CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202343Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	8/15/2011
From	Ilan Irony, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	202343 Original submission under 505 (b)(1)
Applicant	Merck
Date of Submission	07/12/2010
PDUFA Goal Date	10/07/2011
Proprietary Name / Established (USAN) names	Juvisync / sitagliptin simvastatin fixed dose combination tablets
Dosage forms / Strength	Sitagliptin simvastatin 100 mg / 10 mg, 100 mg / 20 mg and 100 mg / 40 mg
Proposed Indication(s)	1. Improve glycemic control in adults with T2DM 2. Reduce risk of cardiovascular mortality, non-fatal MI, stroke and need for revascularization procedures 3. Reduce elevated total cholesterol, LDL-cholesterol, apo-B lipoprotein, and triglycerides in settings for which simvastatin is approved.
Recommended:	Approval

1. Introduction

This is a new drug application for a fixed dose combination tablet (FDC) of sitagliptin, an oral antidiabetic drug for the treatment of adults with type 2 diabetes (T2DM) and simvastatin (a lipid lowering drug. Both components are approved and marketed drugs in the US. While FDCs where both drug components treat the same indication are common, there is precedent within CDER and OND for approval of a FDC with each component treating a separate indication (Caduet is a FDC of amlodipine, an antihypertensive drug and atorvastatin, a lipid lowering statin drug).

From a scientific and regulatory standpoint, this is a fairly straightforward application. The two drugs that comprise the FDC are approved in the US, and each carries substantial postmarketing experience.

Recent published studies and metanalyses [1,2,3] have suggested a small interference of statins as a class (with the exception of pravastatin) on glycemic control, and among pre-diabetics, a slightly higher tendency to progress to overt diabetes among users of statins.

A large rosuvastatin outcome trial (n = 17802 subjects) conducted in patients with elevated C reactive protein and normal LDL cholesterol levels (JUPITER) also showed a small increase in investigator-reported diabetes (2.8 % vs. 2.3% for placebo, HR = 1.27) and an increase in HbA1c among diabetics (refer to Dr. Mary Roberts review of Rosuvastatin NDA 21366 supplement 16, filed on 2/5/2010).

In SPARCL (atorvastatin 80 mg vs placebo), diabetes was reported as an AE in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group. The reported percentage of diabetes was 8.9% in the atorvastatin and 5.3% in the placebo group in subjects with a medical history of diabetes, and 5.5% and 3.5%, respectively, in subjects without a medical history of diabetes.

In ASCOT-LLA (atorvastatin 10 mg vs placebo), a slightly larger percentage of patients in the atorvastatin group also developed diabetes during the course of the study, although the difference did not achieve statistical significance. At 12 months, there was a small statistically significant difference in mean blood sugar change, slightly favoring the placebo group. This difference (mean % increase of 0.26% for the atorvastatin group vs 0.16% for the placebo group) was small.

But the conclusion from these metanalyses, JUPITER, SPARCL and ASCOTT-LLA has been that the benefits of a statin treatment in diabetics far outweigh the risks, and such treatment continues to be recommended for patients with T2DM, due to major impact cardiovascular disease has on the morbidity, mortality and health care costs in the diabetic population. For this particular NDA, a dedicated trial to examine the magnitude of the simvastatin interference with sitagliptin-promoted glycemic control will be a postmarketing requirement, already

[1] Sattar N, Preiss D Murray HM et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375: 735–42

[2] Rajpathak SN, Kumbhani DJ, Crandall J et al. Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis. Diabetes Care 2009; 32:1924 – 1929

[3] Koh KK, Quon MJ, Han SH at al. Atorvastatin causes insulin resistance and increased ambient glycemia in hypercholesterolemic patients. Journal of the American College of Cardiology 2010; 55: 1209-1216

discussed with the applicant during a teleconference in May 2010 and repeated at the pre-NDA meeting.
So the main issue for this application is the demonstration of bioequivalence (BE) between the to-be-marketed formulation of the FDC and its components namely, sitagliptin and simvastatin.
As reported in Dr. Chung's Clinical Pharmacology review, BE was established in a study conducted in healthy volunteers. However, inspection of the clinical and analytical sites by the Division of Bioequivalence and GLP Compliance (DBGC) in the Office of Scientific Investigations (OSI) uncovered violations of the handling of reserve samples of tablets at the clinical study site, Icon Development Solutions in San Antonio TX. DBGC recommended rejecting the BE data, (b) (4) The clinical and clinical pharmacology review teams discussed these recommendations with DBGC, and learned that the lots inspected and used for the BE studies were the same as those submitted in the NDA, and passed all specifications. The applicant received a biowaiver from Bipharmacology with regard to the minor differences between these lots and the to-be-marketed lots.

2. Background

Sitagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, has been approved for treatment of T2DM in the US since October 2006 under NDA 21995. 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 under NDA 19766 and currently has five lipid lowering and cardiovascular (CV) indications (refer to Zocor label).
The filing of the sitagliptin/simvastatin FDC NDA is based on the demonstration of BE between the FDC tablets and coadministration of corresponding doses of sitagliptin and simvastatin (for the latter, 10 and 80 mg to bracket the dose range). 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.
Although the FDC tablet can be regarded as a convenience product (i.e., taking only one tablet daily, rather than two separate tablets), many diabetics have indications for the use of a statin drug, due to their prevalent dyslipidemia and higher cardiovascular risks, and this combination makes sense for the targeted population. The FDC has the disadvantage that patients for whom sitagliptin is being considered as the antidiabetic drug will also be taking a statin (simvastatin) associated with significant interactions with other drugs, as well as the added cost, when compared to adding generic simvastatin to a regimen of brand sitagliptin.
Prior to submitting NDA, the applicant reached agreement with FDA on two issues:
• The 100/80 mg tablet is not approvable because of the recently identified safety issue (increased risk of rhabdomyolysis) associated with the 80 mg simvastatin dose.
• 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 dose strengths and plans to submit a supplemental NDA (sNDA) for them by (b) (4)

3. CMC/Device

The proposed formulation is a bilayer tablet comprised of:
1) A sitagliptin layer (layer weight (b) (4)), which is based on (b) (4) JANUVIA® Tablet formulation, and
2) A (b) (4) simvastatin layer (b) (4) from a common simvastatin (b) (4). This (b) (4) is the same as that used in the manufacture of ZOCOR® Tablets.

During review, CMC noted that the stability analysis of samples of sitagliptin 100 mg / simvastatin 80 mg were out of the applicant's self-defined range of 95 to 105% at release and during the 52 week stability period. In response to an information request, Merck expanded the specification range to 90 – 110% (as allowed per US regulations), and the assay data fell within the range.
Based on the provided real-time stability data, a two and a half (2 1/2) year expiry period is granted for the 100/10, 100/20 and 100/40 mg /mg sitagliptin/ simvastatin FDC tablets supplied in 30 and 90 count bottles.
Based on the provided real-time stability data, a one (1) year expiry period is granted for the 100/10, 100/20 and 100/40 mg /mg sitagliptin/ simvastatin FDC tablets supplied in the 1000 count bottle.

The CMC review team recommends approval; a final review of the facility inspection in ESS is pending at the time of this review.

4. Nonclinical Pharmacology/Toxicology

Due to the concern of possible toxicologic interactions between sitagliptin and simvastatin, especially regarding adverse effects on the skeletal muscle, the sponsor conducted a 3-month toxicology study in rats to assess the potential toxicity due to coadministration of sitagliptin and simvastatin. There was no mortality or significant adverse effects associated with the coadministration of sitagliptin and simvastatin at exposures greater than 20 times those at the maximum clinical dose of either drug in the FDC. Although there were no adverse muscle or pancreas effects associated with either drug administered alone or in combination, coadministration of sitagliptin and simvastatin did cause an increase in adverse liver effects. Administration of the simvastatin high dose (60 mg/kg; ~47-114X MHRD; based on AUC) caused an increase in liver weight, hepatocellular hypertrophy, and an increase in ALT levels (~2-3X compared to controls). Although these effects were not observed in animals administered sitagliptin alone, the coadministration of sitagliptin (180 mg/kg; ~20X MHRD; based on AUC) and simvastatin caused a slightly greater dose-related increase in liver weight (females only) and ALT levels with both the low (30 mg/kg; ~20-66X MHRD; based on AUC) and high (60 mg/kg; ~47-114X MHRD; based on AUC) simvastatin doses suggesting a

possible drug-drug interaction between sitagliptin and simvastatin with regards to liver toxicity. Although the sponsor did not establish a NOAEL for the additional increases in liver weight and ALT levels, these adverse liver effects are clinically monitorable. Co-administration of the simvastatin high dose (60 mg/kg; ~47X MHRD; based on AUC) and sitagliptin (180 mg/kg; ~20X MHRD; based on AUC) also caused bile duct hyperplasia. Given that there were no similar findings in animals administered the simvastatin high dose or sitagliptin alone and that bile duct proliferation/hyperplasia was previously observed in rats in studies conducted under NDA 21995 (sitagliptin) and NDA 19766 (simvastatin), this finding suggests a potential drug-drug interaction. However, as a NOEL (30 mg simvastatin/180 mg sitagliptin) was established for this finding at approximately 20 times the human exposure at the MRHD, this is of minimal concern clinically.
Simvastatin treatment was associated with adverse effects in the nonglandular stomach and thyroid. These findings were not markedly affected by the coadministration of sitagliptin. Moreover, they are consistent with those observed in the rat in toxicology studies conducted in support of simvastatin and are not considered to be clinically relevant.
Information from the genotoxicity, carcinogenicity, and reproductive studies conducted under the sitagliptin) and simvastatin NDAs support chronic administration. Pregnancy category X is recommended for the FDC drug product given that simvastatin is classified in pregnancy category X because lipid lowering drugs offer no benefit during pregnancy when cholesterol and cholesterol derivatives are needed for normal fetal development.

The Pharmacology / Toxicology team recommends approval of the NDA.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

As agreed with the applicant, demonstration of BE between the FDC and each component (sitagliptin and simvastatin) was the pivotal element to support approval of the NDA. Simvastatin is an inactive pro-drug and needs to be converted to its active form, simvastatin acid, after oral administration. Therefore, pharmacokinetic (PK) parameters of simvastatin acid should be considered the primary endpoint for the BE assessment of simvastatin in addition to those of sitagliptin.

The proposed strengths are 100/10, 100/20 and 100/40 mg (mg sitagliptin / mg simvastatin, respectively). The tablet strengths containing 50 mg sitagliptin (i.e., 50/10, 50/20 and 50/40 mg) are currently in development and the applicant agreed to submit a supplement for these dose strengths (b) (4). FDCs containing 50 mg of sitagliptin target the group of diabetics with hyperlipidemia who have moderate renal impairment.
Merck conducted eight clinical pharmacology studies in support of the sitagliptin/simvastatin FDC NDA, as follows:

• Two BE studies - one using the lowest strength (Study P255: sitagliptin 100 mg / simvastatin 10 mg) and the other one using the highest strength (Study P153 Part I and Part II: sitagliptin 100 mg / simvastatin 80 mg)
• One study for the food effect on sitagliptin 100 mg / simvastatin 80 mg

• Two relative bioavailability studies to explore preliminary formulations
• Two studies for assessment of drug-drug interaction

The BE study for the high simvastatin dose of 80 mg was conducted prior to awareness of safety issues associated with that dose strength and prior to the safety labeling changes imposed on simvastatin 80 mg. However, for the purpose of the bracketing approach to BE of the entire dose range of the FDC, the study is valid and data from that study should be accepted to support the BE of lower dose strengths of simvastatin in the FDC tablets, with biowaiver being granted for the lower doses of simvastatin.

The two BE studies (Study P153 Part I and Part II and Study P255) showed BE between sitagliptin / simvastatin FDC and its individual components, because the primary PK parameters (AUC and C_{max}) of sitagliptin, simvastatin and simvastatin acid met the regulatory BE goal post of 90% confidence interval (90% CI) (Table 1).

Table 1. Summary results (geometric mean ratio) of bioequivalence studies of sitagliptin and simvastatin

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

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

Source: Dr. Chung's Clinical Pharmacology review

A high fat breakfast did not affect sitagliptin exposure following sitagliptin / simvastatin FDC administration (refer to the Clinical Pharmacology review for data). Meanwhile, simvastatin AUC decreased by 24% and its C_{max} increased by 20% with the high fat breakfast. In addition, high fat breakfast resulted in increase in simvastatin acid AUC and C_{max} by 37% and 116%, respectively. The clinical significance of the above exposure change in simvastatin and simvastatin acid is not known; our proposed recommendation is for evening administration, similar to the simvastatin labeling.

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

Clinical Pharmacology recommends approval of the NDA.

<u>Office of Scientific Investigation report and recommendation</u>

At our request, DBGC / OSI conducted inspections of clinical and analytical portions of the following studies:

Study: 255: "A Single-Dose Study to Evaluate Definitive Bioequivalence of MK-0431D and Co-administration of Sitagliptin and Simvastatin"

Study: 153: "A 2-Part Single-Dose Study to Evaluate a Probe Formulation of MK-0431D and Evaluate Definitive Bioequivalence of MK-0431D and Co-administration of Sitagliptin and Simvastatin".

The analytical site (b) (4) was inspected, and the few minor deficiencies were resolved. The clinical inspection occurred at Icon Development Solutions, in San Antonio TX, where both BE studies took place. Inspectors identified the following deficiencies:

Icon returned the retained sitagliptin / simvastatin FDC samples to Merck (those bottles not used for dosing in Study P153); Merck, in turn, returned them to Icon. However, the FDA inspector considered Icon's action as failure to meet the regulatory requirements for retention of reserve samples for bioavailability or study (21 CFR 320.38 and 320.63).

In addition, Icon informed the inspector that for both Studies P255 and P153, Merck pre-identified the sample bottles to be retained, by numbering these kits with different serial numbers as the bottles actually used in dosing the subjects. The regulations specify that the clinical site has to randomly select drug products for dosing or for reserve, and therefore, the authenticity of the products could not be verified.

The studies fail to meet the regulatory requirements for retention of reserve samples for bioavailability or study (21 CFR 320.38 and 320.63). The Final Rule for Retention of Bioavailability and Bioequivalence Testing Samples (Federal Register, Vol. 58, No. 80, Pages 25918-25928, 1993) clarifies that:

"The study sponsor should provide to the testing facility batches of the test product and reference standard packages such that the reserve samples can be randomly selected to ensure that they are in fact representative of the batches provided by the study sponsor…"

Since Icon did not randomly select reserve samples and maintain their custody, DBGC could not verify the authenticity of the study drugs tested. Thus, DBGC recommended rejecting data from these two BE studies.

DBGC cited another example where similar findings resulted in a Complete Response action. The Complete Response letter to (b) (4) cites:

(b) (4)

Resolution of the conflicting recommendations
The CMC, clinical and clinical pharmacology teams identified the manufactured lots of study drug and contacted Merck to confirm (the lot numbers listed in the inspection report and those listed in the NDA were different). Merck explained that these lot numbers for the clinical site were the identification of bottles to be used in the BE study. Furthermore, Dr. Sung's review showed that the variability of specification ranges among lots and within lots was very small, and could not result in effects on BE sufficient large to change the conclusion of bioequivalence. This was discussed with DBGC/OSI on September 13th, 2011, and all disciplines agreed that acceptance of the BE data was reasonable, but that OSI must convey these regulatory violations to Merck and to Icon independently of the regulatory action on this NDA.

Biopharmaceutics
Biopharmaceutics granted the requested biowaiver for the minor differences between the final market composition tablets used in the Definitive Bioequivalence studies P153 and P255 and the commercial tablets (lighter brown color and a different manufacturing site). A biowaiver for the intermediate strength tablets of sitagliptin 100 mg / simvastatin 20 mg and sitagliptin 100 mg / simvastatin 40 mg was also granted. Dissolution profiles and criteria for both components were acceptable.

6. Clinical Microbiology

Not applicable. The product is not an anti-microbial.

7. Clinical/Statistical- Efficacy

No Phase 3 clinical trials were conducted to support the sitagliptin / simvastatin FDC. We had agreed with Merck, in several interactions during the IND development of this product, that such trial would not be required to demonstrate a glycemic and lipid lowering effect, as long as PK bioequivalence is demonstrated against each component of the FDC. Due to the findings from the JUPITER trial and the two metanalyses demonstrating slight worsening of glycemia among diabetics using statins, we asked Merck to conduct a metanalysis of their simvastatin studies to assess effects on glycemic control in the diabetic subset of these CV risk-enriched study populations, and to conduct a metanalysis of the sitagliptin trials, comparing the effects on glycemia in patients using simvastatin or other statins who were randomized to sitagliptin or placebo comparator in the sitagliptin trials conducted in support of the Januvia NDA. These analyses were described in Dr. Pratt's review and I will reproduce here only top level results and conclusion (under the Safety heading, below).

8. Safety

Please refer to Dr. Pratt's clinical review, for details regarding the safety analyses of the coadministration of simvastatin and sitagliptin.

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

The applicant demonstrated that there was no clinically significant difference in the change in HbA1c in subjects with T2DM randomized to simvastatin compared to placebo in the simvastatin clinical development program.

- Heart Protection Study (Lancet 360(9326): 7-22, 2002): This trial was conducted in the United Kingdom among subjects at high CV risk, age 40 to 80 years, randomized to simvastatin 40 mg or placebo and followed for 5 years, as endpoint-driven. In a random sample of subjects with T2DM (5963 of the 20,536 subjects) who had HbA1c recorded at baseline (n = 1,087), there was no significant difference (Table 2) between treatment groups in the change in HbA1c.

Table 2. HPS: Change from baseline in HbA1c in a random sample of T2DM

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.

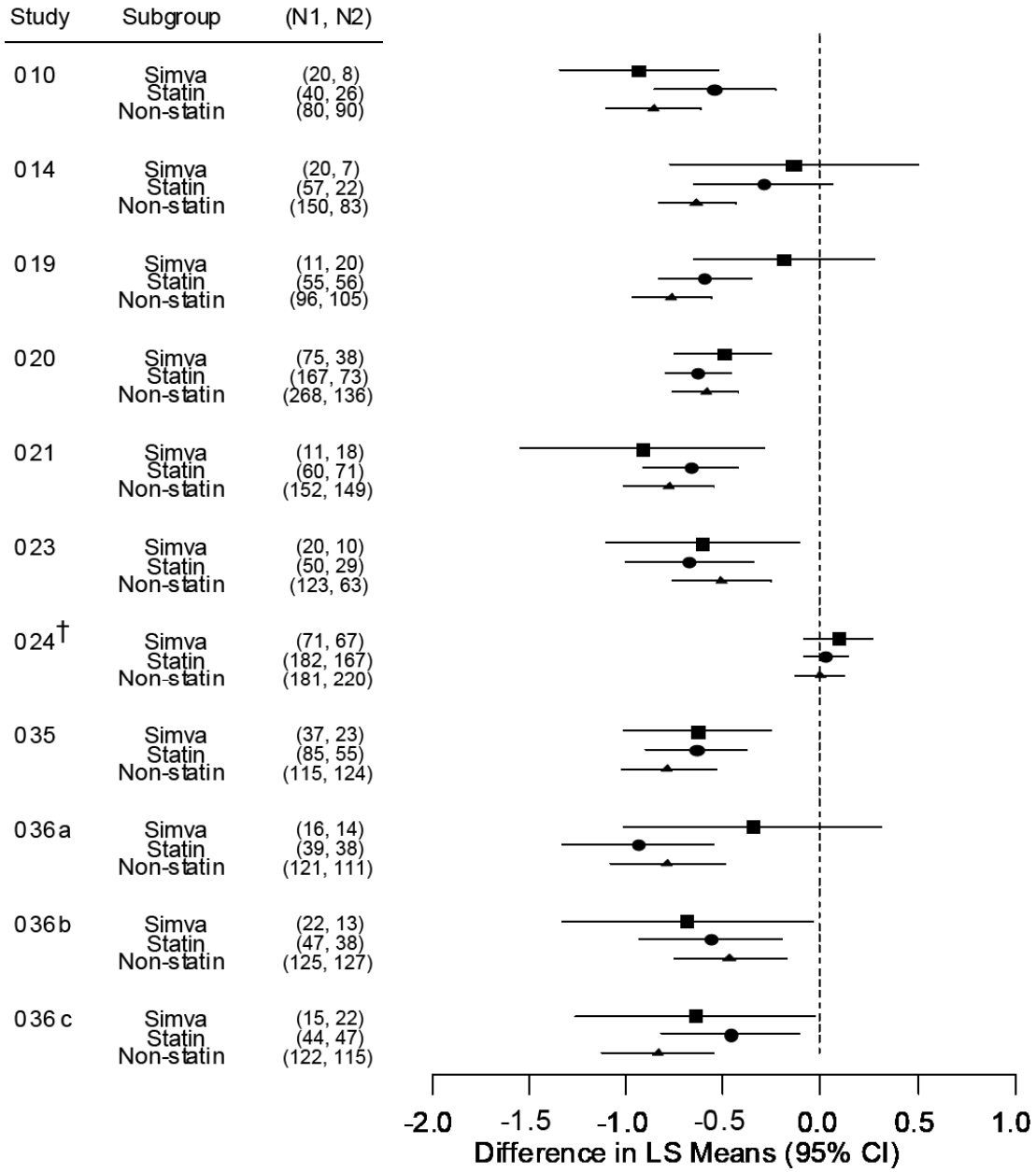
There were also no meaningful differences in the reporting rate of hospital admissions for unstable diabetes (3.1% simvastatin vs. 3.2% placebo) or laser treatment for retinopathy (1.4% simvastatin vs. 1.2% placebo). For the 4,867 T2DM subjects for whom antihyperglycemic agent (AHA) information was available 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.

As Dr. Pratt correctly pointed out in her review, the study was not designed and powered to detect the small differences detected in the published metanalyses.

- Study MK-0733-P187 compared the effect of simvastatin 40 mg versus placebo on the change from baseline to week 24 in LDL cholesterol in 253 diabetics with LDL > 100 mg/dL and HbA1c ≤ 9% (on TZDs) at baseline. There was no significant difference between the simvastatin 40 mg and placebo groups in the change in HbA1c at week 24 (LS Mean for the difference simvastatin minus placebo: 0.2%, 95% CI -0.1, 0.4).

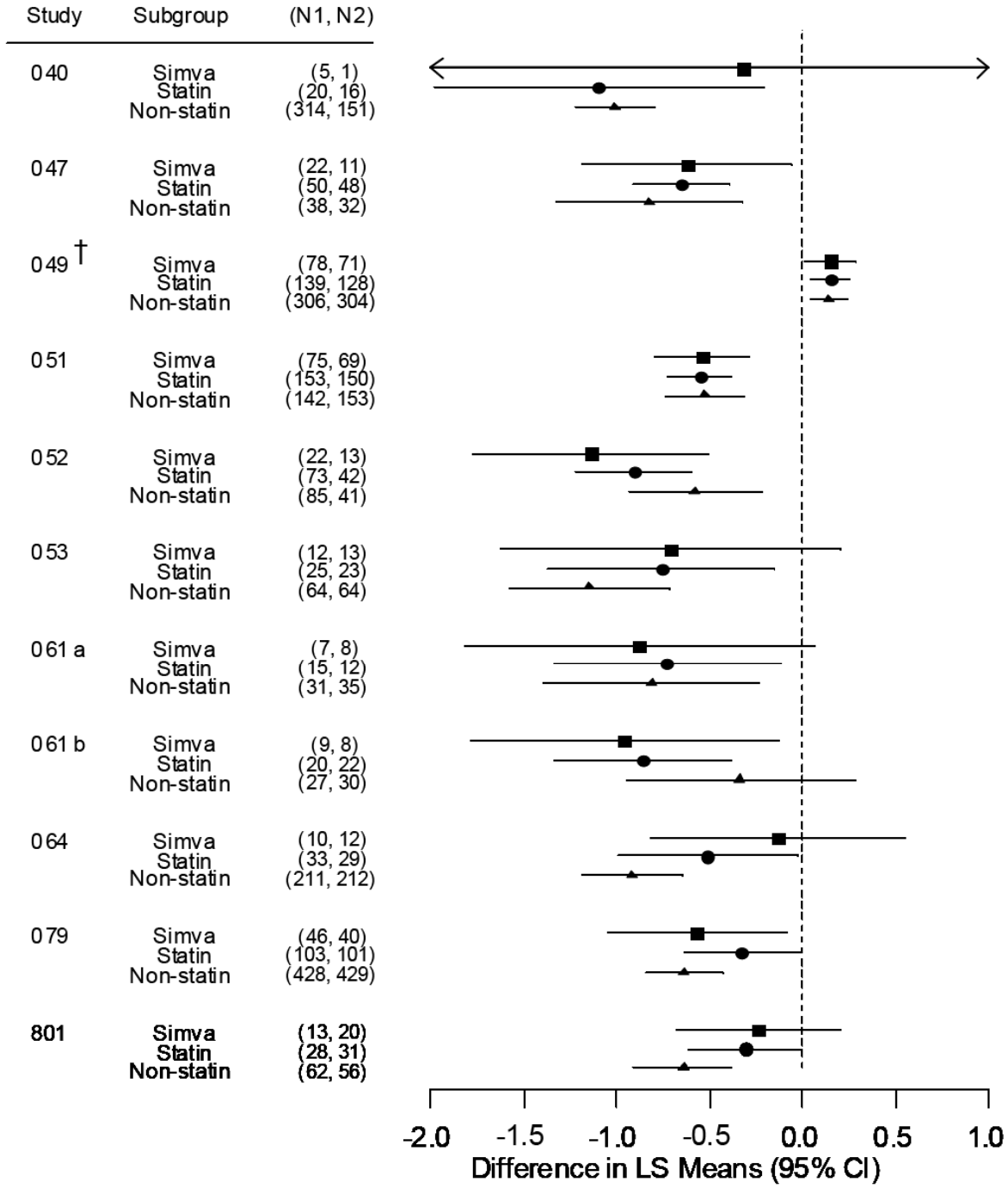
The HbA1c-lowering efficacy of sitagliptin versus placebo/ active comparator was analyzed in the following subgroups in the 19 sitagliptin clinical trials (the same 19 sitagliptin studies that were included in the SCS): simvastatin users, statin users, and non-statin users. The results were generally similar between the groups, although few subjects were on simvastatin or any statin in some of the studies. This resulted in wide 95% CI intervals. These results, and their variability, are best illustrated by the forest plots in Merck's Summary of Clinical Efficacy (Figure 1 and Figure 2).

Figure 1. Analysis of Change from Baseline in A1C (%) by Simvastatin/Statin Use in the Primary Analysis Population of Each Study (Protocols 010 to 036)



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 2. Analysis of Change from Baseline in A1C (%) by Simvastatin/Statin Use in the Primary Analysis Population of Each Study (Protocols 040 to 801)



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)

- Review of the change from baseline HbA1c in patients who initiated simvastatin (n = 95) or other statins (n = 177) 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. This analysis is flawed due to the different times treatment with statins was initiated after randomization, and the relatively strong glycemic effect of sitagliptin or other active comparators against the small expected changes due to statins, based on the metanalyses.

At the Pre-NDA stage, we agreed with Merck that a FDC containing simvastatin 80 mg would not be marketed, due to the risks of severe myopathy and rhabdomyolysis detected with that dose in the SEARCH trial and from other sources of safety data. On June 7, 2011, FDA approved new safety labeling for Zocor regarding the risk of myopathy, including rhabdomyolysis, in patients treated with 80 mg simvastatin.

We also agreed with Merck that manufacturing of FDC doses containing sitagliptin 25 mg or simvastatin 5 mg would not be required due to the low usage rate (2.2% and 0.6%, respectively) in the US.

The applicant analyzed sitagliptin and simvastatin coadministration data from the following 19 sitagliptin trials and studies which were included in the Summary of Clinical Safety (SCS):
• Phase 1 study 061
• Phase 2 studies 010 and 014
• Phase 3 trials 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 coadministered 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.

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

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%).

Comparing subjects on both sitagliptin and simvastatin or other statins to subjects on these statins not exposed to sitagliptin, there were no increases in reports of myopathy or the preferred term of "blood CPK increased" or increases in liver aminotransferases. There were also no increases noted in subjects receiving both sitagliptin and simvastatin or other statins for adverse reactions listed in the Januvia label: pancreatitis, hypoglycemia, renal impairment, or hypersensitivity reactions, compared to subjects on these lipid lowering agents not exposed to sitagliptin.

9. 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. We concluded outside expertise was not necessary for this review.

10. Pediatrics

The sponsor submitted a full waiver for the pediatric assessment for the following aspects:
• The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested,
• DMEP has not required sponsors of lipid-lowering medications to evaluate drugs' effectiveness in the general pediatric population to satisfy the requirements of PREA.
• Pediatric studies with sitagliptin are ongoing.
The PeRC meeting was held on August 17, 2011 and the committee agreed with DMEP's position to grant a full waiver from PREA requirements.

11. Other Relevant Regulatory Issues

- We sent Merck a REMS retraction letter. The product, once approved, will only carry a Medication Guide.

- The DSI audit is described under the Clinical Pharmacology section of this memo.

- The two postmarketing requirements (PMRs) to be listed in the approval letter are:
  PMR 1: Development of fixed dose combination strengths of sitagliptin/simvastatin of 50/10, 50/20, and 50/40 to permit dosing of patients with moderate renal impairment with this combination product.
  PMR 2: A randomized, double-blind, active-controlled clinical trial to study the effect of sitagliptin/simvastatin FDC versus sitagliptin on glycemic control in type 2 diabetic patients on background metformin therapy.

12. Labeling

At the time of this writing, the proprietary name under consideration for this FDC is Juvisync, after (b) (4) had been rejected by DMEPA and / or DDMAC. We are currently negotiating the PI and the Medication Guide with the applicant.
Although Merck had agreed to a number of revisions we proposed to the label, they had not agreed to implement changes (listed in the paragraph below) we had requested in order to align this PI with the Supplemental Request Letter for Zocor we issued on 8/11/11. Merck wants to discuss and agree on changes to the Zocor label first, and then align the new changes to the Juvisync label as a labeling supplement to the Juvisync NDA.

These disputed changes are listed below:

- (b) (4)

Although DRISK's comments and suggested revisions to the Medication Guide were minor, we have not worked on the Medication Guide with the applicant, until we reach agreement on the substantive PI changes listed above.

13. Recommendations/Risk Benefit Assessment

I recommend approval of the sitagliptin/simvastatin FDC NDA. I fully recognize that this is a convenience product, so that patients who need sitagliptin and simvastatin can take only one pill daily. But there are no additional risks for the FDC, compared to coadministration of these two drugs separately.
My recommended PMRs are listed in Section 11 of this memo, and the labeling issues we need to reach agreement with the applicant are listed in Section 12 of this memo.

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

/s/

ILAN IRONY
09/16/2011

MARY H PARKS
09/19/2011