinically significant manner. A dose-related pattern with simvastatin was also not observed.

Serum ALT or AST Consecutive Elevations ≥3x ULN:
The applicant also analyzed the pooled data for subjects with serum ALT and/or AST elevations consecutively ≥3x ULN. Fewer events occurred in the simvastatin population when compared to the all statins and other statins populations. Within the three populations (excluding data after the initiation of glycemic rescue), the incidence of ALT and/or AST elevations were not statistically significantly different between the sitagliptin and non-exposed groups (see Table 22).

Table 22. Subjects with serum ALT and/or AST elevated consecutively ≥3x ULN in controlled portions of pooled studies, excluding data after the initiation of glycemic rescue

Treatment	N, %	Difference in % vs. Non-exposed	
		Estimate (95% CI)	p-value
Simvastatin population			
Sitagliptin 100 mg	827		
Non-exposed	755		
ALT/AST consec. ≥3x ULN			
Sitagliptin 100 mg	2 (0.2)	0.1 (-0.6, 0.7)	0.679
Non-exposed	1 (0.1)		
All statins population			

Sitagliptin 100 mg	1939		
Non-exposed	1726		
ALT/AST consec. ≥3x ULN			
Sitagliptin 100 mg	8 (0.4)	0.1 (-0.2, 0.6)	0.297
Non-exposed	4 (0.2)		
Other statins population			
Sitagliptin 100 mg	1112		
Non-exposed	971		
ALT/AST consec. ≥3x ULN			
Sitagliptin 100 mg	6 (0.5)	0.4 (-0.1, 1.1)	0.164
Non-exposed	2 (0.2)		

Source: SCS Table 2.7.4: 64

Narratives for subjects with ALT and/or AST consecutive elevations ≥3x ULN in the controlled portions of pooled analysis, excluding data after initiation of glycemic rescue (see also Table 23) are as follows. Seven of the 12 (58.3%) had a history of liver problems (e.g. hepatic steatosis, hepatitis).

- 33927 (simvastatin 20 mg, sitagliptin 100 mg): 57 year old female with a history of hepatic enzyme abnormal and hepatic steatosis had ALT elevations ≥3x ULN on days 43 and 57. Prior to randomization (day -63), she had hepatitis B. She took the last dose of study drug on day 50 and was discontinued on day 57 due to a protocol deviation (active viral hepatitis B was an exclusion criterion).
- 42183 (simvastatin 20-40 mg, sitagliptin 100 mg): 38 year old male with ALT elevations on days 551 and 566 (ALT 93 and 85 mIU/ml; AST 40 and 31 mIU/ml). Baseline ALT and AST were 54 and 21 mIU/ml, respectively. Simvastatin was increased to 40 mg on day 484. He took the last dose of study drug on day 573 and was discontinued due to ALT/AST discontinuation criteria.
- 47988 (simvastatin 40 mg, non-exposed): 60 year old male had elevated ALT on days 43, 55, and 62 (ALT 93, 80, and 86 mIU/ml, respectively). On day 1 (baseline), he had hepatic steatosis with ALT 75 mIU/ml. He was discontinued on day 62 according to the ALT/AST discontinuation criteria.
- 30304 (all statins [fluvastatin 40 mg], sitagliptin 100 mg): 58 year old female with history of hepatic steatosis, cholecystectomy, splenomegaly, abdominal pain, and increased liver enzymes had ALT/AST elevations ≥3x ULN on days 70 , 76, and 85. Baseline ALT and AST were 29 and 22 mIU/ml. On day 64, she experienced chills. On day 65, she discontinued the study because she was not comfortable with her glucose readings of 140-180 mg/dl. At the discontinuation visit (day 70), hepatic enzymes were increased (ALT 250 mIU/ml, AST 145 mIU/ml). On day 76, values varied depending upon the lab (ALT 81 and 108 mIU/l, AST 25 and 30 mIU/l). On day 83, she complained of abdominal tenderness. Ultrasound revealed intrahepatic biliary duct dilation and common bile duct enlargement. On day 85, ALT was 97 and AST was 45 mIU/ml. On day 90, she discontinued fluvastatin, aspirin, and celecoxib. Enzymes improved on day 97. On day 99, liver biopsy suggested non-alcoholic steatohepatitis but a

revised report described possible superimposed drug-induced liver disease. A repeat ultrasounds on day 127 was improved.

- 42246 (all statins [atorvastatin 10 mg], sitagliptin 100 mg): 56 year old male with hepatic steatosis had ALT elevations ≥3x ULN on days 644, 654, and 679 (see Table 23). Prior to the elevations (i.e. day 470) and concurrent with the elevations (i.e. day 654), he experienced hyperbilirubinemia. He was discontinue from the study on day 679 due to meeting ALT/AST discontinuation criteria.
- 47838 (all statins [lovastatin 20 mg], sitagliptin 100 mg): 53 year old male with ALT elevations on days 124 and 128 (see Table 23). During the study, he experienced arthralgia and back pain (days 79 and 133, respectively). He discontinued the study on day 137 due to ALT increased.
- 59312 (all statins [atorvastatin], sitagliptin 100 mg): 63 year old female with hepatic steatosis and liver abscess had ALT ≥3x ULN on days 43, 46, and 85 (see Table 23). She discontinued on day 85 due to elevated ALT.
- 65205 (all statins [atorvastatin 10 mg], sitagliptin 100 mg): 54 year old female had ALT and AST elevations ≥3x ULN on days 169 and 181. On day 169, she experienced hepatocellular necrosis. She took her last dose of study drug and completed the study that day. She recovered from hepatic necrosis on day 205.
- 3356 (all statins, sitagliptin 100 mg): 44 year old male had AST elevations ≥3x ULN on days 15 and 19 and ALT elevations ≥3x ULN on days 19 and 23. (See narrative in CPK section above.)
- 42098 (all statins [simvastatin 20 mg, then atorvastatin 10 mg], non-exposed): 30 year old male who had ALT elevations ≥3x ULN on days 167 and 174. He was discontinued on day 181 due to the elevations.
- 42251 (all statins [atorvastatin 10 mg], non-exposed): 44 year old male with history of hepatic enzyme increased and hepatic steatosis experienced ALT ≥3x ULN on days 126, 134, and 163. He was discontinued due to the elevations on day 170.
- 42269 (all statins [atorvastatin 5 mg], non-exposed): 49 year old female with a history of hepatic steatosis had ALT ≥3x ULN on days 238 and 252. On day 192, she also experienced cholelithiasis. She was discontinued on day 267 due to meeting the ALT/AST discontinuation criteria.

Table 23. ALT and AST values for subjects with ALT and/or AST elevations consistently ≥3x ULN, excluding data after initiation of glycemic rescue

Day	Subjects' Liver Enzyme Values (ALT, AST [mIU/ml])											
	33927	42183	47988	0304	42246	47838	59312	65205	3356	42098	42251	42269
-90 to -76		53 & 46, 26 & 20										
-75 to -61	39, 35		26, 17	26, 19		21, 16						

-60 to -46									19, 16			
-45 to -31											57, 27	
-30 to -16				29, 22	34, 15		39, 20	27, 24		38, 16	39, 17	45, 22
-15 to -1									19, 14		48, 21	
1 to 15	54, 47	54, 21	75 & 35, 43 & 19	29, 22	36, 21	22, 10	53, 27	20, 20	19 & 46, 15 & 174	51, 15	59, 26	34, 24
16 to 30		54, 26	35, 23	30, 24	29, 16				174 & 78 & 27, 302 & 35 & 18	35, 16	46, 20	31, 19
31 to 45	77, 65		93, 46	29, 24	30, 16	17, -	84, 45	15, 18		45, 21	56, 27	47, 26
46 to 60	98, 83	52, 23	80, 36				78, 41		15 & 15 & 14 & 13, 14 & 12 & 14 & 13			
61 to 75			86, 25	250 & 217, 145 & 80					17, 15			
76 to 90		50, 20	48, 28	108 & 81 & 97, 30 & 25 & 45	29, 19	17, 15	82, 40	23, 21	12, 13	37, 17	40, 21	59, 33
91 to 105			60, 26	23, 21								
106 to 120												
121 to 135		51, 24	34, 19		31, 17	84 & 85, 74 & 43			25, 17	38, 17	80 & 78, 42 & 36	60, 35

136 to 150						25, 16						
151 to 165									16, 13		84, 42	
166 to 180		38, 17			35, 17			215, 131		82 & 83, 26 & 25	84, 41	66, 38
181 to 195		40 & 30, 17 & 15					130, 83	277, 191		49 & 56, 16 & 25		92 & 62, 49 & 33
196 to 210								44, 37				
211 to 225		36, 15			59, 24							74, 50
226 to 240		34 & 27, 17 & 16							23, 18			77, 49
241 to 255												97, 44
256 to 270		31, 14										62, 40
271 to 285					51, 26							
286 to 300												
301 to 315												
316 to 330		27, 14			60, 33							
331 to 345		44, 20										
346 to 360												
361 to 375		40, 18										
376 to 390					60, 30							
391												

to 405												
406 to 420												
421 to 435		40, 19			50, 28							
436 to 450												
451 to 465												
466 to 480					67, 30							
481 to 495		65, 28			59, 33							
496 to 510												
511 to 525												
526 to 540					61, 33							
541 to 555		93, 40										
556 to 570		85, 31			52, 27							
571 to 585		74, 29										
586 to 600		82, 29										
601 to 615												
616 to 630												
631 to 645					108, 58							
646 to					113, 69							

660												
661 to 675												
676 to 690					81, 45							
691 to 705												
706 to 720												
721 to 735					85, 43							
736 to 765												
766 to 780												

Source: SCS Section 2.7.4.2.5.4.1

Pancreatitis:

The sitagliptin label warns about the risk of pancreatitis. Pancreatitis has also been reported postmarketing in association with simvastatin use. Although the SCS did not analyze pancreatitis events as an AE of special interest, my review of the pooled safety analysis identified one discontinuation in a sitagliptin subject in the all statins population (sitagliptin 0.1%; non-exposed 0%). However, this subject did not receive concomitant simvastatin, for he/she was not identified as a discontinued subject in the simvastatin population.

Pancreatitis (including acute pancreatitis) has been reported as a serious postmarketing event in subjects using sitagliptin concomitantly with simvastatin, atorvastatin, and rosuvastatin. However, the events occurred infrequently (see Table 24).

Table 24. Postmarketing AEs for sitagliptin and concomitant statin (through March 31, 2010)

Postmarketing AEs (Serious)	Simvastatin	Atorvastatin	Rosuvastatin
Pancreatitis (including acute)	20 (20)	18 (18)	10 (10)

Source: Tables 2.7.4: 116, 117, and 118

The applicant proposes a pancreatitis warning for the sitagliptin/simvastatin FDC that is similar to that contained in the sitagliptin label. This is acceptable.

Hypoglycemia:
As described in the sitagliptin label, there is an increased risk of hypoglycemia when sitagliptin is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. However, in both the simvastatin and all statins populations of the SCS, the incidence of hypoglycemia AEs was higher in the non-exposed group when compared with the sitagliptin group and the 95% CI around the between-group difference excluded zero.

- Simvastatin population: Sitagliptin 5.6% vs. non-exposed 10.2% (95% CI: -8.0, -2.4)
- All statins population: Sitagliptin 5.6% vs. non-exposed 9.4% (95% CI: -5.7%, -2.2%)

In addition, when AEs were analyzed by the following subpopulations, hypoglycemia was more commonly reported in the non-exposed group when compared to the sitagliptin group.

- <65 years: 10.0% vs. 5.7%
- ≥65 years: 10.9% vs. 5.3%
- Female: 11.9% vs. 6.7%)
- Male: 9.0% vs. 4.6%
- Asian: 15.8% vs. 8.5%
- White: 9.8% vs. 5.2%
- Non-Hispanic: 11.5% vs. 6.0%

However, one exception was blacks. In that subgroup, hypoglycemia was reported more commonly in the sitagliptin group (8.8% vs 3.6%).

Overall, the concomitant use of sitagliptin and simvastatin does not appear to increase one's risk of hypoglycemia. The applicant proposes a hypoglycemia warning that is similar to that in the sitagliptin label, which is acceptable.

Hypersensitivity:
There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. The Januvia label contains this warning and recommends, in such cases, to promptly stop sitagliptin, to assess for other potential causes, to institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes.

When the SCS was reviewed for allergic events, no events of hypersensitivity were identified. There were no allergies related to co-administration of sitagliptin and simvastatin, although there was one drug reaction in a non-exposed subject.

Thus, the concomitant administration of sitagliptin and simvastatin does not appear to increase one's risk of hypersensitivity. The proposed hypersensitivity labeling which is similar to that in the sitagliptin label is acceptable.

Renal Impairment:
The Dosage and Administration and Warnings and Precautions (including Highlights) sections of the sitagliptin label and the MG were recently revised to describe postmarketing reports of acute renal failure, sometimes requiring dialysis, and encourage assessment of renal function and proper dosage adjustment. (See also section 8 Postmarket Experience.)

That said, it must be noted that T2DM alone increases the risk of nephropathy. In the SCS, 13.4-15.8% of sitagliptin and non-exposed subjects in the simvastatin and all statins populations had past medical conditions in the renal and urinary disorders SOC.

One non-exposed subject in the simvastatin population (0.1%) died of renal failure. As shown in Table 25, the rates of discontinuation due to renal-related AEs in the simvastatin and all statins populations were similar in the sitagliptin and non-exposed groups. As shown in Table 29, the incidence of AEs in the renal and urinary disorders SOC was similar between the sitagliptin and non-exposed groups in the simvastatin and all statins populations, and the 95% CI for the between-group differences included zero.

Table 25. Subjects discontinued due to renal impairment-related AEs in the simvastatin and all statins populations, excluding data after initiation of glycemic rescue (n, %)

Adverse event	Simvastatin		All Statins	
	Sitagliptin	Non-exposed	Sitagliptin	Non-exposed
Blood creatinine increased	1 (0.1)	0 (0.0)	6 (0.3)	3 (0.2)
Creatinine renal clearance abnormal	1 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)
Creatinine renal clearance decreased	-	-	4 (0.2)	2 (0.1)
Renal failure	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Renal failure chronic	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)

Source: SCS Tables 2.7.4: 33 and 34

As described in section 7.4.2 Laboratory Findings, a small decrease in mean serum creatinine from baseline to week 104/106 was seen in both the sitagliptin and non-exposed groups in the simvastatin and all statins populations. In addition, a similar percentage of sitagliptin and non-exposed subjects (1.9% and 1.3%, respectively) met the pre-defined limit of change for serum creatinine (i.e. last value with an increase ≥0.3 mg/dl) in the simvastatin population and the 95% CI included zero (-0.9, 1.8)

When the applicant reviewed the Worldwide Adverse Experience System (WAES) for all spontaneous reports received from healthcare providers and agencies for AEs reported for patients using sitagliptin with either simvastatin, atorvastatin, or rosuvastatin, the rate

of investigation events (not all of which are creatinine-related) was similar between sitagliptin and simvastatin when compared to sitagliptin and atorvastatin. The rate of renal and urinary events was similar to that of sitagliptin and rosuvastatin.

Table 26. Postmarketing reports for sitagliptin used concomitantly with selected statins (through March 31, 2010)

SOC	Sitagliptin/Simvastatin Total Reports (Serious)	Sitagliptin/Atorvastatin Total Reports (Serious)	Sitagliptin/Rosuvastatin Total Reports (Serious)
Investigations	103 (20)	103 (28)	31 (6)
Renal and urinary	13 (7)	28 (18)	10 (5)

Source: SCS Table 2.7.4: 115

In summary, the concomitant use of sitagliptin and simvastatin does not appear to increase one's risk of renal impairment, although the applicant should update the proposed labeling with the renal language recently approved for use in the Januvia (NDAs 21-995) label.

7.3.5 Submission Specific Primary Safety Concerns

See section 7.5.4 Drug-Disease Interactions for a discussion of the need for a sitagliptin/simvastatin FDC containing sitagliptin 50 mg for use in subjects with moderate or severe renal insufficiency.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

My review of the common AEs focused on the simvastatin and all statins populations, rather than the simvastatin dose-specific and other statins populations. This is because the larger sample size of the chosen populations permitted a more robust analysis and those populations were felt to be more relevant given their inclusion of subjects using simvastatin. (See also section 7.5.1 Dose Dependency for Adverse Events.)

The incidence of AEs in the simvastatin and all statins populations in the controlled portions of pooled studies, excluding data after initiation of glycemic rescue, were similar between the sitagliptin and non-exposed groups (62.8-65.1%). The 95% CI between group difference included zero in both populations.

Table 27. Subjects with one or more AEs in the controlled portions of pooled studies, excluding data after initiation of glycemic rescue

Population and Patients	N (%)	Difference in % vs Non-exposed

		Estimate (95% CI)
Simvastatin population		
Sitagliptin 100 mg	531 (64.2)	0.4 (-4.2, 5.0)
Non-exposed	474 (62.8)	
All statins population		
Sitagliptin 100 mg	1263 (65.1)	0.9 (-2.1, 3.9)
Non-exposed	1090 (63.2)	

Source: SCS Tables 2.7.4: 21 and 2.7.4: 25

When the exposure-adjusted incidence rate of subjects with one or more adverse events occurring with simvastatin or all statin use was evaluated, the rates were generally similar between the sitagliptin and non-exposed groups. The 95% CI between group difference excluded zero in both populations (see Table 28).

Table 28. Exposure-adjusted incidence rate of subjects with one or more adverse events occurring with simvastatin or all statin use in controlled portions of pooled studies, excluding data after initiation of glycemic rescue

One or More Adverse Events	Number of Subjects with ≥1 Event/Patient-Years Follow-up Time (100-Patient-Years Incidence Rate)	Difference from Non-Exposed in Incidence Rate (95% CI)
Simvastatin population		
Sitagliptin 100 mg	531/304 (174.7)	-28.9 (-53.2, -5.1)
Non-exposed	474/232 (204.2)	
All statins population		
Sitagliptin 100 mg	1263/676 (186.9)	-13.6 (-29.8, 2.3)
Non-exposed	1090/538 (202.5)	

Source: Reference 5.3.5.3: 2342 and 2350

When AEs were evaluated by system organ class (SOC) in the simvastatin and all statins populations, AEs were reported most frequently in the following three SOCs for both populations: infections and infestations, gastrointestinal disorders, and musculoskeletal and connective tissue disorders. However, only the following SOC's 95% CIs around the between group differences excluded zero.

- Ear and labyrinth disorders: Simvastatin population (sitagliptin 1.0% vs. non-exposed 2.0%)
- Metabolism and nutritional disorders: Simvastatin population (sitagliptin 8.2% vs. non-exposed 13.4%); All statins (sitagliptin 13.4% vs. non-exposed 12.6%)
- Musculoskeletal disorders: All statins population (sitagliptin 17.9% vs. 14.6%)

Table 29. Subjects with AEs by system organ class in the controlled portion of pooled studies, excluding data after initiation of glycemic rescue (Simvastatin and all statins analyses)

System Organ Class	Simvastatin		All Statins	
	N (%)	Estimate (95% CI)	N (%)	Estimate (95% CI)
Patients				

Sitagliptin 100 mg	827		1939	
Non-exposed	755		1726	
One or more AE				
Sitagliptin 100 mg	531 (64.2)	0.4 (-4.2, 5.0)	1263 (65.1)	0.9 (-2.1, 3.9)
Non-exposed	474 (62.8)		1090 (63.2)	
Blood & lymphatic				
Sitagliptin 100 mg	11 (1.3)	0.4 (-0.7, 1.6)	17 (0.9)	0.1 (-0.5, 0.7)
Non-exposed	6 (0.8)		11 (0.6)	
Cardiac				
Sitagliptin 100 mg	31 (3.7)	-1.2 (-3.3, 0.8)	78 (4.0)	0.3 (-1.0, 1.6)
Non-exposed	35 (4.6)		62 (3.6)	
Congenital, familial, & genetic				
Sitagliptin 100 mg	1 (0.1)		4 (0.2)	-0.0 (-0.5, 0.3)
Non-exposed	3 (0.4)		5 (0.3)	
Ear & labyrinth				
Sitagliptin 100 mg	8 (1.0)	-1.3 (-2.7, -0.1)	27 (1.4)	-0.3 (-1.2, 0.5)
Non-exposed	15 (2.0)		28 (1.6)	
Endocrine				
Sitagliptin 100 mg	2 (0.2)		7 (0.4)	0.0 (-0.4, 0.5)
Non-exposed	1 (0.1)		6 (0.3)	
Eye				
Sitagliptin 100 mg	29 (3.5)	-1.0 (-3.0, 1.0)	68 (3.5)	-1.0 (-2.3, 0.2)
Non-exposed	31 (4.1)		74 (4.3)	
Gastrointestinal				
Sitagliptin 100 mg	153 (18.5)	1.3 (-2.5, 5.0)	358 (18.5)	-0.3 (-2.8, 2.2)
Non-exposed	127 (16.8)		319 (18.5)	
General & admin site				
Sitagliptin 100 mg	59 (7.1)	-0.2 (-2.8, 2.4)	154 (7.9)	0.2 (-1.5, 1.9)
Non-exposed	54 (7.2)		129 (7.5)	
Hepatobiliary				
Sitagliptin 100 mg	8 (1.0)	0.1 (-1.0, 1.2)	20 (1.0)	0.1 (-0.6, 0.7)
Non-exposed	6 (0.8)		16 (0.9)	
Immune				
Sitagliptin 100 mg	9 (1.1)	0.4 (-0.6, 1.4)	24 (1.2)	0.5 (-0.2, 1.2)
Non-exposed	4 (0.5)		11 (0.6)	
Infections & infestations				
Sitagliptin 100 mg	259 (31.3)	-0.3 (-4.8, 4.2)	630 (32.5)	1.1 (-1.9, 4.0)
Non-exposed	237 (31.4)		533 (30.9)	
Injury, poisoning, & procedural				
Sitagliptin 100 mg	72 (8.7)	1.5 (-1.2, 4.2)	168 (8.7)	1.4 (-0.3, 3.2)
Non-exposed	52 (6.9)		123 (7.1)	
Investigations				
Sitagliptin 100 mg	88 (10.6)	0.4 (-2.6, 3.4)	225 (11.6)	1.2 (-0.8, 3.2)
Non-exposed	73 (9.7)		169 (9.8)	
Metabolism & nutritional				
Sitagliptin 100 mg	68 (8.2)	-5.8 (-9.0, -2.7)	168 (8.7)	-4.2 (-6.3, -2.3)
Non-exposed	101 (13.4)		218 (12.6)	
Musculoskeletal & conn tissue				
Sitagliptin 100 mg	142 (17.2)	2.6 (-1.0, 6.2)	348 (17.9)	2.7 (0.4, 5.1)
Non-exposed	104 (13.8)		252 (14.6)	
Neoplasms				

Sitagliptin 100 mg	21 (2.5)	0.7 (-0.8, 2.2)	45 (2.3)	0.8 (-0.1, 1.8)
Non-exposed	13 (1.7)		24 (1.4)	
Nervous system				
Sitagliptin 100 mg	94 (11.4)	0.2 (-2.9, 3.3)	236 (12.2)	0.2 (-1.9, 2.3)
Non-exposed	79 (10.5)		196 (11.4)	
Psychiatric				
Sitagliptin 100 mg	31 (3.7)	0.1 (-1.9, 2.0)	83 (4.3)	0.5 (-0.8, 1.8)
Non-exposed	28 (3.7)		65 (3.8)	
Renal				
Sitagliptin 100 mg	24 (2.9)	-0.3 (-2.1, 1.4)	58 (3.0)	0.1 (-1.0, 1.2)
Non-exposed	23 (3.0)		47 (2.7)	
Reproductive & breast				
Sitagliptin 100 mg	24 (2.9)	-0.1 (-1.9, 1.6)	49 (2.5)	-0.1 (-1.1, 1.0)
Non-exposed	23 (3.0)		45 (2.6)	
Respiratory, thoracic, & mediastinal				
Sitagliptin 100 mg	65 (7.9)	0.4 (-2.3, 3.0)	151 (7.8)	0.2 (-1.6, 1.9)
Non-exposed	52 (6.9)		125 (7.2)	
Skin & subcutaneous				
Sitagliptin 100 mg	64 (7.7)	1.4 (-1.1, 4.0)	146 (7.5)	1.5 (-0.2, 3.1)
Non-exposed	46 (6.1)		102 (5.9)	
Social circumstances				
Sitagliptin 100 mg	-		0 (0.0)	
Non-exposed	-		1 (0.1)	
Surgical & medical				
Sitagliptin 100 mg	1 (0.1)		1 (0.1)	
Non-exposed	0 (0.0)		1 (0.1)	
Vascular				
Sitagliptin 100 mg	47 (5.7)	0.1 (-2.3, 2.3)	96 (5.0)	0.6 (-0.7, 2.0)
Non-exposed	39 (5.2)		67 (3.9)	

Source: SCS Tables 2.7.4: 22 and 2.7.4: 27
Note: Subjects with two or more AEs within the same SOC were counted once for that SOC. Any subject with an AE in more than one SOC was counted once for every applicable SOC.

Of the SOCs with 95% CIs around the between group differences excluding zero, only the musculoskeletal and connective tissue disorders SOC's incidence rate was notably higher in the sitagliptin group when compared to the non-exposed group (17.9% vs. 14.6% in the all statins population). Although the difference between groups was not statistically different in the simvastatin population, AE events also occurred more commonly in the sitagliptin group in that population (17.2% vs. 13.8%). However, when events with an incidence ≥2% in one or more treatment groups were reviewed in the SOC, the incidence of arthralgia, back pain, and pain in extremity were not statistically different between treatment groups (see Table 30). There were no cases of myopathy or rhabdomyolysis in the simvastatin or all statins population. When the SOC was analyzed by simvastatin dose, only the 20 mg dose resulted in a 95% CI about the between group differences that excluded zero (see Table 31).

Table 30. Subjects with musculoskeletal and connective tissue disorders occurring with simvastatin or all statins use (Incidence ≥2% in one or more treatment groups) in controlled portions of pooled studies, excluding data after initiation of glycemic rescue

Musculoskeletal & connective tissue SOC	Simvastatin		All Statins	
	N (%)	Estimate (95% CI)	N (%)	Estimate (95% CI)
Sitagliptin 100 mg	142 (17.2)	2.6 (-1.0, 6.2)	348 (17.9)	2.7 (0.4, 5.1)
Non-exposed	104 (13.8)		252 (14.6)	
Arthralgia				
Sitagliptin 100 mg	23 (2.8)	-0.0 (-1.8, 1.6)	66 (3.4)	0.6 (-0.5, 1.8)
Non-exposed	19 (2.5)		45 (2.6)	
Back pain				
Sitagliptin 100 mg	27 (3.3)	-0.2 (-2.0, 1.6)	70 (3.6)	0.3 (-0.9, 1.4)
Non-exposed	23 (3.0)		53 (3.1)	
Pain in extremity				
Sitagliptin 100 mg	21 (2.5)	0.7 (-0.8, 2.2)	54 (2.8)	1.0 (0.1, 2.0)
Non-exposed	12 (1.6)		28 (1.6)	

Source: SCS Tables 2.7.4: 23 and 2.7.4: 29

Table 31. Subjects with musculoskeletal and connective tissue events occurring with simvastatin in controlled portions of pooled studies, excluding data after initiation of glycemic rescue

Musculoskeletal & connective tissue SOC	Simvastatin	
	N (%)	Estimate (95% CI)
Simvastatin 80 mg		
Sitagliptin 100 mg	6 (20.0)	-8.0 (-31.2, 14.7)
Non-exposed	7 (28.0)	
Simvastatin 40 mg		
Sitagliptin 100 mg	35 (14.8)	-0.8 (-7.5, 5.9)
Non-exposed	34 (15.5)	
Simvastatin 20 mg		
Sitagliptin 100 mg	63 (17.5)	7.4 (2.2, 12.6)
Non-exposed	32 (10.1)	
Simvastatin <20 mg		
Sitagliptin 100 mg	16 (15.7)	2.1 (-8.0, 12.2)
Non-exposed	13 (13.5)	
Simvastatin mixed dose		
Sitagliptin 100 mg	12 (40.0)	10.0 (-12.3, 32.2)
Non-exposed	12 (30.0)	

Source: Reference 5.3.5.3: 2327

In summary, the incidence of AEs in the simvastatin and all statin populations in the controlled portions of pooled studies, excluding data after the initiation of glycemic rescue, were similar between the sitagliptin and non-exposed groups (62.8-65.1%), as were the exposure-adjusted incidence rates. AEs were reported most frequently in the infections and infestations, gastrointestinal disorders, and musculoskeletal and connective tissue disorders SOCs. Of these, only the musculoskeletal and connective

tissue disorders SOC had a consistent numerical or percentage difference between the sitagliptin and non-exposed groups (e.g. 17.9% vs. 14.6% in all statins population). However, when events with an incidence ≥2% in one or more treatment groups were reviewed in the SOC, the incidence of arthralgia, back pain, and pain in extremity were not statistically different between treatment groups. Consistent with the simvastatin label, the applicant proposes a Warning and Precaution for skeletal muscle effects and myopathy. This is acceptable.

7.4.2 Laboratory Findings

Overview of Laboratory Testing in the SCS:
The SCS analyzed limited chemistry and hematology values by mean changes from baseline over time and the incidence of measurements meeting predefined limits of change (PDLC), as agreed at the pre-NDA meeting. Specifically, the following were analyzed:

- Chemistry: Alkaline phosphatase, ALT, AST, total bilirubin, creatinine, creatinine kinase (CK)
- Hematology: White blood cell count (WBC), absolute neutrophil count (ANC), and absolute lymphocyte count (ALC)

Like my review of the clinical safety data, my review of the laboratory data focused on the simvastatin and all statin populations. However, the safety laboratory populations included only patients who were on a statin during the entire treatment period, with gaps ≤14 days in simvastatin exposure.

As the 19 clinical studies included in the pooled analysis had different sampling schedules, some time points were combined, as shown in Table 32.

Table 32. Time grid of chemistry panel for individual studies in the SCS

	Protocol																		
Week	10	14	19	20	21	23	24	35	36	40	47	49	51	52	53	61	64	79	801
2	*	*																	
3					*	*	*												
4	*	*																	
6			*	*	*	*	*	*	*	*	*		*	*	*				*
8	*	*																	
12	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*		*
16	*	*																	
18			*	*	*	*	*	*	*	*	*		*	*	*			*	*
24			*	*	*	*	*	*	*		*	*	*		*		*		
25	*	*																	
30				*			*	*						*	*				
34	*	*																	
38				*		*	*	*	*					*			*		
42				*		*	*	*	*					*			*		
44																		*	
46							*	*											
52	*	*					*												
54				*		*		*	*					*			*		
60							*												
61	*	*																	
69							*												
70	*	*																	
78				*			*		*										
82	*	*																	
91							*												
94	*	*																	
104				*			*		*										
106	*	*																	

Note: Weeks listed in the same row were summarized together.
Source: Reference 2512 Appendix 2

See also section 7.3.4 Significant Adverse Events for a discussion of blood CPK increased and serum ALT or AST consecutive elevations ≥3x ULN.

Analysis of Mean Change from Baseline:
Select chemistry values (i.e. alkaline phosphatase, ALT, AST, total bilirubin, creatinine, and CK) were reviewed in the simvastatin and all statin safety populations for the mean change from baseline (see Table 33.) Similar results were obtained for both populations at week 104/106, except for CK which had small populations (i.e. n=1-2) after week 91/94. Generally, no clinically meaningful change from baseline was detected in the chemistry values at endpoint, although notable small variations are as follows:

- Alkaline phosphatase: A slight decrease from baseline was seen (sitagliptin group > non-exposed group)

- AST: A slight increase was seen in the non-exposed group when compared to the sitagliptin group
- Total bilirubin: A small increase was seen in the sitagliptin group in both populations compared to the non-exposed group for week 44/46 to 91/94, but no meaningful change was seen at endpoint
- Creatinine: A small decrease was seen in both treatment groups in both populations
- CK: Results fluctuated more from week 60/1 to 91/4 when sample size was small. Prior to that, no meaningful change was observed.

Table 33. Change from baseline in chemistry values at week 104/106 in controlled portions of pooled studies, excluding data after initiation of glycemic rescue (Simvastatin [sitagliptin n=106, non-exposed n=76] and all statins [sitagliptin n=252, non-exposed n=178] safety populations)

Laboratory & Treatment	Simvastatin Population			All Statins Population
	Baseline Mean (SD)	Time point Mean (SD)	Change from Baseline at Time point Mean (SE)	Change from Baseline at Time point Mean (SE)
Alkaline phosphatase (IU/L)				
Sitagliptin 100 mg	52 (15)	49 (15)	-3 (1)	-5 (1)
Non-exposed	55 (18)	53 (33)	-2 (3)	-3 (2)
ALT (IU/L)				
Sitagliptin 100 mg	19 (7)	19 (11)	-0 (1)	-1 (1)
Non-exposed	20 (11)	20 (16)	0 (2)	-1 (1)
AST (IU/L)				
Sitagliptin 100 mg	16 (5)	16 (6)	-0 (1)	-0 (0)
Non-exposed	16 (7)	18 (14)	2 (2)	1 (1)
Total bilirubin (mg/dl)				
Sitagliptin 100 mg	0.5 (0.2)	0.5 (0.3)	0.0 (0.0)	-0.0 (0.0)
Non-exposed	0.6 (0.2)	0.6 (0.3)	0.0 (0.0)	-0.0 (0.0)
Serum creatinine (mg/dl)				
Sitagliptin 100 mg	1.0 (0.2)	0.9 (0.2)	-0.1 (0.0)	-0.1 (0.0)
Non-exposed	1.0 (0.2)	0.9 (0.2)	-0.1 (0.0)	-0.0 (0.0)

Source: SCS Tables 2.7.4: 95 – 2.7.4: 99 and Tables 2.7.4: 103 – 2.7.4: 107

Table 34. Change from baseline in creatinine kinase at weeks 52/54 and 78/82 in controlled portions of pooled studies (010, 014, 021, 023, 049, 061), excluding data after initiation of glycemic rescue (Simvastatin and all statins safety populations)

Creatinine kinase (IU/L)	Simvastatin Population				All Statins Population	
	N	Baseline Mean (SD)	Time point Mean (SD)	Change from Baseline at Time point Mean (SE)	N	Change from Baseline at Time point Mean (SE)

Week 52/54						
Sitagliptin	30	72.8 (39.5)	71.5 (39.9)	-1.3 (8.8)	67	1.2 (5.1)
Non-expos	18	63.8 (29.7)	70.1 (45.8)	6.3 (7.5)	37	1.3 (5.1)
Week 78/82						
Sitagliptin	1	44.0	41.0	-3.0	2	-44.0 (41.0)
Non-expos	1	43.0	67.0	24.0	2	10.0 (14.0)

Source: SCS Table 2.7.4: 100 and 2.7.4: 108

Hematology parameters WBC, ANC, and ALC were reviewed for the mean change from baseline in the simvastatin and all statins safety populations. A slight but unlikely clinically meaningful increase was seen in WBC and ANC values (generally, sitagliptin group > non-exposed group), although a slight and likely not clinically meaningful decrease was seen in ALC. (See Table 35.)

Table 35. Change from baseline in hematology values at week 104/106 in controlled portions of pooled studies, excluding data after initiation of glycemic rescue (Simvastatin and all statins safety populations)

Laboratory (cells/microL) & Treatment	Simvastatin Population				All Statins Population	
	N	Baseline Mean (SD)	Time point Mean (SD)	Change from Baseline at Time point Mean (SE)	N	Change from Baseline at Time point Mean (SE)
WBC						
Sitagliptin	104	6892 (1970)	7074 (1961)	182 (117)	244	81 (83)
Non-expos	77	6995 (1683)	7031 (2141)	36 (219)	178	11 (119)
ANC						
Sitagliptin	102	4138 (1403)	4384 (1537)	246 (112)	241	219 (75)
Non-expos	73	4128 (1254)	4376 (1864)	249 (209)	169	102 (112)
ALC						
Sitagliptin	102	2103 (871)	2000 (745)	-103 (61)	241	-115 (37)
Non-expos	73	2152 (684)	2065 (602)	88 (62)	169	-48 (34)

Source: SCS Tables 2.7.4: 101, 102, 109, and 110 and References 2493 and 2494

Analysis using the Predefined Limits of Change:

The PDLC were discussed at the pre-NDA meeting and are acceptable. The PDLC from baseline and the number (%) of subjects in the simvastatin population who met the criteria, excluding data after initiation of glycemic therapy, are shown in Table 36. The percentage of subjects who met the PDLC criteria was similar between treatment groups and the 95% CI included zero in all categories, except for subjects with one neutrophil count increase ≥20% and a value >ULN (sitagliptin 3.6% and non-exposed 1.2% [95% CI: 0.5, 3.9]). Similar results were seen in the simvastatin dose-specific population. Specifically, in the simvastatin 20 mg population, 4.4% of the sitagliptin group and 0.7% of the non-exposed group, had one neutrophil value with an increase ≥20% and a value >ULN (95% CI: 1.3, 6.5). However, as a dose-related trend was not observed, I doubt an association between the coadministration of sitagliptin and simvastatin and an increase in neutrophil count.

Table 36. Subjects meeting PDLC in controlled portions of pooled studies, excluding data after initiation of glycemic rescue (Simvastatin population)

	N	n (%)	Difference in % vs. Non-exposed Estimate (95% CI[1])
Hemoglobin (gm/dL)			
Last value with a decrease >= 1.5 gm/dL [‡]			
Sitagliptin 100 mg	789	43 (5.4)	-1.3 (-3.9, 1.2)
Non-exposed	688	47 (6.8)	
WBC Count (cells/microL)			
One value with a decrease >= 50% and value < LLN [‡]			
Sitagliptin 100 mg	789	5 (0.6)	0.3 (-0.5, 1.3)
Non-exposed	688	2 (0.3)	
Last value with a decrease >= 50% and value < LLN [‡]			
Sitagliptin 100 mg	789	0 (0.0)	-0.1
Non-exposed	688	1 (0.1)	
One value with an increase >= 20% and value > ULN [‡]			
Sitagliptin 100 mg	789	49 (6.2)	2.2 (-0.1, 4.5)
Non-exposed	688	26 (3.8)	
Last value with an increase >= 20% and value > ULN [‡]			
Sitagliptin 100 mg	789	17 (2.2)	1.0 (-0.3, 2.4)
Non-exposed	688	8 (1.2)	
Neutrophil Count (cells/microL)			
One value with a decrease >= 20% and value < LLN [‡]			
Sitagliptin 100 mg	782	11 (1.4)	0.8 (-0.3, 2.0)
Non-exposed	679	4 (0.6)	
Last value with a decrease >= 20% and value < LLN [‡]			
Sitagliptin 100 mg	782	4 (0.5)	0.5 (-0.1, 1.3)
Non-exposed	679	0 (0.0)	
One value with an increase >= 20% and value > ULN [‡]			
Sitagliptin 100 mg	782	28 (3.6)	2.1 (0.5, 3.9)
Non-exposed	679	8 (1.2)	
Last value with an increase >= 20% and value > ULN [‡]			
Sitagliptin 100 mg	782	4 (0.5)	0.3 (-0.5, 1.2)
Non-exposed	679	2 (0.3)	
Lymphocyte Count (cells/microL)			
One value with a decrease >= 20% and value < LLN [‡]			
Sitagliptin 100 mg	782	2 (0.3)	0.1
Non-exposed	679	1 (0.1)	
Last value with a decrease >= 20% and value < LLN [‡]			
Sitagliptin 100 mg	782	1 (0.1)	0.1
Non-exposed	679	0 (0.0)	
One value with an increase >= 20% and value > ULN [‡]			
Sitagliptin 100 mg	782	1 (0.1)	-0.3
Non-exposed	679	3 (0.4)	
Last value with an increase >= 20% and value > ULN [‡]			
Sitagliptin 100 mg	782	1 (0.1)	-0.0
Non-exposed	679	1 (0.1)	

	N	n (%)	Difference in % vs. Non-exposed Estimate (95% CI[1])
Platelet Count (10^3/microL)			
One value with a decrease >= 25% and value < LLN [‡]			
Sitagliptin 100 mg	782	5 (0.6)	0.1 (-0.9, 1.0)
Non-exposed	678	3 (0.4)	
Last value with a decrease >= 25% and value < LLN [‡]			
Sitagliptin 100 mg	782	1 (0.1)	-0.2
Non-exposed	678	2 (0.3)	
One value with an increase >= 100% and value > ULN [‡]			
Sitagliptin 100 mg	782	0 (0.0)	-0.1
Non-exposed	678	1 (0.1)	
Last value with an increase >= 100% and value > ULN [‡]			
Sitagliptin 100 mg	782	0 (0.0)	-0.1
Non-exposed	678	1 (0.1)	
BUN (mg/dL)			
Last value with an increase >= 50% and value > ULN [‡]			
Sitagliptin 100 mg	802	22 (2.7)	0.7 (-1.0, 2.4)
Non-exposed	708	15 (2.1)	
Serum Creatinine (mg/dL)			
Last value with an increase >= 0.3 mg/dL [‡]			
Sitagliptin 100 mg	801	15 (1.9)	0.4 (-0.9, 1.8)
Non-exposed	708	9 (1.3)	
Total Bilirubin (mg/dL)			
One value with an increase >= 50% and value > ULN [‡]			
Sitagliptin 100 mg	802	17 (2.1)	-0.8 (-2.6, 0.7)
Non-exposed	708	19 (2.7)	
Last value with an increase >= 50% and value > ULN [‡]			
Sitagliptin 100 mg	802	5 (0.6)	-0.6 (-1.8, 0.4)
Non-exposed	708	8 (1.1)	
AST (IU/L)			
Any value >= 3 x ULN			
Sitagliptin 100 mg	803	2 (0.2)	-0.3 (-1.3, 0.4)
Non-exposed	710	4 (0.6)	
Last value >= 3 x ULN			
Sitagliptin 100 mg	803	2 (0.2)	0.1
Non-exposed	710	1 (0.1)	
Any value >= 5 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	-0.2
Non-exposed	710	1 (0.1)	
Last value >= 5 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	0.0
Non-exposed	710	0 (0.0)	
Any value >= 10 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	0.0
Non-exposed	710	0 (0.0)	
Last value >= 10 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	0.0
Non-exposed	710	0 (0.0)	

	N	n (%)	Difference in % vs. Non-exposed Estimate (95% CI†)
ALT (IU/L)			
Any value >= 3 x ULN			
Sitagliptin 100 mg	803	7 (0.9)	0.3 (-0.7, 1.3)
Non-exposed	710	4 (0.6)	
Last value >= 3 x ULN			
Sitagliptin 100 mg	803	2 (0.2)	-0.0
Non-exposed	710	2 (0.3)	
Any value >= 5 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	-0.2
Non-exposed	710	1 (0.1)	
Last value >= 5 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	0.0
Non-exposed	710	0 (0.0)	
Any value >= 10 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	0.0
Non-exposed	710	0 (0.0)	
Last value >= 10 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	0.0
Non-exposed	710	0 (0.0)	
AST (IU/L) or ALT (IU/L)			
Any value >= 5 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	-0.2
Non-exposed	710	1 (0.1)	
Last value >= 5 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	0.0
Non-exposed	710	0 (0.0)	
Any value >= 10 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	0.0
Non-exposed	710	0 (0.0)	
Last value >= 10 x ULN			
Sitagliptin 100 mg	803	0 (0.0)	0.0
Non-exposed	710	0 (0.0)	
AST (IU/L) or ALT (IU/L) + Total Bilirubin (mg/dL)			
Any value meeting (AST > 3 x ULN or ALT > 3 x ULN) with Bilirubin > 2 x ULN simultaneously			
Sitagliptin 100 mg	803	0 (0.0)	-0.2
Non-exposed	710	1 (0.1)	
Last value meeting (AST > 3 x ULN or ALT > 3 x ULN) with Bilirubin > 2 x ULN simultaneously			
Sitagliptin 100 mg	803	0 (0.0)	0.0
Non-exposed	710	0 (0.0)	
Alkaline Phosphatase (IU/L)			
One value with an increase >= 50% and value > ULN‡			
Sitagliptin 100 mg	777	9 (1.2)	0.2 (-1.1, 1.4)
Non-exposed	695	7 (1.0)	
Last value with an increase >= 50% and value > ULN‡			
Sitagliptin 100 mg	777	3 (0.4)	-0.4 (-1.4, 0.5)
Non-exposed	695	5 (0.7)	

	N	n (%)	Difference in % vs. Non-exposed Estimate (95% CI†)
Serum Creatine Kinase (CK) (IU/L)			
Any value >= 5 x ULN			
Sitagliptin 100 mg	203	0 (0.0)	0.0
Non-exposed	173	0 (0.0)	
Last value >= 5 x ULN			
Sitagliptin 100 mg	203	0 (0.0)	0.0
Non-exposed	173	0 (0.0)	

† Based on Miettinen & Nurminen method stratified by study and computed only for those endpoints with at lease 4 patients having events in one or more treatment groups; if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
‡ Increases and decreases are relative to baseline.
Last value = last measurement obtained during, or within 14 days of, simvastatin use during the Treatment Period.
N = Patients in population.

Source: SCS Table 2.7.4: 111

The number and percentage of subjects who met the PDLC criteria in the all statins population was also reviewed. Consistent with the simvastatin population, no clinically meaningful differences were observed between the chemistry values of the sitagliptin and non-exposed groups; the 95% CIs all included zero. However, a slightly more pronounced effect was observed in the hematology parameters in the all statins population. Specifically, the 95% CI around the between-group difference excluded zero for the following PDLC criteria:

- One WBC count with an increase ≥20% and value >ULN: sitagliptin 6.2% vs. non-exposed 4.1% (95% CI: 0.2, 3.3)
- One neutrophil count with an increase ≥20% and value >ULN: sitagliptin 3.7% vs. non-exposed 1.8% (95% CI: 0.3, 2.6)
- One lymphocyte count with an increase ≥20% and value >ULN: sitagliptin 0.2% vs. non-exposed 0.6% (95% CI: -1.1, -0.1)
- One platelet value with an increase ≥100% and value >ULN: sitagliptin 0% vs. non-exposed 0.3% (95% CI: -0.7, 0.0)

Summary:
The SCS analyzed limited chemistry and hematology values by mean changes from baseline over time and the incidence of measurements meeting predefined limits of change (PDLC). No clinically meaningful differences were observed between treatment groups in the simvastatin and all statins populations.

7.4.3 Vital Signs

The changes from baseline to week 104/106 in blood pressure and heart rate were small and likely not clinically meaningful in both the simvastatin and all statins population (see Table 37). No consistent time-related changes in vital signs were seen in both the simvastatin and all statins populations.

Table 37. Change from baseline to week 104/106 in blood pressure and heart rate in controlled portions of pooled studies, excluding data after initiation of glycemic rescue

Vital Sign	Simvastatin				All Statins			
	N	Baseline Mean (SD)	Time point Mean (SD)	Change from Baseline at Time point Mean (SE)	N	Baseline Mean (SD)	Time point Mean (SD)	Change from Baseline at Time point Mean (SE)
Diastolic BP (mmHg)								
Sitagliptin	92	77.5 (9.2)	78.5 (8.8)	1.1 (1.0)	213	77.2 (8.9)	78.2 (9.2)	1.0 (0.6)
Non-expos	63	78.3 (7.5)	78.7 (8.5)	0.4 (1.1)	148	78.0 (8.1)	77.8 (9.2)	-0.2 (0.7)
Systolic BP (mmHg)								
Sitagliptin	92	132.0 (14.5)	134.0 (15.0)	2.0 (1.5)	213	131.7 (14.8)	133.3 (15.4)	1.7 (1.0)
Non-expos	63	129.9 (14.0)	130.5 (14.5)	0.6 (2.1)	148	129.5 (13.7)	130.2 (15.0)	0.7 (1.3)

Heart Rate (bpm)								
Sitagliptin	92	71.8 (10.5)	70.3 (8.7)	-1.6 (0.9)	213	72.1 (9.8)	71.2 (8.9)	-0.9 (0.6)
Non-expos	62	72.2 (8.6)	72.8 (11.8)	0.6 (1.4)	147	72.1 (9.6)	72.5 (11.5)	0.4 (0.8)

Source: Tables 2.7.4: 113 and 2.7.4: 114 and References 2481, 2484, 2486, and 2488

Furthermore, the applicant has initiated TECOS, a randomized, placebo controlled clinical trial to evaluate cardiovascular (CV) outcomes after treatment with sitagliptin in patients with T2DM and inadequate glycemic control on mono- or dual combination oral antihyperglycemic therapy. This study will include subjects on sitagliptin and simvastatin. Its planned completion date is December 2014.

7.4.4 Electrocardiograms (ECGs)

Simvastatin was approved in December 1991, prior to the 2005 and 2008 guidances which recommended evaluation of the QT/QTc interval and proarrhythmic potential for non-antiarrhythmic drugs. Simcor, simvastatin/niacin XR FDC (NDA 22-078), was approved in 2008 without a thorough QT (tQT) study.

As described in Dr. Ilan Irony's original review of NDA 21-995, a tQT study (P032) was conducted with sitagliptin. There was a shallow relationship between the plasma concentration of sitagliptin and the placebo-subtracted QTcF change from baseline (i.e. maximum 8.2 msec above a mean of 406 msec). However, sitagliptin was not associated with a clinically meaningful QTcF prolongation. (See also section 12.2 Pharmacodynamics of the Januvia label.)

As 1) a tQT of sitagliptin was previously conducted with negative findings, 2) there is approximately 20 years' clinical experience with simvastatin without clinical evidence of prolongation of the QT interval, and 3) there is a recent precedent for approving a simvastatin FDC without a tQT study, a thorough QT (tQT) study of the sitagliptin/simvastatin FDC is not required.

7.4.5 Special Safety Studies/Clinical Trials

NDAs under review must meet the CV safety thresholds ruling out unacceptably increased risk as recommended in the December 2008 final diabetes cardiovascular guidance. As sitagliptin/simvastatin FDC NDA is bridging to sitagliptin NDA 21-995, which is currently conducting CV outcomes trial TECOS (protocol 082), an additional CV study is not required.

Furthermore, my review of the deaths, SAES, and discontinuations described in the SCS did not reveal an imbalance of CV events between the monocomponents against the concomitant use of sitagliptin and simvastatin. A stated indication of simvastatin is to "reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-

fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events".

7.4.6 Immunogenicity

As a small molecule, sitagliptin is unlikely to generate an immune response. However, it inhibits DPP-4, which is identical to CD26, a T lymphocyte surface glycoprotein. As described in section 7.4.1 Common Adverse Events, the rate of events in the Infections and Infestations SOC was similar (range 30.9-32.5%) in the sitagliptin and non-exposed groups in both the simvastatin and all statins populations.

Sitagliptin has been associated with hypersensitivity. A history of a serious hypersensitivity reaction is a contraindication to its use. There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. The applicant proposes similar Warning and Precaution language in the sitagliptin/simvastatin FDC label, which is acceptable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The incidence of discontinuations due to AEs, deaths, SAEs, and subjects with one or more AEs in the simvastatin population was analyzed by simvastatin dose (see Table 38). The incidences were similar in the sitagliptin and non-exposed groups with 95% CI including zero, except for the incidence of SAEs in the 20 mg and <20 mg groups. In the simvastatin 20 mg population, SAEs were more common in the non-exposed group when compared to the sitagliptin group (9.5% vs. 5.3%). However in the simvastatin <20 mg population, SAEs were more common in the sitagliptin group (13.7% vs. 5.2%). These conflicting results as well as the absence of a consistent, dose-related trend in the incidence of SAEs (and other categories analyzed) leads me to conclude that a dose-dependent effect on AEs is not present with the concomitant administration of sitagliptin and simvastatin.

Table 38. Adverse events by simvastatin dose (n, %, 95% CI) in controlled portions of pooled studies, excluding data after initiation of glycemic rescue

Category (n, %, 95% CI)	80 mg Sita n = 30 NE n = 25	40 mg Sita n = 237 NE n=219	20 mg Sita n = 359 NE n=316	<20 mg Sita n=102 NE n=96	Mixed Dose Sita n=30 NE n=40	Unknown Dose Sita n=69 NE n=59
Discontinued						

due to AE						
Sitagliptin	0 (0.0) (-13.5, 11.5)	8 (3.4) (-6.9, 1.4)	12 (3.3) (-4.3, 1.9)	5 (4.9) (-3.0, 9.2)	1 (3.3) (-5.7, 16.8)	1 (1.4) (-12.7, 3.3)
Non-exposed	0 (0.0)	13 (5.9)	14 (4.4)	2 (2.1)	0 (0.0)	3 (5.1)
Died						
Sitagliptin	0 (0.0) (-13.5, 11.5)	1 (0.4) (-2.9, 1.5)	1 (0.3) (-2.0, 1.0)	0 (0.0) (-3.9, 3.6)	0 (0.0) (-8.9, 11.5)	0 (0.0) (-9.0, 3.7)
Non-exposed	0 (0.0)	2 (0.9)	2 (0.6)	0 (0.0)	0 (0.0)	1 (1.7)
SAE						
Sitagliptin	2 (6.7) (-14.0, 18.2)	21 (8.9) (-2.0, 7.9)	19 (5.3) (-8.4, -0.3)	14 (13.7) (0.3, 17.3)	2 (6.7) (-26.7, 6.2)	1 (1.4) (-12.7, 3.3)
Non-exposed	1 (4.0)	13 (5.9)	30 (9.5)	5 (5.2)	7 (17.5)	3 (5.1)
≥1 AE						
Sitagliptin	18 (60.0) (-25.3, 25.7)	153 (64.6) (-9.5, 8.0)	227 (63.2) (-3.0, 11.7)	70 (68.6) (-2.1, 24.5)	26 (86.7) (-23.4, 9.1)	37 (53.6) (-27.2, 6.4)
Non-exposed	15 (60.0)	143 (65.3)	186 (58.9)	55 (57.3)	37 (92.5)	38 (64.4)

Source: SCS Reference 2348

See also section 7.3.4 Significant Adverse Events (Table 20 and pancreatitis subsection), section 7.4.1 Common Adverse Events (Table 31), and section 7.4.2 Laboratory Findings (discussion under the PDLC subsection).

7.5.2 Time Dependency for Adverse Events

Comments pertaining to the time dependency for adverse clinical and laboratory events are contained in the safety sections above, when relevant. (See sections 7.4.2 Laboratory Findings and 7.4.3 Vital Signs.)

7.5.3 Drug-Demographic Interactions

The SCS included an analysis of AEs by age, gender, race, and ethnicity in the simvastatin population of the pooled database, excluding data after initiation of glycemic rescue. As shown in Table 39 below, there was little variation in the occurrence of AEs by demographic group. Upper respiratory tract infections (URIs), nasopharyngitis, and hypoglycemia were among the most common AEs regardless of the demographic group.

Table 39. Most common AEs by demographic group in pooled studies, excluding data after initiation of glycemic rescue (Simvastatin population)

Demographic	Most Common AEs (Sitagliptin vs Non-exposed)		
	First	Second	Third
Age			
<65 years	URI (7.9% vs 7.5%)	Nasopharyngitis (7.1% vs 6.7%)	Hypoglycemia (5.7% vs. 10.0%)
≥65 years	URI (7.2% vs 9.2%)	Nasopharyngitis (5.8% vs 3.3%)	Hypoglycemia (5.3% vs 10.9%)

Gender			
Female	URI (7.4% vs 9.1%)	Nasopharyngitis (6.9% vs 7.2%)	Hypoglycemia (6.7% vs 11.9%)
Male	URI 8.0% vs 7.1%)	Nasopharyngitis (6.7% vs 4.8%)	Dizziness (5.0% vs 2.8%)
Race			
Asian	URI (24.4% vs 21.1%)	Hypoglycemia (8.5% vs 15.8%)	Cough (8.5% vs. 5.3%)
Black	URI (14.7% vs 7.1%)	Headache (8.8% vs 7.1%) Hypoglycemia (8.8% vs 3.6%)	UTI (5.9% vs 3.6%) Nasophyaryngitis (5.9% vs 0%)
White	Nasopharyngitis (7.2% vs 6.3%)	Hypoglycemia (5.2% vs 9.8%)	Diarrhea (5.0% vs 6.0%)
Other/Unknown*			
Ethnicity			
Hispanic	Dizziness (8.1% vs 1.6%)	Influenza (4.8% vs. 7.9%)	Headache (0% vs 7.9%)
Non-Hispanic	URI (8.5% vs 8.4%)	Nasopharyngitis (6.7% vs 6.0%)	Hypoglycemia (6.0% vs 11.5%)
Unknown*			

*Sample size was small; AE incidences were low and similar between treatment groups.
Source: SCS Section 2.7.4.5

As shown in Table 40 below, six of the eleven demographic groups did not have a SOC or AE with greater incidence in the sitagliptin group and 95% CI around the between group difference excluding zero. Of those that did, the SOC or AE was most often of a musculoskeletal, allergic, or infectious nature that is difficult to attribute to the concomitant administration of sitagliptin and simvastatin.

Thus, there appears to be no increased demographic-dependent risk for AE associated with sitagliptin/simvastatin FDC.

Table 40. SOCs and AEs with greater incidence in the sitagliptin group and 95% CI around the between group difference excluding zero in the pooled database, excluding data after initiation of glycemic rescue (Simvastatin population)

Demographic	**SOC/AE with greater incidence in the sitagliptin group and 95% CI excluded 0**			
Age				
<65 years	Immune sys SOC (1.1% vs 0.2%)	Viral infection (1.6% vs 0.2%)	Musculosk chest pain (1.3% vs 0.2%)	Osteoarthritis (1.5% vs 0%)
≥65 years	N/A			
Gender				
Female	Musculosk & conn tiss SOC (21.7% vs 13.8%)	Osteoarthritis (3.1% vs 0.6%)	Neoplasms SOC (2.6% vs 0.6%)	
Male	Gastritis (1.5% vs 0.2%)	UTI (1.3% vs 0%)	Joint injury (1.0% vs 0%)	
Race				

Asian	N/A			
Black	N/A			
White	Viral infection (1.8% vs 0.5%)	Osteoarthritis (1.% vs. 0.3%)	Seasonal allergy (0.8% vs 0%)	
Other/Unknown*	N/A			
Ethnicity				
Hispanic	N/A			
Non-Hispanic	Osteoarthritis (1.9% vs 0%)	Joint injury (0.9% vs 0%)	Rhinitis allergic (0.7% vs 0%)	Seasonal allergy (0.7% vs 0%)
Unknown*	N/A			

Source: SCS Section 2.7.4.5

7.5.4 Drug-Disease Interactions

The SCS did not include an analysis of the effect of renal or liver disease on the co-administration of sitagliptin and simvastatin, although its effect on creatinine and aminotransferases was discussed in section 7.4.2 Laboratory Findings.

Please refer to section 2.1 Product Information for a discussion of the FDC doses that the applicant must develop for subjects with renal insufficiency.

7.5.5 Drug-Drug Interactions

No phase 3 clinical studies were conducted with the sitagliptin/simvastatin FDC or with randomization to the co-administration of sitagliptin and simvastatin. However, section 7 Review of Safety assessed the safety of sitagliptin when used concomitantly with simvastatin in a pooled analysis of 19 clinical trials.

The applicant conducted study P025 as part of sitagliptin NDA 21-995; it evaluated the effect of sitagliptin on simvastatin PK. Clinical pharmacology study P168 assessed the effect of simvastatin 80 mg on the PK of sitagliptin 100 mg. As the 90% CI for the sitagliptin AUC fell within the pre-specified bounds of (0.50, 2.00), simvastatin did not have a clinically meaningful effect on the PK of sitagliptin.

Clinical pharmacology study P169 evaluated the effect of multiple dose, co-administration of sitagliptin and simvastatin on the PK of digoxin. It had an additive effect. Please refer to the clinical pharmacology review for full details, as well as section 7 Drug Interactions of the sitagliptin and simvastatin labels.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No animal studies were conducted with the sitagliptin/simvastatin FDC to evaluate carcinogenicity or mutagenesis. Please refer to the sitagliptin and simvastatin labels for full details. The applicant proposes similar language for the sitagliptin/simvastatin FDC label, which is acceptable.

7.6.2 Human Reproduction and Pregnancy Data

No animal studies were conducted with the sitagliptin/simvastatin FDC to evaluate impairment of fertility.

Sitagliptin is pregnancy category B; there are no adequate and well-controlled studies in pregnant women or its individual components. However, simvastatin is pregnancy category X; it is contraindicated in women who are or may become pregnant. (Please refer to the individual labels for more details.)

The applicant proposes pregnancy category X and language similar to the sitagliptin and simvastatin labels for the sitagliptin/simvastatin FDC. This is acceptable.

It is not known if simvastatin is excreted in human milk. Sitagliptin is secreted in the milk of lactating rats at a milk: plasma ratio of 4:1. The applicant proposes section 8.3 Nursing Mothers language that is similar to the individual sitagliptin and simvastatin labels and supports not taking the FDC while nursing. This is acceptable.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant is currently conducting a pediatric development program for sitagliptin (i.e. studies P081 and P083) and anticipates the drug will be made available for pediatric patients after completion of the studies.

Simvastatin has been studied in adolescent subjects with heterozygous familial hypercholesterolemia (HeFH) and is indicated for these patients (10-40 mg/day). HeFH occurs in approximately 1:500 people but the presence of HeFH in pediatric T2DM patients is low. Simvastatin has not been studied nor approved for use in the general pediatric population.

Although simvastatin is not currently indicated for use in the general pediatric population, it is used in diabetic pediatric patients. The 2011 American Diabetes Association Standards in Medical Care in Diabetes states the addition of a statin in patients after the age of 10 years, who after medical nutrition therapy and lifestyle changes, have LDL cholesterol >160 mg/dl, or LDL cholesterol >130 mg/dl and one or more cardiovascular disease (CVD) risk factors is reasonable.

Since T2DM is a CVD risk factor equivalent, T2DM pediatric patients may be obese with concomitant hyperlipidemia, and the number of these subjects is likely to increase, consideration should be given to requiring the applicant to evaluate the sitagliptin/simvastatin FDC in pediatric patients. However, the applicant has previously and is currently evaluating the PK of simvastatin and sitagliptin, respectively, in adolescents. Clinical pharmacology studies P025 and P168 failed to demonstrate a PK effect of sitagliptin on simvastatin in adults and vice versa. There is no scientific reason to believe the drug-drug interaction between sitagliptin and simvastatin would be different in adolescents.

Furthermore, DMEP's Obesity/Lipids Team has debated internally the benefits of lipid lowering studies in children. If improvements were seen in lipid parameters in a 12-week study in children, would this translate to a change in CV outcome over the long term? A ten to twenty year clinical study is needed to answer this question. Thus, to date, DMEP has not required applicants of lipid-lowering medications to evaluate drugs' outcome effectiveness in the general pediatric population to satisfy the requirements of PREA. (b) (4)

For this reason, I believe the applicant should not be required to evaluate the sitagliptin/simvastatin FDC in pediatric patients. As OSE concluded in its June 8, 2011 consult, the use of sitagliptin and simvastatin as monotherapy or concurrent therapy among patients aged 10-17 years were infrequent. I therefore agree with the applicant's request for a waiver "because it does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients",

On August 17, 2011, PeRC recommended a full waiver of pediatric studies of sitagliptin/simvastatin FDC. I concur with this decision.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant proposes overdosage labeling for the sitagliptin/simvastatin FDC that is consistent with the individual sitagliptin and simvastatin labels. This is acceptable.

7.7 Additional Submissions / Safety Issues

The Division of Medication Error Prevention and Analysis (DMEPA) determined that the proposed proprietary name (b) (4) is vulnerable to name confusion that could lead to medication errors with the currently marketed products, (b) (4). This finding was also identified in the prescription simulation study in which a participant misinterpreted the name (b) (4) for (b) (4). Thus, the applicant was notified that the

proposed name was unacceptable and DMEPA is currently reviewing the applicant's second trade name proposal, which includes (b) (4)

8 Postmarket Experience

Recent Labeling:
Sitagliptin: During the course of the sitagliptin/simvastatin FDC review cycle, DMEP finalized its review and negotiations with the applicant on sitagliptin NDA 21-995 Supplement 17. The supplement originally proposed adding (b) (4) However, after review and discussions with OSE, the Dosage and Administration and Warnings and Precautions (including Highlights) sections of the label were revised in addition to the MG. (See Project Manager Raymond S. Chiang's March 14, 2011 labeling review for full details.)

Simvastatin: On June 7, 2011, the agency approved new safety labeling due to the risk of myopathy, including rhabdomyolysis, in patients treated with 80 mg simvastatin.

As a result, the initially proposed prescribing information (PI) that was submitted with sitagliptin/simvastatin FDC NDA on December 6, 2010 is inadequate. Although NDA 202-343 only proposes sitagliptin 100 mg and simvastatin doses ≤40 mg for use in subjects with normal renal function or mild renal insufficiency (see Indications and Usage), the majority of the new sitagliptin and simvastatin labeling language is relevant to NDA 202-343. Furthermore, the current lack of the sitagliptin 50 mg dose in the sitagliptin/simvastatin FDC makes increased labeling about the need to periodically assess renal function and risk of renal failure even more important. Therefore, the applicant revised the proposed PI and MG to include the new language.

In addition, on August 11, 2011, the applicant was sent a supplement request (SR) letter under simvastatin NDA 19-766. Due to published reports of statins altering glycemic control, the letter requested the following warning be added to the simvastatin label: *Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including Zocor (simvastatin).* Although label negotiations for NDA 202-343 are still ongoing, we have asked the applicant to include similar language in the sitagliptin/simvastatin FDC label and plan to require a postmarketing clinical study to conclusively demonstrate the safety of this convenience product.

Analysis of Postmarketing Data: The applicant searched the WAES for all spontaneous reports received from healthcare providers and agencies for AEs experienced by patients on sitagliptin and simvastatin, atorvastatin, or rosuvastatin. Sitagliptin has been marketed for four years. Simvastatin, atorvastatin, and rosuvastatin have been marketed for 22, 13, and 7 years, respectively.

The incidence of SAEs ranged from 27-35% and was lowest when sitagliptin was used concomitantly with simvastatin (see Table 41). AEs were reported most frequently in the gastrointestinal disorders, investigations, skin and subcutaneous tissue disorders, general disorders, and nervous system disorders SOCs.

Table 41. Summary of postmarketing AE reports for sitagliptin used concomitantly with simvastatin, atorvastatin, and rosuvastatin

System Organ Class	Sitagliptin/ Simvastatin Total Reports (Serious)	Sitagliptin/ Atorvastatin Total Reports (Serious)	Sitagliptin/ Rosuvastatin Total Reports (Serious)
Blood and lymphatic system disorders	7 (4)	9 (5)	2 (1)
Cardiac disorders	22 (14)	18 (15)	8 (5)
Ear and labyrinth disorders	2 (0)	8 (1)	3 (2)
Eye disorders	8 (2)	13 (3)	5 (2)
Gastrointestinal disorders	105 (32)	99 (35)	43 (16)
General disorders and administration	84 (16)	104 (34)	31 (6)
Hepatobiliary disorders	6 (2)	5 (4)	0 (0)
Immune system disorders	4 (0)	3 (1)	2 (0)
Infections and infestations	25 (9)	22 (8)	7 (0)
Injury, poisoning and procedural	21 (8)	26 (12)	6 (2)
Investigations	103 (20)	103 (28)	31 (6)
Metabolism and nutrition disorders	30 (8)	31 (13)	11 (3)
Musculoskeletal and connective tissue	49 (14)	31 (14)	16 (5)
Neoplasms benign, malignant and	6 (6)	6 (6)	2 (2)
Nervous system disorders	74 (18)	59 (21)	19 (7)
Pregnancy, puerperium and perinatal	1 (0)	0 (0)	0 (0)
Psychiatric disorders	13 (6)	20 (6)	8 (3)
Renal and urinary disorders	13 (7)	28 (18)	10 (5)
Reproductive system and breast	3 (0)	5 (2)	2 (1)
Respiratory, thoracic and mediastinal	42 (6)	49 (13)	9 (4)
Skin and subcutaneous tissue disorders	102 (12)	98 (29)	34 (8)
Social circumstances	1 (0)	2 (2)	1 (1)
Surgical and medical procedures	3 (1)	4 (1)	3 (0)
Vascular disorders	17 (4)	10 (4)	4 (2)
DISTINCT NUMBER OF REPORTS	444 (122)	420 (147)	164 (55)
A single report may include adverse events in one or more System Organ Classes. Therefore, the sum of reports from all System Organ Classes can be greater than the total distinct number of reports received.			

Source: SCS Table 2.7.4: 115

In addition, reports of "rhabdomyolysis" were reviewed. Seven reports were identified (simvastatin 5, atorvastatin 3, and rosuvastatin 1). Two of these reports described patients on therapy with two statins (simvastatin and atorvastatin; atorvastatin and rosuvastatin). Four of the seven reports provided little or no additional information. Two reports were confounded by concomitant medications (gemfibrozil, ezetimibe, amiodarone, and olmesartan) associated with rhabdomyolysis. The last report described rhabdomyolysis in an elderly male with diabetic hyperosmolar coma who had been on sitagliptin for 15 days.

In summary, the available postmarketing data do not suggest safety concern with the co-administration of sitagliptin and simvastatin.

See also section 7.3.4 Significant Adverse Events.

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

Please refer to the following sections of this review:

- 2.4 Important Safety Issues With Consideration to Related Drugs
- 7.3.4 Significant Adverse Events
- 7.4.1 Common Adverse Events
- 7.4.6 Immunogenicity
- 7.6.1 Human Carcinogenicity
- 7.6.2 Human Reproduction and Pregnancy Data
- 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound
- 8 Postmarket Experience

9.3 Advisory Committee Meeting

This sitagliptin/simvastatin FDC NDA was not referred to an advisory committee because the drugs are not first in class and the safety profile is similar to that of other drugs approved for these indications. Evaluation of the safety data did not raise significant unexpected safety or efficacy issues. It was therefore felt that outside expertise was not necessary.

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

/s/

VALERIE S PRATT
09/01/2011

ILAN IRONY
09/02/2011
I concur with Dr. Pratt's review and recommendation.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-343 **Applicant: Merck** **Stamp Date: 12/7/10**

Drug Name: **NDA/BLA Type: Standard**
Sitagliptin/simvastatin FDC

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			Sponsor used FAS & PP populations despite pre-NDA (5/24/10) advice to include only FAS. Labeling proposes no new language based on P24 & 49, in which analyses were based on PP population. Stats and clinical accept what was submitted.
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	x			There were multiple discussions with the agency about the

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Number: Study Title: Sample Size: Arms: Location in submission:				proposed doses and future sNDA submission of sitagliptin 50 mg as part of the FDC (may be a PMR or PMC).
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			x	A clinical study to support safety may be a PMR or PMC as discussed at the Pre-NDA meeting. The pivotal studies in this application are BE studies.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		x		This was not submitted. A TQT study was not discussed at the pre-NDA meeting. However, a TQT study was conducted with sitagliptin in the past (Study P032). Simcor (simva/niacin XR FDC) was approved in 2008 w/o TQT study, based on the 9/26/10 pre-NDA discussion. Therefore, we do not plan to require a TQT required for the sita/simva FDC.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			Sitagliptin N=827 in the Summary of Clinical Safety
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?				I could not locate this. Sponsor should direct us to it.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		x		The sponsor should submit or direct us to the narratives for 1) adverse event dropouts and 2) subjects who initiated a statin in the pooled database, as discussed at the pre-NDA meeting.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			The submitted waiver may be insufficient. 1) Sitagliptin & simvastatin have or are being studied in subjects ≥10 years (simva dose ≤40 mg). 2) Simvastatin is being used in the marketplace by ped patients. 3) Need is likely to increase. This should be

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					discussed with PeRC.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		x		Only a list (no CRF or narratives) were identified for these subjects in the Summary of Clinical Safety section 2.7.4.1.1.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			No additional CRFs were requested.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

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

1. You state that because 1) an approved risk evaluation mitigation strategy (REMS) is currently in place for Januvia and 2) there is no clinical evidence that suggests a clinically important interaction between sitagliptin and simvastatin, a separate REMS is not warranted for NDA

202-343. However, you appropriately submitted a medication guide (MG). As MGs are part of a REMS, please submit a REMS for this product.

2. As discussed on September 30, 2010, the Four-Month Safety Update should include an update on the development of sitagliptin 50 mg FDC.
3. Please submit or direct us to the narratives for subjects who initiated a statin in the trials that constitute the pooled database, as discussed at the pre-NDA meeting on May 24, 2010.
4. You submitted a listing of subjects who discontinued due to adverse events. Please submit or direct us to the narratives and case report forms for these subjects.
5. Please direct us to the coding dictionary used for mapping investigator verbatim terms to preferred terms or submit it, if it was not previously submitted.

Internal Comments:

- *The pediatric waiver submitted with this NDA should be discussed with the Pediatric Review Committee (PeRC).*
- *OSE should be consulted for the REMS.*

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

VALERIE S PRATT
02/02/2011

ILAN IRONY
02/03/2011
I concur with Dr. Pratt's opinion and comments to the applicant for the 74-day letter.