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APPLICATION NUMBER:
202270Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA SDN 31
Application Number(s) 202-270
Priority or Standard Standard

Submit Date(s) 08-03-11
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PDUFA Goal Date 02-03-12
Division / Office DMEP/ODEII/OND

Reviewer Name(s) Valerie S. W. Pratt, M.D.
Review Completion Date 11-10-11

Established Name Sitagliptin/metformin XR
(Proposed) Trade Name Janumet XR
Therapeutic Class DPP-4 inhibitor/biguanide
Applicant Merck

Formulation(s) 50/500, 50/1000, & 100/1000
mg tablets
Dosing Regimen Once daily
Indication(s) Type 2 diabetes mellitus
Intended Population(s) Adult type 2 diabetes

**Medical Officer Safety Review
Division of Metabolism and Endocrinology Products**

NDA: 202-270 SDN 31 (Complete Response [CR])

Date of Submission: August 3, 2011

Name of drug: Sitagliptin/metformin fixed dose combination (FDC) tablet

Indication: For use as an adjunct to diet and exercise to improve glycemic control in patients with T2DM

Sponsor: Merck

Medical Reviewer: Valerie Pratt, M.D.

Medical Team Leader: Ilan Irony, M.D.

Background: On July 22, 2011, a CR letter was issued due to deficiencies at the Arecibo, Puerto Rico manufacturing facility. Satisfactory resolution of the Chemistry, Manufacturing, and Controls (CMC) deficiencies is required before the application may be approved. The updated complete study report (CSR) for clinical pharmacology study 147-00 (147) was also required, after review of (b) (4) July 11, 2011 response to our Form FDA 483.

Please refer to my review of NDA 202-270 which recommended approval of the FDC, pending resolution of the Office of Compliance, Division of Manufacturing and Product Quality (OC-DMPQ) issues.

CR: No additional nonclinical or clinical studies of sitagliptin/metformin XR FDC were undertaken by the applicant. Thus, there were no additional data to submit. No additions or changes to the safety profile were reported by the applicant.

As requested in the CR letter, however, the applicant submitted an updated CSR for clinical pharmacology study 147, a pivotal study that characterized the single dose pharmacokinetics (PK) of sitagliptin and metformin following administration of 50/500 mg or 100/1000 mg of the FDC in healthy subjects. (The revised CSR was requested because of (b) (4) July 11, 2011 response to the Form FDA 483 and the applicant's submission of updated study 147 datasets in SAS transport files on July 21, 2011.) As described in Jee Eun Lee's June 17, 2011 original clinical pharmacology review, the 90% CIs of the geometric mean ratios for the pharmacokinetic parameters ($AUC_{0-\infty}$ and C_{max}) for sitagliptin and metformin after administration of single tablet of sitagliptin/metformin XR 100 mg/1000 mg tablet and those after administration of sitagliptin 100 mg + Glumetza (metformin XR) 1000 mg fell within the range of [0.80, 1.25]. Thus, the bioequivalence (BE) between FDC and co-administration of sitagliptin and Glumetza was established for two of the three dose strengths.

When BE was evaluated using the updated datasets as requested in the CR letter, the 90% CIs of the geometric mean ratios for the pharmacokinetic parameters ($AUC_{0-\infty}$ and C_{max}) for sitagliptin and metformin after administration of single tablet of sitagliptin/metformin XR 50/500 mg or 100 mg/1000 mg tablet and those after co-administration of corresponding doses of sitagliptin + Glumetza (metformin XR) again fell within the range of [0.80, 1.25]. Thus, the bioequivalence (BE) between FDC and co-administration of sitagliptin and Glumetza was reestablished for two strength levels. Clinical pharmacology concurs. Please also refer to Dr. Jee Eun Lee's review.

Table 1. Statistical comparison of plasma PK parameters of sitagliptin and metformin after administration of a single 50/500 or 100/1000 mg FDC tablet and co-administration of corresponding doses of sitagliptin and Glumetza (metformin XR) in healthy adults

	Sita/met XR FDC Tablets vs. Co-administration of sitagliptin and Glumetza (metformin XR)	
Parameter	Sita/met XR FDC 50/500 mg	Sita/met XR FDC 100/1000 mg
Sitagliptin		
$AUC_{0-\infty}$	1.00 (0.99, 1.02)	1.01 (0.99, 1.03)
C_{max}	0.96 (0.92, 1.01)	1.00 (0.96, 1.05)
Metformin		
$AUC_{0-\infty}$	1.07 (1.01, 1.13)	0.96 (0.91, 1.01)
C_{max}	1.08 (1.03, 1.14)	1.14 (1.09, 1.19)

Source: CSR 147-00 Tables 11-1 and 11-2

Recommendation: I recommend approval of sitagliptin/metformin XR FDC, pending resolution of the Office of Compliance, Division of Manufacturing and Product Quality (OC-DMPQ) issues.

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/s/

VALERIE S PRATT
11/10/2011

ILAN IRONY
11/10/2011

I concur with Dr. Pratt's review and recommendation for approval, pending OC/OMPQ recommendation.

Cross-Discipline Team Leader Review

Date	7/20/2011
From	Ilan Irony, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	202270 Original Submission
Supplement#	
Applicant	Merck
Date of Submission	9/23/2010
PDUFA Goal Date	7/23/2011
Proprietary Name / Established (USAN) names	Janumet XR / sitagliptin metformin XR
Dosage forms / Strength	Tablets / 50/500, 50/1000 and 100/1000 mg
Proposed Indication(s)	As adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
Recommended:	Complete Response letter

1. Introduction

This is the Cross Discipline Team Leader (CDTL) review of NDA 202270, a sitagliptin / metformin extended release (XR) fixed-dose combination (FDC) for the treatment of Type 2 diabetes mellitus (T2DM) submitted under 505 (b)(2), with Glumetza (metformin XR) being the reference listed drug (RLD).

Reviewer comment: During the review cycle, the team uncovered that the applicant had full right of reference to Depomed's Glumetza, its Prescribing Information and supporting data. All disciplines stated that there were no additional data (beyond Merck's sitagliptin, sitagliptin / immediate-release metformin FDC and Depomed's Glumetza) necessary to support approval of the product under this application; therefore we deem the NDA to be a 505(b)(1) and the applicant has revised the NDA classification accordingly.

2. Background

This is a NDA for a fixed-dose combination of two approved oral drug products. The components are sitagliptin (tradename Januvia), a dipeptidyl peptidase inhibitor approved in October 2006, and metformin formulated for extended-release. The comparator for the latter is Glumetza, the RLD, approved in June 2005. Another fixed-dose combination containing sitagliptin and metformin immediate-release has been approved in March 2007, under the tradename Janumet, for twice-daily administration. So the product reviewed under this NDA is only expected to bring the convenience of once-daily dosing.

The proposed dosing regimen is sitagliptin/metformin XR 50 mg/500 mg and 50 mg/1000 mg to be given as two tablets once daily and sitagliptin/metformin XR 100 mg/1000 mg to be given as one tablet once daily.

3. CMC/Device

- General product quality considerations

The CMC review team had initially recommended approval, pending acceptable recommendations from Biopharmaceutics (biowaiver for the 50/1000 mg strength tablet), Office of Compliance (Form 483 inspection findings, see below) and Office of Surveillance and Epidemiology (labeling). Of note, the Biopharmaceutics review team, found the application acceptable and granted the biowaiver for the middle strength tablet of sitagliptin 50/ metformin 1000 mg strength (refer to further details under the Clinical Pharmacology section of this memo). (b) (4)

Sitagliptin/metformin XR tablets are film-coated tablets containing an immediate-release dose of sitagliptin phosphate surrounding a core of extended-release dose of metformin

hydrochloride for once daily use. A polymeric film coating over the active sitagliptin coating is applied to (b) (4)

Both sitagliptin/metformin IR FDC and this sitagliptin/metformin XR FDC NDA 202270 use metformin drug substance from (b) (4) (DMF (b) (4)). The release specification criterion for sitagliptin in sitagliptin/metformin XR FDC is wider (92.5- 107.5%) relative to sitagliptin/metformin IR FDC (95.0 - 105%). However, as pivotal clinical pharmacology study P147 demonstrated bioequivalence, the change in the specification criterion is acceptable. The expiration dating period grantable for the sitagliptin/metformin XR tablets in 7-, 14-, 30-, 60, 90-, 180-, and 1000-count HDPE bottles is 24 months with storage conditions of 25°C (77°F); excursions permitted to 15- 30°C (59-86°F). For the (b) (4), when the container is subdivided, the repackaged container should be moisture resistant and tightly closed. CMC recommended that this be included in the action letter.

The applicant will submit data to support a site change for the metformin (b) (4) operation only, which occurs (b) (4) with the modified release excipient (hypromellose), as a CBE-30 after NDA approval. The submission will include 3 months of accelerated stability data for three batches tested in each strength (long term data will be sent to the annual report), dissolution data, and cGMP certification for the new site. Even though the drug product is a modified-release product, the site change will require supportive data as described in the Scale-up and Post-Approval Changes Guidance for Immediate-release Products (SUPAC-IR).

- Facilities review/inspection

FDA conducted inspections of the manufacturing site in Puerto Rico on 3/28/11 and 4/14/11, and concluded there were multiple findings that support a “Withhold” recommendation at this time. Briefly, these findings listed in FDA Form 483 consist of:

(b) (4)

These findings were reviewed by the Central Office of Compliance (OC) and referred to Merck for response and action.

With the withhold recommendation by OC, CMC recommended a **Complete Response** action (see Memo to File by the CMC review team, dated 5/25/1011).

Merck responded to the findings in their manufacturing site in Arecibo, Puerto Rico. After review of the responses, the Division of Manufacturing and Product Quality maintained that

the response to **Observation 1** (i.e., (b) (4) was inadequate, and maintained the recommendation to Withhold (based on verbal communication to DMEP; no review filed in DARTS at the time of writing this CDTL memo).

4. Nonclinical Pharmacology/Toxicology

Please refer to Dr. Patricia Brundage's Pharmacology / Toxicology review for details. The applicant conducted a 3-month toxicity study in rats and two in vitro genotoxicity studies (microbial mutagenesis assay and chromosomal aberration assay) in order to qualify an (b) (4) degradate of sitagliptin identified in sitagliptin/metformin XR at the proposed limit of (b) (4) which exceeds the qualification threshold (ICH Q3B(R2)). Microbial mutagenesis and in vitro chromosomal aberration assays using an (b) (4) batch of sitagliptin containing (b) (4) and (b) (4) lysis degradation products were negative supporting a (b) (4) limit for the (b) (4) degradation product. A 3-month rat toxicity study, in which rats were administered a 60 mg/kg (360 mg/m²) dose of sitagliptin with and without the two (b) (4) degradation products (b) (4) showed that the hydrolysis degradates had no toxicological effect. Given that the expected level of degrade at (b) (4) associated with the MHRD of sitagliptin (100 mg; 62 mg/m²) is approximately 6-fold less than the level assessed in the 3-month toxicity study in rats, the (b) (4) degradate is not expected to cause a toxicological effect in humans. Collectively, the findings of the 3-month toxicity study in rats and two negative in vitro genotoxicity studies (microbial mutagenesis assay and chromosomal aberration assay) support the (b) (4) limit for (b) (4) degradation product of sitagliptin.

The Pharmacology/ Toxicology review team recommends approval of this NDA, with proposed labeling language referring to the metformin component to comply with the Glumetza PI language under Section 8.1 Pregnancy and under Section 13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to the Dr. Jee Eun Lee's clinical pharmacology review for more detail. The discipline team recommends approval of the NDA, for the three dose strengths of fixed-dose combinations between sitagliptin and extended-release metformin. Prior studies conducted by this applicant have assessed the effects of metformin and sitagliptin on incretin hormones. Sitagliptin stabilizes and increases active GLP-1 and GIP concentrations, while metformin administration results in increased total GLP-1. When metformin and sitagliptin were given in combination, the effects on active GLP-1 levels were complementary, with active GLP-1 levels about 4-fold higher compared with levels observed for placebo and about 2-fold higher compared with levels observed for sitagliptin alone. While this study was conducted in healthy volunteers, a similar study conducted in subjects with T2DM confirmed these results. There is no drug-drug interaction regarding PK parameters for sitagliptin and metformin.

The clinical pharmacology program includes a pivotal bioequivalence (BE) study to compare the final market composition (FMC) of sitagliptin / metformin XR to the co-administration of sitagliptin and an approved metformin XR product (Glumetza). Demonstration of BE was needed to bridge the existing safety and efficacy data from trials with sitagliptin, metformin XR and the combination of sitagliptin and metformin IR to sitagliptin / metformin XR.

Study 147 (BE Study)

Briefly, this was an open label, randomized sequence, 5-period crossover study in 48 healthy adult volunteers who received study drug after an overnight fast and 30 minutes after consumption of a high fat breakfast.

The 5 treatments were:

Treatment A: Co-administration of sitagliptin 50 mg and Glumetza 500 mg

Treatment B: Administration of a single sitagliptin /metformin XR 50 mg/500 mg tablet

Treatment C: Co-administration of sitagliptin 100 mg and Glumetza 1000 mg

Treatment D: Administration of a single sitagliptin /metformin XR 100 mg/1000 mg tablet

Treatment E: Administration of two sitagliptin /metformin XR 50 mg/500 mg tablets

The three PK comparisons were between:

1. Sitagliptin 50 mg co-administered with Glumetza 500 mg versus single dose of sitagliptin / metformin XR 50 mg / 500 mg;
2. Sitagliptin 100 mg co-administered with Glumetza 1000 mg versus single dose of sitagliptin / metformin XR 100 mg / 1000 mg and
3. Sitagliptin / metformin XR 50 mg/ 500 mg (2 tablets administered once) versus sitagliptin / metformin XR 100 mg / 1000 mg, following FDA's recommendation at the End of Phase 2 meeting.

The PK results are shown in Table 1 (for sitagliptin data) and Table 2 (for metformin data).

Table 1. Summary statistics and statistical comparisons for plasma PK parameters of *sitagliptin* after administration of a single sitagliptin / metformin XR (MK-0431A XR) 50 mg/500 mg or 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza), or two sitagliptin / metformin XR 50 mg/500 mg tablets in healthy volunteers

Treatment	A		B		C		D		E	
PK Parameter	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)
AUC _{0-∞} [†] (nM•hr)	44	3993 (3830, 4163)	44	4006 (3842, 4177)	45	7766 (7449, 8097)	43	7831 (7511, 8166)	44	7828 (7508, 8162)
AUC _{0-last} [†] (nM•hr)	44	3892 (3732, 4059)	44	3912 (3752, 4080)	45	7661 (7346, 7989)	43	7721 (7403, 8052)	44	7712 (7395, 8042)
C _{max} [†] (nM)	44	356 (332, 381)	44	342 (320, 367)	45	778 (727, 833)	43	778 (727, 834)	44	746 (697, 799)
T _{max} (hr)	44	2.5 (1.0, 7.0)	44	3.0 (1.0, 7.0)	45	2.0 (1.0, 7.0)	43	3.0 (1.0, 5.0)	44	3.0 (1.0, 6.0)
Apparent terminal t _{1/2} [§] (hr)	44	12.9 (3.5)	44	12.6 (3.2)	45	12.3 (2.8)	43	12.2 (3.1)	44	12.5 (3.4)
Between-Treatment Comparison										
Geometric Mean Ratio (90% CI)										
	FMC MK-0431A XR Tablets vs. Co-administration of Sitagliptin and Metformin XR (Glumetza)						2 x MK-0431A XR 50 mg/500 mg Tablets vs.			
Parameter	MK-0431A XR 50 mg/500 mg Tablet				MK-0431A XR 100 mg/1000 mg Tablet		1 x MK-0431A XR 100 mg/1000 mg Tablet			
AUC _{0-∞}	1.00 (0.99, 1.02)				1.01 (0.99, 1.03)		1.00 (0.98, 1.02)			
AUC _{0-last}	1.01 (0.99, 1.02)				1.01 (0.99, 1.02)		1.00 (0.98, 1.02)			
C _{max}	0.96 (0.92, 1.01)				1.00 (0.96, 1.05)		0.96 (0.92, 1.00)			
[†] Back-transformed least-squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values										
Median (min, max) reported for T _{max}										
[§] Harmonic mean, jack-knife standard deviation reported for apparent terminal t _{1/2}										
Treatment A: Co-administration of sitagliptin 50 mg and metformin XR 500 mg (Glumetza) as individual tablets										
Treatment B: Administration of a single FMC MK-0431A XR 50 mg/500 mg tablet										
Treatment C: Co-administration of sitagliptin 100 mg and metformin XR 1000 mg (Glumetza) as individual tablets										
Treatment D: Administration of a single FMC MK-0431A XR 100 mg/1000 mg tablet										
Treatment E: Administration of two FMC MK-0431A XR 50 mg/500 mg tablets										
GM = Geometric Least-Squares Mean; CI = Confidence Interval; FMC = Final Market Composition; XR = Extended Release										

Source: Study P147 synopsis

Table 2. Summary statistics and statistical comparisons for plasma PK parameters of *metformin* after administration of a single sitagliptin / metformin XR (MK-0431A XR) 50 mg/500 mg or 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza) or two sitagliptin / metformin XR 50 mg/500 mg tablets in healthy volunteers

Treatment	A		B		C		D		E	
PK Parameter	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)
AUC _{0-∞} [†] (ng•hr/mL)	36	6639 (6128, 7192)	36	7047 (6504, 7636)	39	12490 (11540, 13519)	35	12009 (11077, 13019)	39	12302 (11367, 13315)
AUC _{0-last} [†] (ng•hr/mL)	44	6576 (6096, 7094)	44	6874 (6372, 7416)	45	12194 (11305, 13152)	43	11845 (10976, 12783)	44	12015 (11138, 12962)
C _{max} [‡] (ng/mL)	44	560 (526, 597)	44	607 (570, 647)	45	868 (815, 924)	43	988 (927, 1052)	44	1000 (939, 1065)
T _{max} (hr)	44	6.0 (3.0, 10.0)	44	6.0 (3.0, 10.0)	45	10.0 (5.0, 16.0)	43	7.0 (4.0, 12.0)	44	5.5 (3.0, 10.0)
Apparent terminal t _{1/2} [§] (hr)	36	11.8 (6.4)	36	12.6 (7.9)	39	12.2 (3.8)	35	12.0 (6.8)	39	13.5 (7.4)
Between-Treatment Comparison										
Geometric Mean Ratio (90% CI)										
	FMC MK-0431A XR Tablets vs. Co-administration of Sitagliptin and Metformin XR (Glumetza)						2 x MK-0431A XR 50 mg/500 mg Tablets vs.			
Parameter	MK-0431A XR 50 mg/500 mg Tablet			MK-0431A XR 100 mg/1000 mg Tablet			1 x MK-0431A XR 100 mg/1000 mg Tablet			
AUC _{0-∞}	1.06 (1.01, 1.12)			0.96 (0.91, 1.01)			1.02 (0.97, 1.08)			
AUC _{0-last}	1.05 (1.00, 1.09)			0.97 (0.93, 1.01)			1.01 (0.97, 1.06)			
C _{max}	1.08 (1.03, 1.14)			1.14 (1.09, 1.19)			1.01 (0.97, 1.06)			
[†] Back-transformed least-squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values										
Median (min, max) reported for T _{max}										
[§] Harmonic mean, jack-knife standard deviation reported for apparent terminal t _{1/2}										
Treatment A: Co-administration of sitagliptin 50 mg and metformin XR 500 mg (Glumetza) as individual tablets										
Treatment B: Administration of a single FMC MK-0431A XR 50 mg/500 mg tablet										
Treatment C: Co-administration of sitagliptin 100 mg and metformin XR 1000 mg (Glumetza) as individual tablets										
Treatment D: Administration of a single FMC MK-0431A XR 100 mg/1000 mg tablet										
Treatment E: Administration of two FMC MK-0431A XR 50 mg/500 mg tablets										
GM = Geometric Least-Squares Mean; CI = Confidence Interval; FMC = Final Market Composition; XR = Extended Release										

Source: Study P147 synopsis

Thus, the 90 % confidence intervals of geometric mean ratios of AUC_{0-inf} and C_{max} for both sitagliptin and metformin were within the pre-specified bounds of 0.8 to 1.25, and therefore met the BE criteria.

Of the 48 subjects randomized, 39 completed, while 9 were discontinued for the following reasons: five for AEs (including one SAE of urinary retention with hospitalization, with past history of urethral stricture), two for protocol deviation and two for consent withdrawal.

The Division of Bioequivalence and GLP Compliance (DBGC), within the newly formed Office of Scientific Investigations investigated the clinical and analytical sites of the pivotal BE study 147. The clinical site and analytical sites are the Covance Clinical Research Unit Inc. (Dallas, Texas) and (b) (4) respectively. DBGC's memo in DARRTS, dated 7/15/11, did not reveal significant issues at the clinical site. On the other hand, one of the deficiencies cited in their FDA Form 483 and conveyed to Merck and to (b) (4) had not been completely addressed. This is the text of the deficiency cited:

(b) (4)

The assigned DBGC inspector reviewed (b) (4) response and concluded (the CDTL change the last sentence to **bold** type for emphasis):

In response to this observation, (b) (4)

(b) (4)

However, the OCP reviewer should ask the sponsor to repeat the bioequivalence determination using the new reintegrated data and reevaluate the study outcomes."

DBGC maintained that the lack of a repeat BE determination using the new reintegrated data submitted to the NDA would support their decision to recommend "Withhold".

OCP and DMEP, in response to this recommendation, agreed to ask for these data and a revised study 147 report as a "major amendment", with possible extension of the review clock (if Merck's response came before the PDUFA goal date). However, the manufacturing deficiency uncovered by DMPQ and not adequately addressed by Merck precluded any timely review of these new BE data in this review cycle.

Since our decision was to issue a CR letter based on the manufacturing deficiency noted above (as of this writing, 7/20/2011), we will include the lack of the repeat BE determination as a second deficiency to be addressed as part of the applicant's Complete Response.

Study P164 (Food Effect Bioavailability Study)

The submission also includes a food effect study, where the PK characteristics of the FDC components are assessed with or without a standardized high fat breakfast. The results indicated that there was a significant food effect on metformin PK following administration of sitagliptin / metformin XR. After administration of two sitagliptin / metformin XR 50 mg/1000 mg tablets following consumption of a high-fat breakfast, the AUC_{0-inf} for metformin increased by 62% compared with the fasted state. The AUC_{0-inf} and C_{max} for sitagliptin and the C_{max} for

metformin decreased by approximately 6%, 17%, and 9%, respectively, compared with the fasted state. This effect of food on the PK of metformin was generally consistent with the effect of food for marketed metformin XR formulations (e.g., Glucophage XR: fed state metformin AUC increased by 50%, no food effect on C_{max}).

Study P165 (PK of sitagliptin and metformin after multiple doses)

Study P165 was conducted to evaluate the safety, tolerability and PK of sitagliptin / metformin XR at the clinical dose for sitagliptin and the highest proposed total daily dose for metformin (two sitagliptin / metformin XR 50 mg/1000 mg tablets, or a total dose of 100 mg of sitagliptin and 2000 mg of metformin). Twelve subjects received this dose with the evening meal for 7 days and PK, safety and tolerability were assessed. This is consistent with the FDA guidance, which recommends that “a steady-state study on the highest strength is to be performed for modified-release products.” Steady-state for sitagliptin and metformin was reached by Day 4 and 5, respectively. The PK of sitagliptin / metformin XR 50 mg / 1000 mg tablets qd X 7 days were consistent with what would be predicted from the PK parameters after administration of a single sitagliptin / metformin XR tablet at the same tablet strength, and suggests that there are no time-dependent non-linearities for sitagliptin and metformin after multiple-dose administration of MK-0431A XR.

Biopharmaceutics Review

The applicant requested a biowaiver of the in vivo BE requirements for the sitagliptin / metformin XR 50/1000 mg strength based on dissolution profile comparisons of all strengths in different media.

The Biopharmaceutics reviewer, Dr. Sandra Sharp, focused on:

- Acceptability of the dissolution method and specifications
- The in vitro alcohol interaction study
- Acceptability of a waiver request supporting the approval of the 50/1000 mg strength;
- Acceptability of a biowaiver request supporting the approval of the manufacturing process change
- The role of dissolution in Quality by Design (QbD): this was applicable to the metformin component only.

The Biopharmaceutics team found the dissolution methods and the alcohol interaction study acceptable and granted the waiver for the intermediate dose strength (50/1000 mg) and the biowaiver requested.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

As stated in the Dr. Pratt’s clinical review, the pivotal study to support this NDA is a clinical pharmacology study, P147, to establish BE between the final market formulation tablet of sitagliptin / metformin XR and the co-administration of sitagliptin and metformin XR.

Dr. Pratt reviewed data from Study P053, a trial of sitagliptin versus placebo added to a background of metformin in subjects with T2DM conducted in 2006 and 2007 that had not been previously reviewed by FDA. The main difference between this trial and a prior pivotal trial of sitagliptin added on to metformin background (Study P020) is that in Study P053, subjects had to have moderate degrees of hyperglycemia (HbA_{1c} between 8 and 11 % at randomization, fasting glucose between 130 and 280 mg/dL), despite near maximal metformin dose of ≥ 1500 mg qd in order to be deemed eligible. The applicant did not propose to include data from this trial in the Januvia, Janumet or this product's label.

Trial P053 – Design

This was a multicenter, double-blind, placebo-controlled, randomized (1:1), parallel group trial of 30 weeks duration. The primary efficacy endpoint was the placebo-subtracted change in HbA_{1c} from baseline to week 18 in the Full Analysis Set population. The trial continued with the same randomized groups to week 30, and the change in HbA_{1c} from baseline at week 30 was one of the secondary endpoints. The other important secondary endpoints were change in fasting and post-prandial (MMTT) glucose from baseline to week 18.

Trial P053 – Results

The trial was conducted from 8/21/2006 to 8/27/2007 at 24 sites, being half of these located in the US and the others distributed in Israel, Mexico, Peru and Austria. Of 544 subjects screened, 190 were enrolled meeting the glycemic range criterion mentioned above. Of the 190 subjects enrolled, 159 completed the 30-week treatment period (87%) with similar rates of discontinuation among the placebo and sitagliptin groups. The groups were well balanced with regard to demographic and baseline disease characteristics. The mean baseline HbA_{1c} for the combined groups was 9.2%, higher than most recent trials in T2DM. Those subjects in either group who met protocol-specified thresholds of hyperglycemia in the course of the trial were rescued with glipizide.

Table 3 shows a summary of the results reported for Trial P053.

Table 3. Summary results in Trial P053: Least square mean changes in HbA_{1c} from baseline to week 18 (primary endpoint) and to week 30 (secondary endpoint) and in changes in fasting and 2-hour postprandial glucose from baseline to week 18 (secondary endpoints) – Full Analysis Set

Treatment Group	Week 18			Week 30
	HbA _{1c} (%)	Fasting Plasma Glucose (mg/dL)	2-Hour Post-Prandial Glucose (mg/dL)	HbA _{1c} (%)
Sitagliptin 100 mg	-1.00 (-1.24, -0.75)	-32.0 (-40.6, -23.3)	-67.6 (-82.1, -53.2)	-0.98 (-1.25, -0.70)
Placebo	0.02 (-0.23, 0.27)	-6.5 (-15.1, 2.2)	-13.5 (-28.2, 1.2)	0.04 (-0.24, 0.31)
Difference from Placebo [†]				
Sitagliptin 100 mg vs. Placebo	-1.02 (-1.36, -0.67)	-25.5 (-37.7, -13.3)	-54.1 (-74.7, -33.6)	-1.01 (-1.4, -0.6)
[†] All comparisons vs. placebo had p < 0.001.				

Source: Applicant's Table under Efficacy in the Synopsis

The placebo-adjusted mean glycemic effect of sitagliptin in Trial P053 (assessed by HbA1c, fasting or postprandial glucose) at week 18 and week 30 is greater than seen in prior trials where the mean HbA1c at baseline was lower (8.0 to 8.5%).

The analyses of glycemic parameters in the completers population yielded almost identical results (Table 4).

Table 4. Between groups difference in the change in HbA1c and fasting plasma glucose from baseline to week 18 in the Completers population

Between Treatment Difference: Sitagliptin 100 mg versus placebo	Difference in LS Means (95% CI)	p-value
HbA1c (%)	-1.0 (-1.3, -0.6)	<0.001
Fasting Plasma Glucose (mg/dL)	-25 (-37, -13)	<0.001

These effects were also consistent among subgroups of the Full Analysis Set, based on demographic and disease baseline characteristics.

Other secondary and exploratory endpoints will not be discussed in this memo, but are discussed in Dr. Pratt's clinical review.

8. Safety

No new safety issues are noteworthy from the clinical pharmacology studies and the newly reviewed clinical trial P053 submitted under this NDA.

In the BE study P147, of the 48 subjects enrolled, there were no deaths. One SAE was reported: a 36 year old male hospitalized due to urinary retention four days after receiving sitagliptin / metformin XR 50/500 mg, who had a past medical history of urethral stricture. This subject was discontinued from the study. Four other subjects were discontinued from the study due to AEs: one subject with abdominal pain, two subjects due to rash and one subject due to urticaria. Common AEs were balanced among the groups. There were no laboratory-related AEs.

In the clinical trial P053, there were no deaths or SAEs among the 96 subjects randomized to sitagliptin; one subject on placebo died of myocardial ischemia and four other SAEs were reported for placebo-treated subjects. Two subjects on placebo discontinued due to clinical AEs, and two subjects on sitagliptin discontinued due to lab-related AEs: one with "blood creatinine increased" on day 169 and one with "alanine aminotransferase increased" on day 131. There is no new, noteworthy pattern of common AEs reported in this trial. Seventy nine subjects treated with sitagliptin 100 mg qd completed the 30-week trial.

With the 4-month safety update, three additional clinical study reports were submitted. Dr. Pratt and I focused only on safety data from these trials. The safety of sitagliptin / metformin FDC (Janumet) in trials P066, P068 and P079 is consistent with the experience already reviewed for this product, and does not change the risk / benefit profile of sitagliptin or sitagliptin / metformin FDC.

9. Advisory Committee Meeting

This application was not discussed before an advisory committee for the following reasons:

- it is not a first-in-class anti-diabetic therapy;
- the indication sought is based on a well-established efficacy endpoint relied upon for approval of other drugs across the 11 classes of anti-diabetic therapies;
- clinical trials assessing efficacy and safety are typical of diabetes programs evaluated by FDA for approval of other anti-diabetic therapies;
- no unexpected safety concerns were identified in the nonclinical or clinical development program.

10. Pediatrics

(b) (4)

[REDACTED]

After completing a PK study with sitagliptin 25 mg, 50 mg and 100 mg at single doses in the pediatric population, Merck plans to conduct Study 083 entitled: (b) (4)

[REDACTED]

Merck is delayed in conducting these pediatric studies, according to the timelines listed in the sitagliptin approval letter.

The applicant's rationale (b) (4) As discussed in detail in Dr. Pratt's review, the applicant will have one or two pediatric post-marketing requirement (PMR) studies to evaluate dosing, safety, and efficacy of sitagliptin/metformin XR in pediatric patients 10 through 17 years (inclusive) of age with T2DM. This PMR will include:

- (1) A (b) (4) pharmacokinetic study of Janumet XR in pediatric patients 10 through 17 years (inclusive) of age with T2DM. (b) (4)

(b) (4)

(2) A (b) (4), randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Janumet XR vs. metformin (b) (4) in pediatric patients who are inadequately controlled. As part of this study, the swallowability of the formulation will be evaluated. (b) (4)

(b) (4)

1. PK study: submission 1 year after approval; trial completion 15 months later, submission 1 year after completion.
 2. Safety and Efficacy Study: submission 6 month after approval; completion 4 years later; submission 8 months after completion (b) (4)
- Therefore FDA's proposed dates will move submission of the final report up to the end of 2016, pending the date of NDA approval.

FDA discussed in a teleconference with the applicant the pediatric plan for the sitagliptin / metformin XR FDC, and explained the rationale for the required (b) (4) safety and efficacy trial in pediatric patients on June 28th, 2011. The applicant inquired whether we can accept the final report on the safety and efficacy of sitagliptin / metformin XR in the pediatric population prior to the completion of the trial with sitagliptin in monotherapy, as they anticipate enrollment will be faster for a trial of the FDC compared to sitagliptin monotherapy. FDA concurred. At the time of writing this CDTL memo, FDA is waiting for the revised PREA PMR to be received by the applicant, based on this discussion.

11. Other Relevant Regulatory Issues

As stated in the Introduction to this CDTL memo, the applicant submitted the NDA under 505 (b)(2), with the listing of Glumetza as the RLD. Since the applicant has full right of reference to Depomed's Glumetza, the application was reclassified as 505(b)(1).

Although FDA had asked the applicant in December 2010 to submit a REMS with Medication Guide (similar to the REMS for Januvia and Janumet), after issuance of the FDA guidance allowing Medication Guide-only products to be approved without a REMS, the REMS requirement was waived for this product, and for the other sitagliptin-based products as well.

12. Labeling

With the original NDA submission, (b) (4)

(b) (4)

The proprietary name is still under review by DMEPA (medications errors) at the time of writing this CDTL memo. DDMAC had no objection to this proprietary name, regarding the potential for promotion.

The product will have a Medication Guide to convey to patients the risks of pancreatitis,

(b) (4)

These are the same issues covered in the Medication Guides for Januvia and Janumet.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

At the time of writing this CDTL memo, I recommend a Complete Response letter to the applicant, listing the manufacturing deficiency noted by DMPQ during inspection and the DBGL deficiency (lack of BE determination based on reanalysis of reintegrated data).

- Risk Benefit Assessment

Pending resolution of the manufacturing issues, the risk benefit assessment for sitagliptin / metformin XR is favorable, similar to sitagliptin / metformin immediate-release.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

This application will not need a REMS. Risks will be managed by appropriate professional labeling, a Medication Guide and continued pharmacovigilance.

- Recommendation for other Postmarketing Requirements and Commitments

The requirement for PREA-related PMRs is discussed in Section 10 of this memo and in Dr. Pratt's clinical review.

- Recommended Comments to Applicant

Labeling (package insert and Medication Guide) discussions with the applicant are ongoing at this time, as are timelines for the pediatric studies. No other comments need to be conveyed to the applicant.

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
07/20/2011

MARY H PARKS
07/21/2011

CLINICAL REVIEW

Application Type NDA
Application Number(s) 202-270
Priority or Standard Standard

Submit Date(s) 9-23-10
Received Date(s) 9-23-10
PDUFA Goal Date 7-23-11
Division / Office DMEP/ODEII/OND

Reviewer Name(s) Valerie S. W. Pratt, M.D.
Review Completion Date 5-31-11

Established Name Sitagliptin/metformin XR
(Proposed) Trade Name Janumet XR
Therapeutic Class DPP-4 inhibitor/biguanide
Applicant Merck

Formulation(s) 50/500, 50/1000, & 100/1000
mg tablets
Dosing Regimen Once daily
Indication(s) Type 2 diabetes mellitus
Intended Population(s) Adult type 2 diabetes

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of the sitagliptin/metformin extended release (XR) fixed dose combination (FDC) new drug application (NDA) 202-270 for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM), pending resolution of the Office of Compliance, Division of Manufacturing and Product Quality (OC-DMPQ) issues.

1.2 Risk Benefit Assessment

Sitagliptin (NDA 21-995) has been approved for treatment of T2DM in the United States (US) since October 2006. Janumet (NDA 22-044), a FDC of sitagliptin and metformin immediate release (IR), contains metformin hydrochloride (HCl) drug substance held by (b) (4) (master file [MF] (b) (4)) and was approved for use on March 30, 2007. Metformin XR (Glumetza NDA 21-748) also contains metformin HCl held by (b) (4) (MF (b) (4)) and was approved for the treatment of T2DM on June 3, 2005.

The applicant submits an 505(b)(2) NDA for the following sitagliptin/metformin XR FDC tablet strengths. Glumetza is the reference listed drug (RLD).

- 50/500 mg to be given as 2 tablets once daily (QD)
- 50/1000 mg to be given as 2 tablets QD
- 100/1000 mg to be given as 1 tablet QD

The sponsor aimed to demonstrate bioequivalence (BE) between sitagliptin/metformin XR and the coadministration of sitagliptin and metformin XR (Glumetza) so as to bridge to the existing safety and efficacy data from sitagliptin (Januvia), metformin XR (Glumetza), and sitagliptin/metformin IR (Janumet) to sitagliptin/metformin XR (Janumet XR). Thus, the pivotal study was clinical pharmacology study P147, which established bioequivalence by comparing the to-be-marketed product formulation with coadministration of sitagliptin and metformin XR.

Of the clinical trial reports submitted (i.e. protocols 015, 020, 024, 035, 036, 052, and 053), only P053 was not previously reviewed and is reviewed here. Study P053 was a multicenter, double blind, study to evaluate the safety and efficacy of the addition of sitagliptin 100 mg versus placebo in 190 randomized T2DM patients who had inadequate glycemic control on metformin monotherapy (≥ 1500 mg QD). The primary endpoint was the change in HbA1c at week 18. The addition of sitagliptin resulted in a

significant improvement in HbA1c (mean change -1.0%, $p < 0.001$) when compared to placebo (mean change 0.0%) in the full analysis set (FAS) population.

I believe the risks associated with sitagliptin/metformin XR FDC are similar to that of coadministration of the individual products, which is done in clinical practice. Labeling for NDA 202-270 should reflect that of the sitagliptin and metformin XR product labels. I recommend approval of the sitagliptin/metformin XR FDC as the clinical benefit of this convenience product outweighs its risks, pending resolution of the Office of Compliance, Division of Manufacturing and Product Quality (OC-DMPQ) issues.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Both sitagliptin (Januvia) and sitagliptin/metformin IR FDC (Janumet) has a medication guide due to the risk of pancreatitis associated with sitagliptin. As the sitagliptin/metformin XR FDC also contains sitagliptin, I recommend a similar MG for pancreatitis.

1.4 Recommendations for Postmarket Requirements and Commitments

The December 2008 Guidance for Industry *Diabetes Mellitus – Evaluating Cardiovascular (CV) risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* recommends sponsors demonstrate that a new antidiabetic therapy is not associated with an unacceptable increase in CV risk. FDC products containing two approved products (which themselves have been evaluated or are being evaluating for CV risk) are exempt from this requirement. However, under sitagliptin IND 65,495, the sponsor 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 metformin. Its planned completion date is December 2014.

I recommend the following studies be required in pediatric (i.e. 10-17 years) T2DM subjects so as to satisfy the Pediatric Research Equity Act (PREA):

- A single dose pharmacokinetic study of Janumet XR in pediatric patients 10 through 17 years (inclusive) of age with T2DM. As part of this study the sponsor will evaluate whether pediatric patients can safely swallow the Janumet XR tablets. At least 30% of randomized subjects will be 10-14 years.
- A 52-week, randomized, double-blind placebo-controlled trial to evaluate the efficacy and safety of Janumet XR vs. metformin (immediate and/or extended release) in pediatric T2DM patients who are inadequately controlled. As part of this study, the sponsor must evaluate whether pediatric patients can safely swallow Janumet XR. At least 30% of randomized subjects will be 10-14 years.

At least 1/3 and not more than 2/3 of the patients in either age subset (10-14, 15-17 years) will be female.

2 Introduction and Regulatory Background

2.1 Product Information

Merck has submitted this 505(b)(2) NDA for the use of sitagliptin/metformin XR FDC (MK-0431A XR; Janumet® XR) as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

Sitagliptin, a dipeptidyl peptidase 4 (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 United States (US) since October 2006 under NDA 21-995.

Metformin is an oral biguanide that decreases hepatic glucose production and improves insulin sensitivity. It was first approved as Glucophage (NDA 20-357), an immediate release tablet, in March 1995. Metformin is currently approved in both immediate and sustained release forms in various prescription and generic products, including FDCs.

Janumet (NDA 22-044), a FDC of sitagliptin and metformin immediate release (IR), contains metformin hydrochloride (HCl) drug substance held by (b) (4) (master file [MF] (b) (4) and was approved for use on March 30, 2007. The RLD Glumetza (metformin XR NDA 21-748) also contains metformin HCl held by (b) (4) (MF (b) (4) and was approved for the treatment of T2DM on June 3, 2005.

The sponsor has developed the sitagliptin/metformin XR FDC in the following tablet strengths:

- 50/500 mg to be given as 2 tablets once daily (QD)
- 50/1000 mg to be given as 2 tablets QD
- 100/1000 mg to be given as 1 tablet QD

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
 - o Tolazamide (Tolinase)
 - o Chlopropramide (Diabinese)
 - o Glyburide (Micronase)

- o Glipizide (Glucotrol and Glucotrol XL)
 - o Glimepiride (Amaryl)
- Meglitinide analogs: Repaglinide (Prandin)
- D-Phenylalanine: Nateglinide (Starlix)
- Biguanides: Metformin (e.g., Glucophage and Glucophage XR)
- Thiazolidinediones (TZDs)
 - o Rosiglitazone (Avandia)
 - o Pioglitazone (Actos)
- α -Glucosidase inhibitors
 - o Acarbose (Precose)
 - o Miglitol (Glyset)
- Incretin-mimetics
 - o Exenatide (Byetta)
 - o Liraglutide (Victoza)
- Amylinomimetics
 - o Pramlintide (Symlin)
- Dipeptidyl peptidase 4 inhibitors
 - o Sitagliptin (Januvia)
 - o Saxagliptin (Onglyza)
 - o Linagliptin (Tradjenta)
- Bile acid sequestrants
 - o Colesevelam (WelChol)
- Dopamine receptor agonists
 - o Bromocriptine mesylate (Cycloset)
- FDCs of the various oral medications listed above

2.3 Availability of Proposed Active Ingredient in the United States

Sitagliptin (NDA 21-995) and metformin IR (NDA 20-357) have been approved for the treatment of T2DM in the US since October 2006 and March 1995, respectively. Both are contained within the FDC Janumet® (NDA 22-044) which was approved for use on March 30, 2007.

Metformin XR (Glumetza NDA 21-748) has been approved for the treatment of T2DM since June 2005.

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 metformin include the following:

- Risk of lactic acidosis, which increases with sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure
- Contraindication in patients with renal dysfunction (e.g. serum creatinine ≥ 1.5 mg/dl [males], ≥ 1.4 mg/dl [females] or abnormal creatinine clearance)
- Use with intravascular iodinated contrast materials or excessive alcohol intake, when hypoxic, and when undergoing surgery
- Hypersensitivity
- Decrease in vitamin B12 levels and associated anemia
- Hypoglycemia, especially in the elderly and debilitated patients when caloric intake is deficient or during concomitant use of other glucose-lowering agents (e.g. SU and insulin) or alcohol
- Hyperglycemia, during times of stress

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sitagliptin/metformin XR FDC IND 101,964 was opened May 2, 2008. The request for an end of phase 2 (EOP2) meeting was denied, although the sponsor's questions were answered via letter on March 5, 2009. The key points communicated were as follows:

- No additional preclinical studies with the XR formulation are required, although support for any differences in the impurity/degradant profile of the new formulation were requested
- The sponsor should provide metformin pharmacokinetic (PK) comparability or clinical equivalency data between sitagliptin/metformin XR FDC and Janumet
- The following clinical pharmacology components are required to support registration:
 - o Completed FDC probe formulation biocomparison study in fed subjects
 - o Definitive BE study (treatment may be administered with morning meal)
 - o Multiple dose safety, tolerability, and PK study with sitagliptin/metformin XR FDC tablets
 - o Food-effect study with a high fat meal, using only the highest doses of each of the respective components (i.e. 100/2000 mg)
 - o Sitagliptin/metformin drug-drug interaction study
 - o Dosage form equivalence study comparing 2 tablets of 50/500 mg and 1 tablet of 100/1000 mg
 - o Biowaiver request for the 50/1000 mg dose
 - o Metformin PK comparability or clinical equivalency data described above

- Glumetza is the appropriate comparator for the BE study

The May 10, 2010 pre-NDA meeting was cancelled because our preliminary meeting comments adequately addressed the sponsor's questions. Key responses were as follows:

- The agency concurred that sufficient data are available to support bridging between Glumetza (a metformin reference for the sitagliptin/metformin XR FDC) and a generic metformin formulation (a metformin reference for Janumet)
- The agency concurred that the sponsor's plan for filing the biowaiver for the 50/1000 mg tablet strength was acceptable.
- In addition to the phase 1 clinical pharmacology studies listed in the background package and the references to the Glumetza product label and Janumet NDA, the sponsor should address the dose-dumping potential of the XR formulation with alcohol. This may be evaluated *in vitro* and if necessary *in vivo*.
- The sponsor should include the pediatric waiver request and rationale in the NDA.

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of appropriate quality. The sponsor electronically submitted the required clinical pharmacology and biopharmaceutical studies described above. The information submitted was well organized.

On December 23, 2010, the sponsor responded to the agency's request for information; the submitted information included a revised pediatric development plan.

On January 10, 2011, the sponsor clarified that metformin IR was used in clinical studies 020, 024, 035, 036, 052, and 053 but in study 015 subjects took their own metformin and it was not specified if metformin IR or XR was required.

On January 21, 2011, the sponsor submitted the four-month safety update which contained three sitagliptin/metformin IR clinical study reports (protocols 66, 68, and 79).

3.2 Compliance with Good Clinical Practices

The clinical trial reviewed below, P053, was conducted with Good Clinical Practice standards. There was one protocol deviation that resulted in a subject not being randomized.

Based on its inspection of the manufacturing facilities, the OC's district office recommends non-approval. Please refer to the OC's May 25, 2011 review.

The Division of Scientific Investigations (DSI) investigation of pivotal BE study 147, *A definitive BE study for sitagliptin/metformin XR FDC tablets in healthy subjects*, is still pending. The clinical site and analytical contacts are Dr. William W. Lewis of Covance Clinical Research Unit Inc. (Dallas, Texas) and (b) (4) of (b) (4) respectively.

3.3 Financial Disclosures

In accordance with the 1998 guidance *Financial Disclosure by Clinical Investigators*, clinical investigators were requested to submit information related to their financial interests. The financial disclosure information cutoff data was August 30, 2010. Multiple requests were made when possible to clinical investigators who did not respond.

Seven studies (P053, P095, P112, P147, P163, P164, and P165) met the 21 CFR 54.2(e) definition of a "covered" clinical study for the purpose of financial disclosure. Two studies (P050 and P110) were defined as "non-covered" clinical studies.

These studies involved a grand total of 89 investigators and subinvestigators. All but 5 were certified regarding the absence of financial interests and arrangements. Four of the noncertified investigators did not return requested information, and one was no longer at the site. No certified investigators/subinvestigators held financial interests or arrangements requiring disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The goal of CMC development was to manufacture an immediate release sitagliptin and an extended release metformin that matched the RLD metformin XR, Glumetza. Both sitagliptin/metformin IR FDC NDA 22-044 and this sitagliptin/metformin XR FDC NDA

202-270 use metformin drug substance from (b) (4) (MF (b) (4)). The release specification criteria for sitagliptin in sitagliptin/metformin XR FDC is wider (92.5-107.5%) relative to sitagliptin/metformin IR FDC (95.0 - 105%). However, as pivotal clinical pharmacology study P147 demonstrated bioequivalence, the change in specification criteria is acceptable.

However, at the time this review was finalized, the Office of Compliance, Division of Manufacturing and Product Quality (OD-DMPQ) recommended a “withhold” based on manufacturing facility inspections conducted by the district office. Please refer to the OC’s May 25, 2011 and Dr. Olen Stephens’ CMC reviews (dated April 28 and May 25, 2011).

Biopharmaceutics reviewed the dissolution method and specifications, waiver requests for the middle strength (i.e. 50/1000 mg) and manufacturing change ((b) (4)), and the in vitro alcohol-interaction study. It concluded the following:

- The dissolution method and specifications were agreed upon with the sponsor. The same dissolution specifications were recommended for all the Janumet XR strengths
 - There were no signs of an uncontrolled drug release from the formulation of Janumet ER tablets when dissolved in 5 %, 20%, or 40% ethanol
 - The waiver request of the BE requirements for the middle strength, namely Janumet ER 50/1000 mg, tablets is granted pending DSI review outcome.
 - The biowaiver supporting the approval of the manufacturing changes is granted.
- Please refer to Dr. Sandra Suarez’s May 19, 2011 biopharmaceutical review for full details.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The toxicology data previously submitted to the sitagliptin/metformin IR and metformin XR NDAs (Janumet 22-044 and Glumetza 21-748, respectively) also support this sitagliptin/metformin XR FDC NDA. No preclinical pharmacology studies were conducted with sitagliptin/metformin XR.

A 3-month oral toxicity study in rats, a microbial mutagenesis assay, and an in vitro chromosomal aberration assay were conducted with sitagliptin to support 2 (b) (4) degradation products, specifically (b) (4). The studies support a 0.6% (w/w) specification for each degradation product. The 3-month rat toxicity study showed that the degradants, at doses that exceed daily clinical dose, had no toxicologic effect.

The proposed pharmacology/toxicology labeling sections are identical to the current sitagliptin/metformin IR FDC label.

Please refer to Dr. Patricia Brundage's May 23, 2011 nonclinical review.

4.4 Clinical Pharmacology

The sponsor aimed to demonstrate BE between sitagliptin/metformin XR and the coadministration of sitagliptin and metformin XR (the RLD Glumetza) so as to bridge to the existing safety and efficacy data from sitagliptin (Januvia), metformin XR (Glumetza), and sitagliptin/metformin IR (Janumet) to sitagliptin/metformin XR (Janumet XR). The PK comparability of metformin between sitagliptin/metformin XR and sitagliptin/metformin IR (i.e. Glumetza and generic metformin, respectively) and Glucophage IR provided additional support.

The sponsor conducted the following clinical pharmacology studies, shown in Table 1. Key conclusions were as follows:

- Pivotal study P147, which was a comparison of the to-be-marketed product and co-administration of sitagliptin and metformin XR, established bioequivalence when analyzed with and without normalization of the tablet content.
- Food effect study P164 demonstrated the food effect of metformin is consistent with the marketed products

Please refer to Dr. Jee Eun Lee's clinical pharmacology review.

Table 1. Clinical pharmacology studies supporting the registration of sitagliptin/metformin XR FDC

Study Type	Protocol Number
Biopharmaceutics Studies	
A Low-Dose Probe Formulation Biocomparison Study [†]	112
A High-Dose Probe Formulation Biocomparison Study [†]	163
A Food-Effect Study [†]	164
A Definitive Bioequivalence Study [†]	147
Clinical Pharmacology/Pharmacokinetic Studies	
A Sitagliptin-Metformin Drug Interaction Study [‡]	012
A Multiple-Dose Safety, Tolerability and Pharmacokinetic Study [†]	165
Pharmacodynamic Studies	
A Mechanism-of-Action Study in Healthy Subjects [‡]	050
A Mechanism-of-Action Study in Treatment-Naïve Patients with T2DM [‡]	110
[†] Studies where MK-0431A XR was administered	
[‡] Studies where metformin IR was administered	

Source: Summary of clinical pharmacology studies table 2.7.2: 1

4.4.1 Mechanism of Action

Janumet XR contains two antihyperglycemic agents, sitagliptin and metformin XR.

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.

Metformin XR is a once daily antihyperglycemic agent that lowers both basal and postprandial plasma glucose. It decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Insulin secretion remains unchanged, while fasting insulin levels and day-long plasma insulin response may decrease. As a result, patients do not experience hyperinsulinemia or hypoglycemia (except in special circumstances, see section 2.4 Important Safety Issues).

4.4.2 Pharmacodynamics

The sponsor conducted study P110 to assess the effects of sitagliptin and metformin on post-prandial incretin hormone concentrations in treatment-naïve T2DM subjects. This was a randomized, placebo controlled, double blind, double dummy, four period crossover study in which 18 subjects received either sitagliptin 100 mg daily (QD), metformin 500 mg twice daily (BID), sitagliptin 100 mg QD + metformin 500 mg BID, or placebo for 2 days with a minimum 7 day washout.

The geometric mean ratio (GMR; coadministration [sitagliptin + metformin]/placebo) and 95% confidence interval (CI) for the incremental postprandial 4 hour weighted mean active GLP-1 concentration on day 2 was 4.66 (3.53, 6.16). This suggests that mean active GLP-1 concentrations increased with the coadministration of sitagliptin and metformin compared to placebo. Please refer to Table 2 below.

Note: The analysis for active and/or total GIP and GLP-2 concentrations was ongoing at the time of submission.

Table 2. P110: Comparison of the incremental postprandial 4 hour weight means by treatment group on day 2 in T2DM subjects (n~18)

GMR [†] (95% CI)			
Endpoint	Sitagliptin / PBO	Metformin / PBO	(Sitagliptin + Metformin) / PBO
Active GLP-1	3.87 (2.93, 5.12)	2.64 (2.00, 3.50)	4.66 (3.53, 6.16)
Total GLP-1	0.79 (0.61, 1.03)	1.69 (1.30, 2.21)	0.89 (0.69, 1.16)
Ratio of Active to Total GLP-1 [§]	2.36 (2.20, 2.53)	1.06 (0.99, 1.14)	2.69 (2.51, 2.89)
β-cell sensitivity	1.26 (0.87, 1.83)	1.67 (1.15, 2.41)	1.71 (1.19, 2.46)
Difference [‡] (95% CI)			
Endpoint	Sitagliptin - PBO	Metformin - PBO	(Sitagliptin + Metformin) - PBO
Glucose	-8.72 (-15.95, -1.49)	-21.69 (-28.93, -14.45)	-31.00 (-38.23, -23.77)
Glucagon	-4.90 (-10.65, 0.85)	11.71 (5.95, 17.47)	0.81 (-4.94, 6.56)
C-peptide	0.16 (-0.42, 0.73)	-0.68 (-1.26, -0.11)	-1.17 (-1.74, -0.61)
Insulin	3.07 (-12.09, 18.22)	-10.42 (-25.59, 4.74)	-22.28 (-37.14, -7.43)
[†] Geometric least-squares mean ratio (active/placebo). [‡] Least-squares mean difference (active -placebo). [§] Across the four treatment regimens, about 42.5% of observed post-prandial ratio of active to total GLP-1 were lower than the baseline ratio and resulted in the zero incremental weighted mean. Therefore, instead of incremental weighted mean, post-prandial 4 hour weighted mean ratio of active to total GLP-1 was calculated and used in the statistical analysis. CI = Confidence interval; PBO = Placebo.			

Source: Study P110 synopsis

Please also refer to the Janumet label.

4.4.3 Pharmacokinetics

The sponsor conducted definitive BE study P147 in 48 healthy, fed subjects (38 completers). This was an open label, randomized, five period crossover study to determine the PK of sitagliptin and metformin after administration of the final market composition (FMC) of sitagliptin/metformin XR 50/500 mg and 100/1000 mg tablets and coadministration of corresponding doses of sitagliptin and metformin XR (Glumetza) as individual tablets. The study also assessed the PK of two FMC sitagliptin/metformin XR 50/500 mg tablets and a single 100/1000 mg tablet.

The 90% confidence interval (CI) for the GMR of the AUC_{0-∞} and C_{max} for both sitagliptin and metformin after administration of a single FMC sitagliptin/metformin XR 50/500 mg or 100/1000 mg tablet and coadministration of corresponding doses as individual tablets were within the prespecified bounds of [0.80, 1.25] required to establish BE. The same was true of the comparison of a single FMC sitagliptin/metformin XR 100/1000 mg tablet and 2 FMC sitagliptin/metformin XR 50/500 mg tablets.

Table 3. P147: Pharmacokinetic parameters of sitagliptin after administration of a single sitagliptin/metformin XR 50/500 mg or 100/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR as individual tablets, or two 50/500 mg tablets in healthy adult subjects

Treatment	A		B		C		D		E	
PK Parameter	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)
AUC _{0-∞} [†] (nM•hr)	44	3993 (3830, 4163)	44	4006 (3842, 4177)	45	7766 (7449, 8097)	43	7831 (7511, 8166)	44	7828 (7508, 8162)
AUC _{0-12h} [†] (nM•hr)	44	3892 (3732, 4059)	44	3912 (3752, 4080)	45	7661 (7346, 7989)	43	7721 (7403, 8052)	44	7712 (7395, 8042)
C _{max} [†] (nM)	44	356 (332, 381)	44	342 (320, 367)	45	778 (727, 833)	43	778 (727, 834)	44	746 (697, 799)
T _{max} [‡] (hr)	44	2.5 (1.0, 7.0)	44	3.0 (1.0, 7.0)	45	2.0 (1.0, 7.0)	43	3.0 (1.0, 5.0)	44	3.0 (1.0, 6.0)
Apparent terminal t _{1/2} [§] (hr)	44	12.9 (3.5)	44	12.6 (3.2)	45	12.3 (2.8)	43	12.2 (3.1)	44	12.5 (3.4)
Between-Treatment Comparison										
Geometric Mean Ratio (90% CI)										
	FMC MK-0431A XR Tablets vs. Co-administration of Sitagliptin and Metformin XR (Glumetza)						2 x MK-0431A XR 50 mg/500 mg Tablets vs. 1 x MK-0431A XR 100 mg/1000 mg Tablet			
Parameter	MK-0431A XR 50 mg/500 mg Tablet			MK-0431A XR 100 mg/1000 mg Tablet						
AUC _{0-∞}	1.00 (0.99, 1.02)			1.01 (0.99, 1.03)			1.00 (0.98, 1.02)			
AUC _{0-12h}	1.01 (0.99, 1.02)			1.01 (0.99, 1.02)			1.00 (0.98, 1.02)			
C _{max}	0.96 (0.92, 1.01)			1.00 (0.96, 1.05)			0.96 (0.92, 1.00)			
[†] Back-transformed least-squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values										
[‡] Median (min, max) reported for T _{max}										
[§] Harmonic mean, jack-knife standard deviation reported for apparent terminal t _{1/2}										
Treatment A: Co-administration of sitagliptin 50 mg and metformin XR 500 mg (Glumetza) as individual tablets										
Treatment B: Administration of a single FMC MK-0431A XR 50 mg/500 mg tablet										
Treatment C: Co-administration of sitagliptin 100 mg and metformin XR 1000 mg (Glumetza) as individual tablets										
Treatment D: Administration of a single FMC MK-0431A XR 100 mg/1000 mg tablet										
Treatment E: Administration of two FMC MK-0431A XR 50 mg/500 mg tablets										
GM = Geometric Least-Squares Mean; CI = Confidence Interval; FMC = Final Market Composition; XR = Extended Release										

Source: Study P147 synopsis

Table 4. P147: Pharmacokinetic parameters of metformin after administration of a single sitagliptin/metformin XR 50/500 mg or 100/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR as individual tablets, or two 50/500 mg tablets in healthy adult subjects

Treatment	A		B		C		D		E	
PK Parameter	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)
AUC _{0-∞} [†] (ng•hr/mL)	36	6639 (6128, 7192)	36	7047 (6504, 7636)	39	12490 (11540, 13519)	35	12009 (11077, 13019)	39	12302 (11367, 13315)
AUC _{0-last} [‡] (ng•hr/mL)	44	6576 (6096, 7094)	44	6874 (6372, 7416)	45	12194 (11305, 13152)	43	11845 (10976, 12783)	44	12015 (11138, 12962)
C _{max} [‡] (ng/mL)	44	560 (526, 597)	44	607 (570, 647)	45	868 (815, 924)	43	988 (927, 1052)	44	1000 (939, 1065)
T _{max} [§] (hr)	44	6.0 (3.0, 10.0)	44	6.0 (3.0, 10.0)	45	10.0 (5.0, 16.0)	43	7.0 (4.0, 12.0)	44	5.5 (3.0, 10.0)
Apparent terminal t _{1/2} [§] (hr)	36	11.8 (6.4)	36	12.6 (7.9)	39	12.2 (3.8)	35	12.0 (6.8)	39	13.5 (7.4)
Between-Treatment Comparison										
Geometric Mean Ratio (90% CI)										
	FMC MK-0431A XR Tablets vs. Co-administration of Sitagliptin and Metformin XR (Glumetza)						2 x MK-0431A XR 50 mg/500 mg Tablets vs. 1 x MK-0431A XR 100 mg/1000 mg Tablet			
Parameter	MK-0431A XR 50 mg/500 mg Tablet			MK-0431A XR 100 mg/1000 mg Tablet						
AUC _{0-∞}	1.06 (1.01, 1.12)			0.96 (0.91, 1.01)			1.02 (0.97, 1.08)			
AUC _{0-last}	1.05 (1.00, 1.09)			0.97 (0.93, 1.01)			1.01 (0.97, 1.06)			
C _{max}	1.08 (1.03, 1.14)			1.14 (1.09, 1.19)			1.01 (0.97, 1.06)			
[†] Back-transformed least-squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values										
[‡] Median (min, max) reported for T _{max}										
[§] Harmonic mean, jack-knife standard deviation reported for apparent terminal t _{1/2}										
Treatment A: Co-administration of sitagliptin 50 mg and metformin XR 500 mg (Glumetza) as individual tablets										
Treatment B: Administration of a single FMC MK-0431A XR 50 mg/500 mg tablet										
Treatment C: Co-administration of sitagliptin 100 mg and metformin XR 1000 mg (Glumetza) as individual tablets										
Treatment D: Administration of a single FMC MK-0431A XR 100 mg/1000 mg tablet										
Treatment E: Administration of two FMC MK-0431A XR 50 mg/500 mg tablets										
GM = Geometric Least-Squares Mean; CI = Confidence Interval; FMC = Final Market Composition; XR = Extended Release										

Source: Study P147 synopsis

In multiple dose safety, tolerability, and PK study P165, 12 healthy subjects received 2 FMC sitagliptin/metformin XR 50/1000 mg tablets daily for 7 days. The AUC_{0-24hr} and C_{max} for sitagliptin and metformin are shown in Table 5 below. Steady state for sitagliptin and metformin was reached on days 4 and 5, respectively.

Table 5. P165: Pharmacokinetic parameters for sitagliptin and metformin after administration of 2 FMC sitagliptin/metformin XR 50/1000 mg tablets daily for 7 days in healthy adults (n=12)

	$AUC_{0-24hr}^{\dagger}$ (nM·hr)	$C_{max}^{\dagger}$ (nM)	$C_{24hr}^{\dagger}$ (nM)	$T_{max}^{\ddagger}$ (hr)	Apparent Terminal $t_{1/2}^{\S}$ (hr)
Sitagliptin	6851 (6298, 7453)	736 (653, 829)	66 (54, 81)	3.0 (1.0, 5.0)	12.0 (4.6)
	$AUC_{0-24hr}^{\dagger}$ (ng·hr/mL)	$C_{max}^{\dagger}$ (ng/mL)	$C_{24hr}^{\dagger}$ (ng/mL)	$T_{max}^{\ddagger}$ (hr)	Apparent Terminal $t_{1/2}^{\S}$ (hr)
Metformin	20199 (17872, 22829)	1687 (1492, 1908)	200 (162, 247)	8.0 (6.0, 12.0)	14.1(4.2)
[†] Geometric mean (95% confidence interval) for AUC_{0-24hr} , C_{max} and C_{24hr} .					
[‡] Median (Min, Max) for T_{max} .					
[§] Harmonic mean (jackknife standard deviation) for apparent terminal $t_{1/2}$.					

Source: Study P165 synopsis

Food effect study P164 evaluated the effect of a high fat breakfast on the FMC sitagliptin/metformin XR tablets at the 100/2000 mg dose (i.e. two 50/1000 mg tablets) using an open label, randomized, four period crossover design in 12 healthy subjects. The $AUC_{0-\infty}$ for metformin increased by 62% compared to the fasted state. The $AUC_{0-\infty}$ and C_{max} for sitagliptin and C_{max} for metformin decreased by ~6%, 17%, and 9%, respectively, compared to the fasted state. Thus, the food effect on the PK of metformin is consistent with the food effect for marketed metformin XR formulations.

Please also refer to the Janumet label.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 6. Phase 2/3 clinical studies of sitagliptin + metformin IR

Study #	Study Design Primary Objective	Population & Treatment	Endpoints	Reviewer and date
P015	Randomized, double blind, placebo controlled, crossover study	28 T2DM subjects on sita 50 mg BID + met ≥ 1500 mg QD x 4 wk (Protocol did not specify if met IR or XR was required.)	24h weighted mean glucose FPG, fructosamine, SBGM Clinical evaluation & labs EKG	Ilan Irony, M.D. 8/31/06
P020	Randomized, double blind, safety and efficacy study	464 T2DM subjects on sita 100 mg QD + met IR ≥ 1500 mg QD x 24 wk placebo-controlled period (& 80 wk active-controlled period)	HbA1c, FPG Meal tolerance test Clinical evaluation & labs EKG	Ilan Irony, M.D. 8/31/06
P024	Randomized, double blind, safety and efficacy study of sita vs. glipizide 5-20 mg	588 T2DM subjects on sita 100 mg QD + met IR ≥ 1500 mg QD x 104 wk (primary endpt wk 52)	HbA1c, FPG Meal tolerance test Clinical evaluation & labs EKG	Ilan Irony, M.D. S-002 9/17/07
P035	Randomized, double blind, placebo controlled, safety and efficacy study	116 T2DM subjects on glimepiride ≥ 4 mg QD, met IR ≥ 1500 mg QD, & sita 100 mg QD x 24 wk (& 30 wk active-controlled period)	HbA1c, FPG, lipids Meal tolerance test Clinical evaluation & labs EKG	Ilan Irony, M.D. S-002 9/17/07
P036	Randomized, double blind, factorial study	372 T2DM subjects on sita/met IR 50/500 or 50/1000 mg BID 117 T2DM subjects with severe hyperglycemia (HbA1c $> 11\%$ or FPG > 280 mg/dl) on open label sita/met IR 50/1000 mg BID 54 wk (primary endpt wk 24)	HbA1c, FPG, fructosamine Meal tolerance test Clinical evaluation & labs EKG	Ilan Irony, M.D. S-003 9/17/07
P052	Randomized, placebo controlled, safety and efficacy study	170 T2DM subjects on met IR ≥ 1500 mg QD, rosiglitazone ≥ 4 mg QD, & sita 100 mg QD x 54 wk (primary endpt wk 18)	HbA1c, FPG Meal tolerance test Clinical evaluation & labs EKG	Hyon Kwon, Pharm.D. S-010 9/3/09
P053	Randomized, double blind, safety and efficacy study	96 T2DM subjects on sita 100 mg QD & met IR ≥ 1500 mg QD vs. T2DM subjects on placebo + met IR ≥ 1500 mg QD 30 wk (primary endpt wk 18)	HbA1c, FPG Meal tolerance test Clinical evaluation & labs EKG	Not previously reviewed

5.2 Review Strategy

My review focused on the one phase 2/3 clinical study that was not previously reviewed, study P053, although the sponsor does not propose adding study-specific labeling.

As there were no additional completed or ongoing studies of sitagliptin/metformin XR at the time the four-month safety update was submitted, the sponsor submitted three sitagliptin/metformin IR clinical study reports (protocols 66, 68, and 79) which are discussed briefly in 7.4.5 Special Safety Studies/Clinical Trials.

5.3 Discussion of Individual Studies/Clinical Trials

Please refer to Table 6 above for a summary of the phase 2/3 clinical trials in which sitagliptin was coadministered with metformin IR.

Study P053: A multicenter, double blind, randomized, study to evaluate the safety and efficacy of the addition of sitagliptin to patients with T2DM who have inadequate glycemic control on metformin monotherapy (Version 4)

Study Phase and Dates Conducted: This phase 3 study was conducted from August 21, 2006 to August 15, 2007.

Objectives: The study was conducted to assess the safety and efficacy of the addition of sitagliptin in T2DM subjects with moderate to moderately severe hyperglycemia on metformin monotherapy.

Primary:

- After 18 weeks, to assess the effect of the addition of treatment with sitagliptin compared to placebo on HbA1c
- To assess the safety and tolerability of sitagliptin

Secondary:

- After 18 weeks, to assess the effect of the addition of treatment with sitagliptin compared to placebo on the post-meal glucose (e.g. 2 hour postprandial [PPG], glucose area under the concentration-time curve [AUC]) after a meal tolerance test
- After 18 weeks, to assess the effect of the addition of treatment with sitagliptin compared to placebo on fasting plasma glucose (FPG)
- After 30 weeks, to assess the effect of the addition of treatment with sitagliptin compared to placebo on HbA1c

Study Design: This was a multicenter, double blind, randomized, parallel group, placebo controlled study that included the following (see Figure 1):

- 1 week screening period

- Up to 12 week metformin dose-titration/dose-stable and diet/exercise period
- 2 week, single blind, placebo run-in period
- 30 week double blind treatment period

At the diet/exercise run-in starting visit (visit 2), eligible subjects *currently on metformin* discontinued their current anti-hyperglycemic agent (AHA) and were switched to sponsor-supplied metformin. Management of these subjects was based on their metformin dose at screening (visit 1), as follows:

- Subjects on a dose ≥ 1500 mg daily, not requiring further uptitration, entered the 6-week metformin dose-stable/diet-exercise run-in period (visit 2 - 4)
- Subjects on a dose < 1500 mg daily were titrated to at least 1500 mg daily over up to 4 weeks and then entered the 6-week metformin dose-stable/diet-exercise run-in period.

At visit 2, eligible subjects *who were on a single oral AHA other than metformin (except a TZD)* discontinued the current AHA and switched to sponsor-supplied metformin. They then entered the diet-exercise and metformin dose-titration run-in period of up to 4 weeks, during which metformin was uptitrated to at least 1500 mg daily. This was then followed by an 8 week dose-stable/diet-exercise run-in period.

At visit 2, eligible subjects *who were on metformin-based dual oral AHA therapy (except a TZD)* discontinued the AHAs and were switched to sponsor-supplied metformin. Management of these subjects and their metformin dose was then similar to that of subjects currently on metformin (see 2 bullets above).

Note: For subjects with whom the investigator was familiar and who were assessed as highly likely to meet the visit 1 eligibility criteria, the investigator could combine visits 1 and 2.

Subjects meeting all the inclusion criteria and not meeting any of the exclusion criteria at week -2 (visit 4) were eligible for randomization after completing the 2 week single-blind placebo run-in period. These subjects were randomized (1:1) to sitagliptin 100 mg or placebo daily for this 30 week study. After entering the metformin dose-stable period, the metformin dose was not adjusted. Subject who experienced hyperglycemia were rescued with glipizide, according to the study protocol.

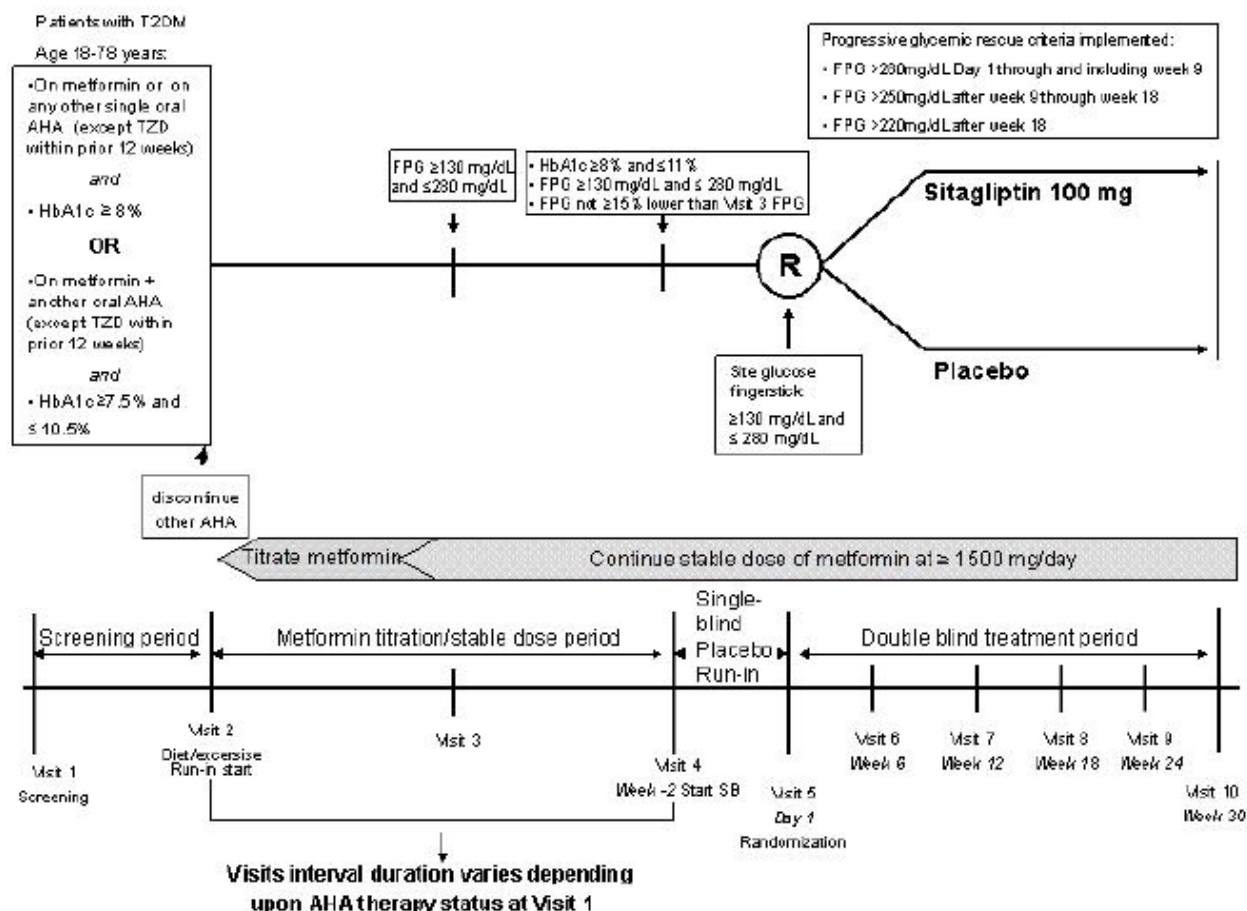


Figure 1. P053: Study design

Patient's Medication and Dose at Screening	Visit 1 Screening Visit HbA _{1c} Level	Metformin Titration Period (Starts at Visit 2)	Metformin Dose-Stable Period Prior to Visit 4/Week -2	Week to Schedule Visit 3
Oral Antihyperglycemic Agent Monotherapy				
Metformin ≥ 1500 mg/day		N/A	6 weeks	Week -6
Metformin <1500 mg/day	$\geq 8\%$	Up to 4 weeks	6 weeks	Week -7 or Week -6
AHA other than metformin		Up to 4 weeks	8 weeks	Week -7 or Week -6
Oral Metformin-Based Combination Dual Antihyperglycemic Therapy				
Metformin ≥ 1500 mg/day	$\geq 7.5\%$ and $\leq 10.5\%$	N/A	6 weeks	Week -8 or Week -7
Metformin <1500 mg/day		Up to 4 weeks	6 weeks	Week -8 or Week -7

Figure 2. P053: Metformin dose-titration and dose-stable period management

Table 7. P053: Study schedule

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 Random- ization	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Poststudy Telephone Contact	Discon- tinuation Visit
				Week -2	Week 0/Day 1	Week 6	Week 12	Week 18	Week 24	Week 30	+ 14 days	
STUDY PROCEDURE												
Obtain informed consent [†]	X											
Obtain informed consent for genetic sample [‡]		X										
Evaluate Inclusion/Exclusion criteria	X	X	X	X	X							
Monitor Adverse Experiences		X	X	X	X	X	X	X	X	X	X	X
Collect medical history		X										
Review prior/concomitant medication.	X	X	X	X	X	X	X	X	X	X		X
Perform physical exam		X			X					X		X
Measure vital signs (HR, BP measured twice)	X	X	X	X	X	X	X	X	X	X		X
Measure weight	X		X		X	X	X	X	X	X		X
Measure height	X											
Perform 12-lead ECG (locally read)		X			X					X		X
Counsel patient to discontinue current AHA therapy and start open-label SPONSOR-supplied Metformin		X										
Diet/exercise counseling		X [§]										
Diet/exercise monitoring			X	X	X	X	X	X	X	X		
Dispense Hypoglycemia Assessment Log and instruct on hypoglycemia symptoms and management.		X										
Dispense glucose meter and provide instruction to Self Blood Glucose Monitoring (SBGM)		X										
Dispense open label metformin		X	X	X	X	X	X	X	X			
Dispense single-blind placebo medication				X								
Monitor for single-blind medication compliance					X							
Dispense double-blind study medication					X	X	X	X	X			
Monitor for double-blind medication compliance						X	X	X	X	X		X
Review SBGM measurements			X	X	X	X	X	X	X	X		X
Review of Hypoglycemia Assessment Log			X	X	X	X	X	X	X	X		X

Clinical Review
Valerie S. W. Pratt, M.D.
NDA 202-270
Janumet XR / sitagliptin + metformin XR

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 Random- ization	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Poststudy Telephone Contact	Discon- tinuation Visit
				Week -2	Week 0/Day 1	Week 6	Week 12	Week 18	Week 24	Week 30	+ 14 days	
MONITORING AND CENTRAL LABORATORY TESTS												
Site fingerstick HbA _{1c} [†]	X											
Site fingerstick glucose					X							
Meal Tolerance Test (0, 60, and 120 minutes samples for glucose, C-peptide, proinsulin, and insulin determination)					X			X				X [†]
Fasting plasma glucose (FPG)	X		X	X	X	X	X	X	X	X		X
HbA _{1c}	X		X	X	X	X	X	X	X	X		X [¶]
C-peptide ^{††}		X										
Complete Blood Count (CBC)/Differential	X				X	X	X	X	X	X		X
Chemistry panel	X				X	X	X	X	X	X		X
Lipid panel ^{††}	X			X	X			X		X		X
TSH	X			X ^{§§}								
Dipstick Urinalysis ^{††}	X				X			X		X		X
Urine Pregnancy test (for women of childbearing potential)	X		X	X	X	X	X	X	X	X		X ^{¶¶}
Blood sample (serum and plasma) for archive					X					X		
If consent obtained, blood sample for genetic analysis					X							
[†] A patient consent form must be signed prior to any study specific procedures. [‡] Genetic consent can also be obtained at any time prior to collecting sample. [§] Patients will be seen by a dietitian or a qualified health professional for diet/exercise counseling at Visit 2 only. Site fingerstick HbA _{1c} may be used, at the discretion of the investigator, for screening [¶] At a Discontinuation Visit, the MTT should be performed only if patient is still on double blind study drug ^{¶¶} Blood sample for HbA _{1c} should be not be collected if Discontinuation Visit occurs prior to Week 6. ^{††} For patients assessed by the investigator as possibly having type 1 diabetes. ^{†††} If the patient is not fasting at Visit 1/Screening Visit, a fasting lipid profile should be obtained at or prior to Visit 2 rather than at Visit 1. Lipid panel only required at Visit 4/ Week -2 if adjusting patient's lipid medication or if otherwise required to re-assess patient's lipid profile. ^{§§} TSH only required at Visit 4/ Week -2 if abnormal at Visit 1. ^{††††} If dipstick (midstream urine specimen) is positive for blood, leukocyte esterase, nitrates, or protein, then a urine sample for complete urinalysis (dipstick and microscopy) must be sent to the central laboratory. ^{†††††} Women of childbearing potential will have a urine pregnancy test (and serum pregnancy test if required by site's Institutional Review Board (IRB)/ Ethics Committee (EC). Patients with a positive urine pregnancy test during double-blind treatment period, will have a serum pregnancy test.												

Key Inclusion criteria:

- At visit 1:
 - o T2DM
 - o ≥ 18 and ≤ 78 years of age
 - o Is in one of the following categories and is considered likely to meet the visit 4 inclusion criterion of HbA1c $\geq 8\%$ and $\leq 11\%$ after the dose-stable period on metformin monotherapy at a dose ≥ 1500 mg daily
 - Currently on monotherapy with metformin or on another single oral antihyperglycemic agent (AHA) (not including a TZD) and has a screening visit HbA1c $\geq 8\%$
 - Currently on metformin in combination with another oral AHA (not including a TZD) and has a screening visit/visit 1 HbA1c $\geq 7.5\%$ and $\leq 10.5\%$
- At visit 4, subject has an HbA1c $\geq 8\%$ and $\leq 11\%$
- At visit 5 randomization, subject has $\geq 85\%$ compliance with placebo treatment during run-in, as measured by site performed tablet count

Key Exclusion Criteria:

- At visit 1:
 - o Type 1 diabetes mellitus or history of ketoacidosis
 - o Required insulin within the prior 8 weeks
 - o Taking a TZD or exenatide within the prior 12 weeks
 - o Serum creatinine ≥ 1.4 mg/dl in men and ≥ 1.3 mg/dl in women or estimated creatinine clearance (CrCl) < 60 ml/min as reported from the study central laboratory
 - o TSH value outside the normal range (i.e. < 0.3 mU/ml or > 5 mU/l)
 - o Severe active peripheral vascular disease (e.g. claudication with minimal activity, a non-healing ischemic ulcer, or disease which is likely to require intervention such as bypass or angioplasty)
 - o Inadequately controlled hypertension (i.e. systolic blood pressure [SBP] > 160 mmHg or diastolic blood pressure [DBP] > 95 mmHg)
 - o History of recurrent poor compliance to medications or not likely to maintain consistent high compliance to study drug during the study period
- At visit 3: FPG consistently (i.e. repeat measurement within 7 days after notification from the central laboratory) < 130 mg/dl or consistently > 280 mg/dl which is not expected to improve with diet and exercise
- At visit 4:
 - o FPG < 130 mg/dl or > 280 mg/dl
 - o Visit 4 FPG concentration is $\geq 15\%$ lower than the visit 3 FPG concentration
 - o Abnormal TSH value at visit 1 and the repeat TSH value at visit 4 is still outside the normal range or the subject is on stable thyroid medication for < 5 weeks prior to visit 4
- At visit 5: Fasting fingerstick < 130 mg/dl or > 280 mg/dl

Treatments and Management: Subjects were randomized to sitagliptin 100 mg or placebo daily.

Subjects were required to take open-label, sponsor-supplied metformin IR ≥ 1500 mg daily. It was provided in 500 mg tablets with the directions “take daily with meals as directed by study physician”. However, patients already being treated with metformin could use their existing supplies as the add-on therapy instead of the sponsor-supplied open-label metformin. The investigator or designee recorded the lot number, expiration date, and drug dispensed. Subjects, who were on metformin 850 mg tablets and preferred to maintain this dose formulation, could also continue the locally supplied tablets (maximum daily dose 2550 mg).

For countries where metformin was commercially available, the local subsidiary supplied the product. For countries where metformin was not commercially available, the U.S. subsidiary supplied the product.

Glipizide rescue therapy was given to subjects who met the following criteria:

- FPG consistently (i.e. repeat measurement within 3 – 7 days) >280 mg/dl after randomization visit through week 9
- FPG consistently >250 mg/dl after week 9 up to and including week 18
- FPG consistently >220 mg/dl after week 18

Subjects who were not eligible for glipizide were discontinued from the study as were subjects who completed glipizide titration and were on a stable, maximum dose for ≥ 2 weeks with FPG >200 mg/dl.

Other reasons for discontinuation including the following:

- Informed consent withdrawn or subject requests discontinuation
- Hyperglycemia (see above)
- Hypoglycemia: repeated (i.e. 2 or more episodes since the prior study visit) FPG or fingerstick glucose <50 mg/dl with or without symptoms of hypoglycemia or <70 mg/dl with symptoms of hypoglycemia, and without a reasonable explanation
- Elevation in ALT/AST
 - If ALT or AST $>3\times$ ULN but $\leq 5\times$ ULN, consider keeping the subject on study drug until the laboratory is repeated (within 3 days)
 - If ALT or AST $>5\times$ ULN, interrupt study drug immediately
 - If study drug is interrupted, it can only be reinstated after consultation with the sponsor.
- Serum creatinine is consistently ≥ 1.5 mg/dl in men and ≥ 1.4 mg/dl in women, or for subjects who entered the study base on measured CrCl, if the serum creatinine is consistently ≥ 0.2 mg/dl above the baseline creatinine value
- Requirement of an excluded medication

- A condition for which metformin is contraindicated in the participating subject's country
- Pregnancy
- Any medical condition or circumstance which exposes the subject to risk by continuing in the study or dose not allow the subject to adhere to the requirements of the protocol

Study Sites including Enrollment: Study P053 was conducted at 24 sites (US 12, Israel 2, Mexico 3, Peru 3, and Austria 4) in 190 randomized T2DM subjects (sitagliptin 96, placebo 94). A total of 159 subjects (sitagliptin 79, placebo 80) completed the study.

Efficacy Assessments:

Primary: HbA1c at week 18

Secondary: Two-hour PPG (post standard meal challenge), FPG, HbA1c (at week 30)

Other: C-peptide, insulin, and proinsulin levels at time 0, 60, and 120 minutes relative to a standard meal challenge; C-peptide AUC; the ratio of insulin AUC to glucose AUC; the ratio of fasting proinsulin to insulin; change from baseline for HOMA- β at week 18; fasting lipids

Safety Assessments: Adverse events (AEs), vital signs, body weight, and safety laboratories (i.e. chemistry, hematology, urinalysis, and urine pregnancy tests)

6 Review of Efficacy

Efficacy Summary

The sponsor submitted NDA 202-270 for the use of sitagliptin/metformin XR FDC as an adjunct to diet and exercise to improve glycemic control in patients with T2DM. The sponsor proposes development of the following tablet strengths:

- 50/500 mg to be given as 2 tablets QD
- 50/1000 mg to be given as 2 tablets QD
- 100/1000 mg to be given as 1 tablet QD

The sponsor aimed to demonstrate BE between sitagliptin/metformin XR and the coadministration of sitagliptin and metformin XR (Glumetza) so as to bridge to the existing safety and efficacy data from sitagliptin (Januvia), metformin XR (Glumetza), and sitagliptin/metformin IR (Janumet) to sitagliptin/metformin XR (Janumet XR). Thus, the pivotal studies were clinical pharmacology studies. Of the clinical study reports submitted (i.e. protocols 015, 020, 024, 035, 036, 052, and 053), only P053 was not previously reviewed and is reviewed here.

Study P053 was a multicenter, double blind, randomized, study to evaluate the safety and efficacy of the addition of sitagliptin 100 mg versus placebo to T2DM patients who had inadequate glycemic control on metformin monotherapy (≥ 1500 mg). The primary

endpoint was the change in HbA1c at week 18. Secondary endpoints included FPG and PPG at week 18 as well as the change in HbA1c at week 30.

A total of 190 subjects were randomized (sitagliptin 96, placebo 94) in study P053. Baseline demographics were generally similar between the two groups. The baseline HbA1c and duration of T2DM ranged from 9.1-9.3% and 7.4-8.4 years, respectively. The rate of discontinuation was similar between the two groups (sitagliptin 17.7% vs. placebo 14.9%). More sitagliptin than placebo subjects discontinued study P053 due to lack of efficacy (6.3% vs. 3.2%). However, more placebo subjects received glycemic rescue by week 30 (24.5% vs. 6.3%).

The primary efficacy endpoint was the effect of sitagliptin 100 mg versus placebo on HbA1c at week 18. The addition of sitagliptin resulted in a significant improvement in HbA1c (mean change -1.0%, $p < 0.001$) when compared to placebo (mean change 0.0%) in the FAS population. A similar significant result was observed when using the completers population (mean change -1.1%, $p < 0.001$). The secondary endpoints, FPG and 2-hour PPG, were also significant. The effect on HbA1c was persistent to week 30 (sitagliptin -1.0% vs. placebo 0.1%, $p < 0.001$). Statistically significant improvements in HbA1c were seen at week 18 in subgroups of the study population based on demographic and baseline disease characteristics.

6.1 Indication

The sponsor submitted this NDA for the use of sitagliptin/metformin XR FDC as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

6.1.1 Methods

As described in section 4.4 Clinical Pharmacology, the sponsor aimed to demonstrate BE between sitagliptin/metformin XR and the coadministration of sitagliptin and metformin XR (Glumetza) so as to bridge to the existing safety and efficacy data from sitagliptin (Januvia), metformin XR (Glumetza), and sitagliptin/metformin IR (Janumet) to sitagliptin/metformin XR (Janumet XR). Thus, the pivotal studies were clinical pharmacology studies, as described in section 2.5 Summary of Presubmission Regulatory Activity Related to Submission.

Of the clinical study reports submitted (i.e. protocols 015, 020, 024, 035, 036, 052, and 053), only P053 was not previously reviewed and is reviewed here.

6.1.2 Demographics

Demographics and baseline characteristics are shown in Table 8. The demographics were similar between study groups with the following exceptions:

- More sitagliptin subjects were male (51.0% vs. 41.5%) or on metformin monotherapy (56.3% vs. 47.9%)
- More placebo subjects used combination therapy (50.0% vs. 39.6%)

Table 8. P053: Demographics and baseline characteristics

Characteristic	Sitagliptin (n=96)	Placebo (n=94)
Age (mean years [SD])	53.6 (9.5)	56.1 (9.5)
Gender (male n [%])	49 (51.0)	39 (41.5)
Race (n [%])		
White	40 (41.7)	44 (46.8)
Black	3 (3.1)	1 (1.1)
Hispanic	31 (32.3)	24 (25.5)
Asian	1 (1.0)	0 (0.0)
Other	21 (21.9)	25 (26.6)
BMI (mean [SD])	30.1 (4.4)	30.4 (5.3)
Baseline HbA1c (mean % [SD])	9.3 [0.9]	9.1 [0.8]
Duration of DM (mean years [SD])	8.4 (6.5)	7.4 (5.3)
Use of AHA at screening (n [%])		
Combination therapy	38 (39.6)	47 (50.0)
Monotherapy – other	4 (4.2)	2 (2.1)
Monotherapy – metformin	54 (56.3)	45 (47.9)

6.1.3 Subject Disposition

A total of 544 subjects were screened for study P053; 190 were randomized (sitagliptin 96, placebo 94). A total of 159 (83.7%) completed the 30 week study (sitagliptin 79 [83.7%], placebo 80 [85.1%]). The rate of discontinuation was similar between the two groups (17.7% vs. 14.9%). The reasons for discontinuation are shown in Table 9. More sitagliptin than placebo subjects discontinued study P053 due to lack of efficacy. However, more placebo subjects received glycemic rescue.

Table 9. P053: Discontinuations

Discontinuations	Sitagliptin (n=96)	Placebo (n=94)
Total discontinued	17 (17.7%)	14 (14.9%)
Clinical AE	0 (0.0%)	2 (2.1%)

Laboratory AE	2 (2.1%)	0 (0.0%)
Lack of efficacy	6 (6.3%)	3 (3.2%)
Loss to follow up	3 (3.1%)	3 (3.2%)
Died	0 (0.0%)	1 (1.1%)
Patient withdrew consent	6 (6.3%)	5 (5.3%)

The primary endpoint and the majority of secondary endpoints were assessed at week 18. The FAS and completers (i.e. subset of FAS including all subjects with week 18 data) at this time point are shown below.

Table 10. P053: Analysis sets at week 18

Population	Number (%)		
	Sitagliptin	Placebo	Total
Total randomized	96	94	190
Included in the FAS analysis	95 (99.0)	92 (97.9)	187 (98.4)
Included in the completers analysis	88 (91.7)	74 (78.7)	162 (85.3)

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the effect of sitagliptin 100 mg versus placebo on HbA1c at week 18. The addition of sitagliptin resulted in a significant improvement in HbA1c (mean change -1.0%, $p < 0.001$) when compared to placebo (mean change 0.0%) in the FAS population. A similar significant result was observed when using the completers population (mean change -1.1%, $p < 0.001$).

The between treatment difference (sitagliptin 100 mg vs. placebo) in LS means in the FAS population was -1.0% with a 95% CI (-1.36, -0.67) and p-value < 0.001 .

Table 11. P053: Change in HbA1c (%) from baseline at week 18

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-value
FAS							
Sitagliptin	95	9.3 (0.9)	8.2 (1.4)	-1.0 (0.1)	-1.0 (0.1)	(-1.24, -0.75)	<0.001
Placebo	92	9.1 (0.8)	9.1 (1.3)	0.0 (0.1)	0.0 (0.1)	(-0.23, 0.27)	0.872
Completers							
Sitagliptin	88	9.2 (0.9)	8.1 (1.3)	-1.1 (0.1)	-1.1 (0.1)	(-1.37, -0.88)	<0.001
Placebo	74	9.1 (0.8)	9.0 (1.3)	-0.1 (0.1)	-0.2 (0.1)	(-0.43, 0.10)	0.218

Source: P053 study report tables 11-1 and 14-12

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints in study P053 included the following:

- After 18 weeks, the effect of the addition of sitagliptin compared to placebo on FPG and the post-meal glucose (e.g. 2 hour postprandial [PPG], glucose area under the concentration-time curve [AUC]) after a meal tolerance test
- After 30 weeks, to assess the effect of the addition of treatment with sitagliptin compared to placebo on HbA1c

Fasting Plasma Glucose: The addition of sitagliptin 100 mg resulted in a significant improvement in the mean change from baseline in FPG when compared to placebo in the FAS population at week 18 (-33 mg/dl vs. -6 mg/dl, p<0.001). A similar significant result was observed when using the completers population (mean change -37, p<0.001).

Table 12. P053: Change from baseline in FPG (mg/dl) at week 18

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-value
FAS							
Sitagliptin	96	201 (46)	169 (43)	-33 (5)	-32 (4)	(-40.6, 23.3)	<0.001
Placebo	92	198 (44)	192 (53)	-6 (5)	-7 (4)	(-15.1, 2.2)	0.144
Completers							
Sitagliptin	88	199 (46)	162 (37)	-37 (5)	-35 (4)	(-43.5, -27.0)	<0.001
Placebo	74	191 (40)	184 (47)	-8 (6)	-10 (4)	(-19.0, -1.6)	0.021

Source: P053 study report tables 11-2 and 14-13

Table 13. P053: Between treatment difference in FPG

Difference between sitagliptin & placebo	Diff in LS Means (95% CI)	p-value
FAS population	-26 (-37.7, -13.3)	<0.001
Completers population	-25 (-37.0, -12.9)	<0.001

Source: P053 study report tables 11-2 and 14-13

Two-hour PPG: The addition of sitagliptin 100 mg resulted in a significant mean change from baseline in 2-hour PPG when compared to placebo in the FAS population at week 18 (-65 mg/dl vs. -13 mg/dl, p<0.001).

Table 14. P053: Change from baseline in 2-hour PPG (mg/dl) at week 18

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-value
FAS							
Sitagliptin	79	285 (74)	220 (69)	-65 (8)	-67.6 (7.3)	(-82.1, -53.2)	<0.001
Placebo	74	284 (61)	271 (78)	-13 (9)	-13.5 (7.4)	(-28.2, 1.2)	0.071

Source: P053 study report table 11-3

Table 15. P053: Between treatment difference in PPG

Difference between sitagliptin & placebo	Diff in LS Means (95% CI)	p-value
FAS population	-54 (-75, -34)	<0.001

Source: P053 study report tables 11-3

HbA1c at Week 30: The between treatment difference (sitagliptin 100 mg vs. placebo) in LS means was -1.0% (95% CI: -1.40, -0.62) in the FAS population. The addition of sitagliptin 100 mg resulted in a significant change from baseline in HbA1c at week 30 when compared to placebo ($p < 0.001$). A similar significant result was observed when using the completers population, although there was a smaller difference between the two groups (between treatment difference in LS means -0.7%, $p < 0.001$). The reduced difference between the two groups in the completers analysis is likely due to more values carried forward in the placebo group, as a result of glycemic rescue and early discontinuation.

Table 16. P053: Change from baseline in HbA1c (%) at week 30

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-value
FAS							
Sitagliptin	95	9.3 (0.9)	8.3 (1.5)	-1.0 (0.2)	-1.0 (0.1)	(-1.25, -0.70)	<0.001
Placebo	92	9.1 (0.8)	9.2 (1.3)	0.1 (0.1)	0.0 (0.14)	(-0.24, 0.31)	0.801
Completers							
Sitagliptin	75	9.2 (0.8)	8.0 (1.5)	-1.2 (0.2)	-1.2 (0.2)	(-1.48, -0.89)	<0.001
Placebo	55	9.1 (0.8)	8.7 (1.1)	-0.4 (0.2)	-0.5 (0.2)	(-0.79, -0.11)	0.010

Source: P053 study report tables 11-4 and 14-14

In the FAS population, mean HbA1c continuously improved in the sitagliptin group up to week 24, after which there was a slight rise to week 30.

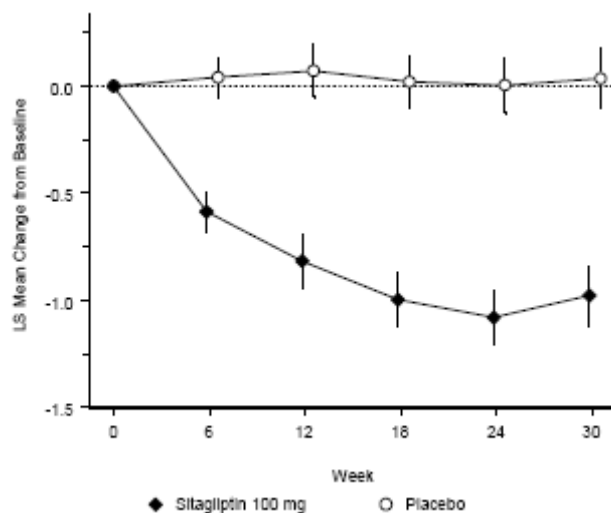


Figure 3. Least square mean HbA1c (%) over time by treatment group (FAS)

Source: P053 study report figure 11-4

6.1.6 Other Endpoints

The other efficacy endpoints in study P053 are defined in section 5.3 Individual Studies/Clinical Trials.

Discussion of

The Homeostatic Model Assessment (HOMA)-B (an index of fasting insulin secretion) and HOMA-IR (an index of insulin sensitivity) were also assessed for sitagliptin in study P053. At week 18, HOMA-B ratios demonstrated increased fasting insulin secretion in sitagliptin subjects when compared to placebo subjects. However, no change in HOMA-IR was observed with sitagliptin or placebo.

Note: The above mathematical models are not well-validated surrogates for insulin sensitivity and beta-cell function, and therefore, do not yet rise to a level of evidence to support inclusion in labeling.

Table 17. P053: Change from baseline in HOMA-B and HOMA-IR at week 18 (FAS)

Treatment	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-value
HOMA-B							
Sitagliptin	74	28.9 (28.1)	46.0 (35.8)	17.1 (3.2)	17.0 (2.9)	(11.3, 22.6)	<0.001
Placebo	65	29.1 (21.9)	31.6 (23.3)	2.5 (2.7)	2.5 (3.0)	(-3.4, 8.4)	0.406
HOMA-IR							
Sitagliptin	74	5.5 (6.4)	5.0 (4.0)	-0.5 (0.7)	-0.3 (0.4)	(-1.0, 0.4)	0.393
Placebo	65	4.5 (3.3)	4.3 (3.1)	-0.2 (0.3)	-0.6 (0.4)	(-1.3, 0.2)	0.153

Source: P053 study report tables 11-10 and 11-11

6.1.7 Subpopulations

The sponsor analyzed the change in HbA1c by subgroups such as median age, gender, BMI, baseline HbA1c, and diabetic therapy (see Table 18). Statistically significant improvements in HbA1c (LS mean difference range: -0.82 to -1.26) were seen at week 18 in the subgroups presented below; this was generally consistent among all subgroups analyzed.

Table 18. P053: Subgroup analysis for HbA1c change from baseline at week 18 (FAS)

Characteristic/Treatment	N	LS Mean	95% CI	LS Mean Difference	95% CI
Median age					

At or below 55 years					
Sitagliptin	55	-1.0	(-1.32, -0.67)	-0.9	(-1.34, -0.40)
Placebo	46	-0.1	(-0.47, 0.22)	-	-
Above 55 years					
Sitagliptin	40	-1.0	(-1.38, -0.64)	-1.2	(-1.68, -0.66)
Placebo	46	0.2	(-0.19, 0.52)	-	-
Gender					
Female					
Sitagliptin	47	-1.0	(-1.35, -0.65)	-1.1	(-1.52, -0.57)
Placebo	54	0.1	(-0.28, 0.37)	-	-
Male					
Sitagliptin	48	-0.99	(-1.34, -0.65)	-0.98	(-1.49, -0.46)
Placebo	38	-0.02	(-0.40, 0.37)	-	-
Median BMI					
At or below BMI 30.1					
Sitagliptin	47	-1.1	(-1.47, -0.78)	-1.0	(-1.45, -0.46)
Placebo	46	-0.2	(-0.51, 0.18)	-	-
Above BMI 30.1					
Sitagliptin	47	-0.9	(-1.23, -0.54)	-1.1	(-1.57, -0.60)
Placebo	46	0.2	(-0.14, 0.55)	-	-
Baseline HbA1c					
HbA1c <9%					
Sitagliptin	35	-0.7	(-1.11, -0.31)	-0.8	(-1.35, -0.28)
Placebo	45	0.1	(-0.25, 0.46)	-	-
HbA1c ≥9%					
Sitagliptin	60	-1.2	(-1.50, -0.88)	-1.2	(-1.63, -0.71)
Placebo	47	-0.0	(-0.37, 0.32)	-	-
Prior therapy					
Monotherapy					
Sitagliptin	58	-0.9	(-1.23, -0.61)	-0.8	(-1.29, -0.37)
Placebo	47	-0.1	(-0.44, 0.25)	-	-
Metformin-based combo					
Sitagliptin	37	-1.1	(-1.51, -0.73)	-1.3	(-1.78, -0.74)
Placebo	45	0.1	(-0.21, 0.49)	-	-

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor has developed a FDC of sitagliptin and metformin XR in the following tablet strengths:

- 50/500 mg to be given as 2 tablets once daily (QD)
- 50/1000 mg to be given as 2 tablets QD

- 100/1000 mg to be given as 1 tablet QD

The proposed dose strengths are acceptable and consistent with approved sitagliptin/metformin NDA 22-044, which is available in doses 50/500 and 50/1000 mg. twice daily.

Although sitagliptin is also available in 50 and 25 mg doses for patients with moderate and severe or end-stage renal disease, metformin is contraindicated in patients with renal dysfunction (e.g. serum creatinine ≥ 1.5 mg/dl [males], ≥ 1.4 mg/dl [females], or abnormal creatinine clearance).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The primary efficacy endpoint was the effect of sitagliptin compared to placebo on HbA1c at week 18. Sitagliptin resulted in a significant improvement in HbA1c at week 18 compared to placebo (see section 6.1.4 Analysis of Primary Endpoint(s)).

The sponsor also assessed the effect of sitagliptin compared to placebo on HbA1c at week 30. Sitagliptin also resulted in a significant improvement in HbA1c at week 30 compared to placebo (see section 6.1.5 Analysis of Secondary Endpoints(s)). Thus, there was persistence of efficacy with sitagliptin to week 30.

6.1.10 Additional Efficacy Issues/Analyses

Time to Rescue: The time to rescue was significantly longer with sitagliptin versus placebo ($p < 0.001$). A smaller percentage of sitagliptin subjects required rescue by week 30 when compared to placebo (6.3% vs. 24.5%; $p < 0.001$).

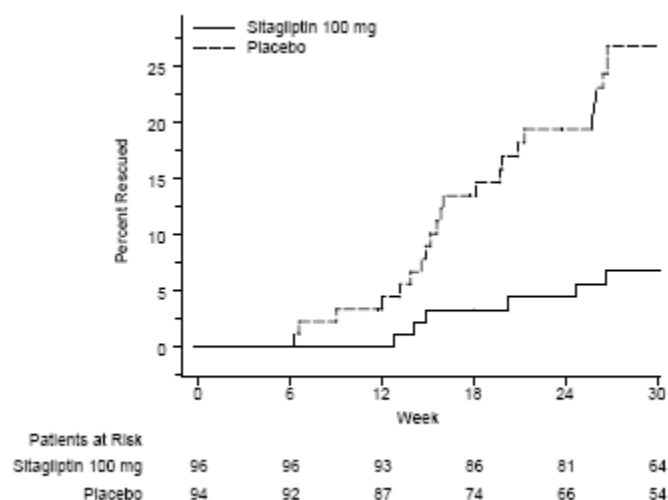


Figure 4. P053: Subjects receiving rescue medication

Source: Study P053 report figure 11-11

Lipid Panel: Small increases from baseline in total-C, LDL-C, HDL-C, non-HDL-C, TG, and TG/HDL-C ratio were seen in both groups. However, the increase in the sitagliptin group was generally smaller than that with placebo. There were no statistically significant differences between the two groups.

Table 19. P053: Lipid panel changes at week 30 (FAS)

Treatment	N	Mean (SD)		Diff in sitaglipt LS mean vs. placebo (95% CI)
		Baseline	Week 30	
T-Cholesterol				
Sitagliptin	89	191.5 (41.1)	191.9 (36.8)	-4.3 (-9.8, 1.1)
Placebo	82	188.7 (36.9)	198.1 (41.9)	
LDL-C				
Sitagliptin	89	107.1 (31.2)	109.8 (30.1)	-5.6 (-15.1, 3.9)
Placebo	82	107.9 (31.2)	115.3 (34.4)	
HDL-C				
Sitagliptin	89	45.1 (10.1)	44.7 (10.2)	-2.7 (-6.9, 1.6)
Placebo	82	47.1 (9.2)	48.0 (11.0)	
Non-HDL-C				
Sitagliptin	89	146.4 (39.2)	147.2 (36.8)	-4.5 (-12.1, 3.0)
Placebo	82	141.6 (35.1)	150.1 (41.3)	
Triglycerides				
Sitagliptin	89	208.7 (141.7)	203.6 (130.7)	-1.0 (-14.7, 12.7)
Placebo	82	168.7 (68.2)	181.7 (107.7)	
TG to HDL-C ratio				

Sitagliptin	89	5.0 (3.9)	5.0 (3.7)	2.8 (-14.0, 19.6)
Placebo	82	3.8 (1.8)	4.1 (3.0)	

Source: Study report P053 tables 11-30 though 11-35

7 Review of Safety

Safety Summary

The pivotal studies in NDA 202-270 were clinical pharmacology studies, specifically study P147 which compared the to-be-marketed product with coadministration of sitagliptin and metformin XR. Of the clinical study reports submitted (i.e. protocols 015, 020, 024, 035, 036, 052, and 053), only P053 was not previously reviewed and is reviewed here. My review primarily focused on safety events which occurred prior to the initiation of rescue therapy. However, events occurring after initiation of rescue therapy were also analyzed in some cases.

In study P053, 79 subjects completed 30 weeks of treatment with sitagliptin 100 mg and metformin. In the 7 clinical studies submitted to the NDA, a total of 1,834 subjects were exposed to sitagliptin and metformin.

One death occurred in study P053; placebo-treated subject AN 57022 died of myocardial ischemia on day 40. No nonfatal serious AEs were reported in sitagliptin subjects. However, 4 placebo subjects reported 5 nonfatal serious AEs, including the time period after initiation of glycemic rescue therapy. In that same time period, two placebo subjects and no sitagliptin subjects were discontinued due to clinical AEs (i.e. upper limb fracture and lymphoma). Two sitagliptin subjects and no placebo subjects discontinued due to laboratory AEs (i.e. blood creatinine increased and ALT increased).

Regarding significant AEs,

- Hypoglycemia: Excluding data after initiation of glycemic rescue therapy, one sitagliptin subject experienced 2 episodes of hypoglycemia. Neither event required assistance.
- Gastrointestinal: The number and percentage of subjects with the pre-specified GI AES abdominal pain, diarrhea, nausea, and vomiting was similar between treatment groups, excluding data after initiation of glycemic rescue (sitagliptin 9.4% vs. placebo 7.4%).
- Pancreatitis: No events of pancreatitis occurred during study P053.
- Hypersensitivity: One sitagliptin subject had a hypersensitivity event in the immune system disorder SOC (sitagliptin 1.0% vs. placebo 0.0%).

Regarding common AEs, SOC with more events in the sitagliptin group were as follows:

- Infections and infestations (32.3% vs. 28.7%)

- Nervous system (15.6% vs. 9.6%)
- Musculoskeletal and connective tissue (12.5% vs. 8.5%)
- Cardiac (5.2% vs. 1.1%): This was mainly due to an increase in angina pectoris events (n=3 [3.1%] vs. n=0 [0.0%]). All other cardiac events were single events.

However, there was no statistically significant difference in the rate of events by SOC. Only 1 event (increased blood glucose) occurred at a significantly different rate between groups; it was more common in placebo subjects (95% CI: -19.0, -0.7).

The mean (SE) change from baseline was similar for the sitagliptin and placebo groups for most laboratory parameters, as shown in Table 25. For laboratory parameters with small differences note, the general trends in these laboratory parameters were similar between sitagliptin and placebo and were felt not to be clinically significant.

The percentage of subjects meeting the predefined limits of change (PDLC) in laboratory parameters was similar between the sitagliptin and placebo groups, except in the following categories which had a difference $\geq 3\%$: hemoglobin, WBC, AST, ALT, alkaline phosphatase, and neutrophil count. However, a statistically significant difference between treatment groups was seen with only 2 of the PDLC criteria (hemoglobin and ALT). A labeled safety risk of metformin is anemia. In the sitagliptin/metformin XR label, the sponsor proposes a warning to “measure hematologic parameters annually”. The PDLC for ALT was an increase $>100\%$ over baseline and value $>ULN$. However, a significant change in liver tests (ALT or AST) was not seen with increase $>200\%$ or 400% . No subject met Hy’s Law for drug-induced liver injury. The sponsor proposes labeling which contains a warning against using Janumet XR in patients with hepatic disease and use of excessive alcohol intake, based on the current metformin labels. This is acceptable.

More sitagliptin subjects experienced laboratory AEs than placebo subjects (15.6% vs. 4.3%). All laboratory AEs occurred as single events in the sitagliptin group, except for hemoglobin decreased (n=4), blood triglycerides increased (n=2), and blood uric acid increased (n=2). In addition, the pre-specified analysis of 95% CI for the between-group differences in the incidence of specific laboratory AEs was negative (i.e. no between-group differences excluded zero).

The mean changes from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were generally small and similar between the sitagliptin and placebo treatment groups. The rate of ECG abnormalities was balanced. The sponsor 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.

I recommend the following PREA-related PMRs, which will be discussed with the Pediatric Review Committee (PeRC) on June 8, 2011:

- A single dose PK study of sitagliptin/metformin XR FDC in T2DM subjects 10-17 years
- A 52-week safety and efficacy study of sitagliptin/metformin XR FDC versus metformin (IR and/or XR) in T2DM subjects 10-17 years who are inadequately controlled

(b) (4) will also evaluate if subjects can safely swallow the FDC tablets.

Please refer to the sitagliptin (NDA 21-995) and sitagliptin/metformin IR FDC (NDA 22-044) product labels for more information.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The pivotal studies in NDA 202-270 were clinical pharmacology studies, specifically study P147 which compared the to-be-marketed product with coadministration of sitagliptin and metformin XR. In study 147, there were no deaths, one SAE which resulted in discontinuation (urinary retention due to underlying stricture), and four other discontinuations (1 abdominal pain, 2 rash, and 1 urticaria). Of the clinical study reports submitted (i.e. protocols 015, 020, 024, 035, 036, 052, and 053), only P053 was not previously reviewed and is reviewed here. My review primarily focused on safety events which occurred prior to the initiation of rescue therapy. However, events occurring after initiation of rescue therapy were also analyzed in some cases.

As there were no additional completed or ongoing studies of sitagliptin/metformin XR at the time the four-month safety update was submitted, the sponsor submitted three sitagliptin/metformin IR clinical study reports (protocols 66, 68, and 79) which are discussed briefly in 7.4.5 Special Safety Studies/Clinical Trials.

7.1.2 Categorization of Adverse Events

The sponsor's coding and categorization of AEs was adequate. Study P053 used MedDRA version 10.0.

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

As study P053 is the only study that was not reviewed previously and is reviewed here, data were not pooled across studies.

7.2 Adequacy of Safety Assessments

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

In study P053, 79 subjects completed 30 weeks of treatment with sitagliptin 100 mg and metformin. In the 7 clinical studies submitted to the NDA, a total of 1,834 subjects were exposed to sitagliptin and metformin.

As described in the May 17, 2010 annual report for related sitagliptin/metformin IR NDA 22-440, over 321 million sitagliptin/metformin 50/500 and 50/1000 mg tablets were distributed in the US from April 1, 2009 to March 31, 2010 alone.

Taken together, the clinical exposure to sitagliptin and metformin is adequate.

7.2.2 Explorations for Dose Response

Not applicable. Please refer to the appropriate sections of sitagliptin NDA 21-995 and sitagliptin/metformin IR NDA 22-044.

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/metformin.

7.2.4 Routine Clinical Testing

The sponsor obtained laboratory tests, vital signs, and ECGs at reasonable time points in study P053 and under consistent settings, where applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Metformin is also excreted unchanged in the urine and does not undergo hepatic metabolism nor biliary excretion.

Please refer to the sitagliptin (NDA 21-995) and sitagliptin/metformin IR FDC (NDA 22-044) product labels for more information, including drug-drug interactions.

The sponsor conducted study P012, a sitagliptin and metformin drug interaction study in subjects with T2DM. The study was submitted to support sitagliptin NDA 21-995 and sitagliptin/metformin FDC NDA 22-044. It was a single center, randomized, double

blind, double dummy, placebo controlled, three period, crossover study in 13 T2DM subjects on stable metformin monotherapy. Sitagliptin had no significant effect on the PK of metformin and vice versa. The 90% CI for the ratios of LS means were within the protocol-prespecified similarity bounds of (0.50, 2.00). Please refer to Dr. Jee Eun Lee's clinical pharmacology review for full details.

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

Please refer to section 2.4 Important Safety Issues With Consideration to Related Drugs for a list of the labeled safety concerns with sitagliptin and metformin. There are two other approved DPP-4 inhibitors: saxagliptin (NDA 22-350) and linagliptin (NDA 201-280); their prescribing information is similar to that of sitagliptin.

7.3 Major Safety Results

7.3.1 Deaths

One death occurred in study P053. Placebo subject AN 57022 died of myocardial ischemia on day 40.

7.3.2 Nonfatal Serious Adverse Events

No nonfatal serious AEs were reported in sitagliptin subjects in study P053. However, four placebo subjects reported five nonfatal serious AEs, which are shown below, regardless of whether they occurred before or after rescue therapy. Two of these subjects were discontinued due to the AE.

Table 20. P053: Nonfatal serious adverse events

Study #	AN	M/F	Age	Period*	Therapy	Onset day	AE	Duration	Action
0530010	57255	M	55	A	Placebo	83	Adenocarcinoma pancreas	Cont	-
0530012	57202	F	75	A	Placebo	125	Upper limb fx	13 d	Discont
0530018	57130	M	77	B	Off 1 d	140	Upper GI hemorrhage	4 d	Interrupt
0530021	57108	M	61	A: rescued	Placebo	96	Lymphoma	Cont	Discont
				A: PS- rescue	Off 29 d	135	Colon cancer	1 d	-

* Period A and B represent the 18- and 30-week data sets, respectively.

Source: P053 study report table 12-10

7.3.3 Dropouts and/or Discontinuations

Discontinuations due to adverse clinical or laboratory experiences were reviewed, regardless of whether or not the subject initiated rescue therapy. Two placebo subjects and no sitagliptin subjects were discontinued due to clinical AEs. Two sitagliptin subjects and no placebo subjects discontinued due to laboratory AEs.

Table 21. P053: Discontinued subjects

Study #	AN	M/F	Age	Period*	Therapy	Onset day	AE
0530012	57202	F	75	A	Placebo	125	Upper limb fracture
0530021	57108	M	61	A: rescued	Placebo	96	Lymphoma
0530015	57059	M	54	B	Sitagliptin	169	Blood creatinine increased
0530018	57128	M	41	B	Sitagliptin	131	ALT increased

* Period A and B represent the 18- and 30-week data sets, respectively.

Source: P053 study report tables 12-11 and 12-12

Narratives for the 2 sitagliptin subjects are as follows:

- AN 57059: 54 year old male who experience increased serum creatinine (1.5 mg/dl) on day 169. On day 179, creatinine was 1.6 mg/dl. This met protocol-specified discontinuation criteria. Screening creatinine was 1.2 mg/dl. He discontinued study drug on day 199 and had serum creatinine of 1.4 mg/dl on day 200.
- AN 57128: 41 year old male who experienced increased ALT on day 131. Screening for CMV and hepatitis A and B were negative, although as shown below, he had elevated ALT levels at screening and randomization. He was treated with fluconazole from day -10 to 86 and day 113 to 120 for skin mycosis.

Table 22. P053: Subject AN 57128's ALT values (IU/L)

Screening	Day 1	Day 42	Day 84	Day 104	Day 131	3 d post-Rx	19 d post-Rx
45	117	86	131	119	162	141	119

When used with metformin, sitagliptin does not appear to increase the discontinuation rate.

7.3.4 Significant Adverse Events

The adverse events of special interest were hypoglycemia, gastrointestinal AEs, pancreatitis, and hypersensitivity.

Hypoglycemia: Symptomatic events assessed by the investigator as likely to be hypoglycemia were reported as AEs of hypoglycemia, regardless of whether a blood glucose determination was performed at the time.

Excluding data after initiation of glycemic rescue therapy, one sitagliptin subject experienced 2 episodes of hypoglycemia. Neither event required assistance. Both events were considered related to study drug and a skipped meal or snack. The 95% CI when compared to placebo is -3.0, 5.7 (p-value >0.999).

Including data after initiation of glycemic rescue, one subject in each of the placebo and sitagliptin groups experienced 2 events. The 95% CI was -4.8, 4.7 (p-value >0.999).

Gastrointestinal Adverse Events: The number and percentage of subjects with the pre-specified GI AES abdominal pain, diarrhea, nausea, and vomiting was similar between treatment groups, excluding data after initiation of glycemic rescue (see Table 23). Similar results were obtained when data after initiation of glycemic rescue was included.

Table 23. P053: Number (%) of subjects with selected GI AEs, excluding data after initiation of glycemic rescue

	Sitagliptin 100 mg (N = 96)		Placebo (N = 94)	
	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	9	(9.4)	7	(7.4)
Patients With No Adverse Experience	87	(90.6)	87	(92.6)
Gastrointestinal Disorders	9	(9.4)	7	(7.4)
Abdominal Pain Lower	1	(1.0)	0	(0.0)
Abdominal Pain Upper	1	(1.0)	0	(0.0)
Diarrhoea	5	(5.2)	5	(5.3)
Nausea	2	(2.1)	2	(2.1)
Vomiting	0	(0.0)	1	(1.1)
Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				

Source: P053 study report table 12-13

Pancreatitis: When study report P053 was searched for the term “pancreatitis”, only 1 event was identified. It was a secondary diagnosis in Table 14-7 (i.e. part of the past medical history). No events of pancreatitis occurred during study P053.

Hypersensitivity: One sitagliptin subject had a hypersensitivity event in the immune system disorder SOC (sitagliptin 1.0% vs. placebo 0.0%). Additional information was not provided.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 24 below shows the number and percentage of subjects with AEs by system organ class (SOC), excluding data after initiation of glycemic rescue. A similar percentage of subjects in each group experienced AEs (57.3% vs. 58.5%).

- SOCs with more events in the sitagliptin group:
 - o Infections and infestations (32.3% vs. 28.7%)
 - o Nervous system (15.6% vs. 9.6%)
 - o Musculoskeletal and connective tissue (12.5% vs. 8.5%)
 - o Cardiac (5.2% vs. 1.1%)
- SOCs with more events in the placebo group:
 - o Investigations (17.0% vs. 8.3%)
 - o Injury, poisoning, and procedural complications (8.5% vs. 5.2%)

However, there was no statistically significant difference in the rate of events by SOC. Only 1 event (increased blood glucose) occurred at a significantly different rate between groups; it was more common in placebo subjects (16.0% vs. 6.3%) (95% CI: -19.0, -0.7).

Cardiac disorders were more common in the sitagliptin group (n=5 [5.2%] vs. n=1 [1.1%]). This was mainly due to an increase in angina pectoris events (n=3 [3.1%] vs. n=0 [0.0%]). All other cardiac events were single events.

Table 24. P053: Number (%) of subjects with AEs by SOC, excluding data after initiation of glycemic rescue

	Sitagliptin 100 mg (N = 96)		Placebo (N = 94)	
	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	55	(57.3)	55	(58.5)
Patients With No Adverse Experience	41	(42.7)	39	(41.5)
Cardiac Disorders	5	(5.2)	1	(1.1)
Angina Pectoris	3	(3.1)	0	(0.0)
Bundle Branch Block Right	1	(1.0)	0	(0.0)
Coronary Artery Disease	1	(1.0)	0	(0.0)
Left Ventricular Dysfunction	1	(1.0)	0	(0.0)
Myocardial Ischaemia	1	(1.0)	1	(1.1)
Sick Sinus Syndrome	1	(1.0)	0	(0.0)
Ventricular Extrasystoles	1	(1.0)	0	(0.0)
Ear And Labyrinth Disorders	0	(0.0)	1	(1.1)
Vertigo	0	(0.0)	1	(1.1)
Eye Disorders	1	(1.0)	2	(2.1)
Foreign Body Sensation In Eyes	1	(1.0)	0	(0.0)
Glaucoma	0	(0.0)	1	(1.1)
Pterygium	0	(0.0)	1	(1.1)
Gastrointestinal Disorders	11	(11.5)	12	(12.8)
Abdominal Pain Lower	1	(1.0)	0	(0.0)
Abdominal Pain Upper	1	(1.0)	0	(0.0)
Aphthous Stomatitis	0	(0.0)	1	(1.1)
Dental Caries	0	(0.0)	1	(1.1)

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Infections And Infestations	31	(32.3)	27	(28.7)
Bronchitis	1	(1.0)	0	(0.0)
Cellulitis	2	(2.1)	0	(0.0)
Ear Infection	1	(1.0)	0	(0.0)
Fungal Skin Infection	2	(2.1)	0	(0.0)
Gastroenteritis	2	(2.1)	1	(1.1)
Gastroenteritis Viral	2	(2.1)	0	(0.0)
Helicobacter Gastritis	0	(0.0)	1	(1.1)
Influenza	1	(1.0)	3	(3.2)
Labyrinthitis	0	(0.0)	1	(1.1)
Malaria	1	(1.0)	0	(0.0)
Nasopharyngitis	7	(7.3)	6	(6.4)
Neurocysticercosis	0	(0.0)	1	(1.1)
Onychomycosis	0	(0.0)	1	(1.1)
Otitis Media	1	(1.0)	0	(0.0)
Parasitic Infection Intestinal	1	(1.0)	0	(0.0)
Periodontal Infection	1	(1.0)	0	(0.0)
Pharyngitis	4	(4.2)	6	(6.4)
Pharyngotonsillitis	3	(3.1)	1	(1.1)
Respiratory Tract Infection	0	(0.0)	2	(2.1)
Sinusitis	0	(0.0)	1	(1.1)
Tinea Pedis	4	(4.2)	2	(2.1)
Gastrointestinal Disorders	11	(11.5)	12	(12.8)
Diarrhoea	5	(5.2)	5	(5.3)
Enterocolitis	1	(1.0)	1	(1.1)
Gastritis	1	(1.0)	3	(3.2)
Gastrooesophageal Reflux Disease	0	(0.0)	1	(1.1)
Nausea	2	(2.1)	2	(2.1)
Toothache	1	(1.0)	1	(1.1)
Upper Gastrointestinal Haemorrhage	0	(0.0)	1	(1.1)
Vomiting	0	(0.0)	1	(1.1)
General Disorders And Administration Site Conditions	3	(3.1)	2	(2.1)
Asthemia	2	(2.1)	0	(0.0)
Non-Cardiac Chest Pain	0	(0.0)	2	(2.1)
Pyrexia	1	(1.0)	0	(0.0)
Hepatobiliary Disorders	2	(2.1)	1	(1.1)
Cholelithiasis	1	(1.0)	1	(1.1)
Hepatic Stenosis	1	(1.0)	1	(1.1)
Immune System Disorders	1	(1.0)	0	(0.0)
Hypersensitivity	1	(1.0)	0	(0.0)
Infections And Infestations	31	(32.3)	27	(28.7)
Acute Sinusitis	0	(0.0)	1	(1.1)
Acute Tonsillitis	1	(1.0)	0	(0.0)
Body Tinea	1	(1.0)	0	(0.0)

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Infections And Infestations	31	(32.3)	27	(28.7)
Tooth Abscess	1	(1.0)	0	(0.0)
Tooth Infection	1	(1.0)	1	(1.1)
Upper Respiratory Tract Infection	2	(2.1)	2	(2.1)
Urethritis	0	(0.0)	1	(1.1)
Urinary Tract Infection	4	(4.2)	3	(3.2)
Vaginal Infection	0	(0.0)	1	(1.1)
Viral Upper Respiratory Tract Infection	1	(1.0)	2	(2.1)
Injury, Poisoning And Procedural Complications	5	(5.2)	8	(8.5)
Back Injury	0	(0.0)	1	(1.1)
Contusion	0	(0.0)	1	(1.1)
Eye Injury	0	(0.0)	1	(1.1)
Foreign Body Trauma	1	(1.0)	0	(0.0)
Head Injury	0	(0.0)	1	(1.1)
Limb Injury	1	(1.0)	1	(1.1)
Multiple Injuries	1	(1.0)	0	(0.0)
Post-Traumatic Pain	1	(1.0)	1	(1.1)
Thermal Burn	0	(0.0)	1	(1.1)
Upper Limb Fracture	0	(0.0)	1	(1.1)
Wound	1	(1.0)	0	(0.0)
Investigations	8	(8.3)	16	(17.0)
Blood Glucose Increased	6	(6.3)	15	(16.0)
Investigations	8	(8.3)	16	(17.0)
Weight Decreased	0	(0.0)	1	(1.1)
Weight Increased	2	(2.1)	0	(0.0)
Metabolism And Nutrition Disorders	3	(3.1)	4	(4.3)
Hyperglycaemia	0	(0.0)	3	(3.2)
Hyperlipidaemia	2	(2.1)	0	(0.0)
Hypertriglyceridaemia	0	(0.0)	1	(1.1)
Hypoglycaemia	1	(1.0)	0	(0.0)
Musculoskeletal And Connective Tissue Disorders	12	(12.5)	8	(8.5)
Arthralgia	0	(0.0)	1	(1.1)
Arthritis	0	(0.0)	1	(1.1)
Back Pain	2	(2.1)	1	(1.1)
Chondritis	1	(1.0)	0	(0.0)
Exostosis	1	(1.0)	0	(0.0)
Gouty Arthritis	1	(1.0)	0	(0.0)
Musculoskeletal Chest Pain	1	(1.0)	2	(2.1)
Musculoskeletal Pain	1	(1.0)	1	(1.1)
Neck Pain	0	(0.0)	1	(1.1)
Osteoarthritis	1	(1.0)	0	(0.0)
Pain In Extremity	3	(3.1)	2	(2.1)
Rotator Cuff Syndrome	1	(1.0)	0	(0.0)
Tendonitis	1	(1.0)	1	(1.1)

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Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1	(1.0)	1	(1.1)
Adenocarcinoma Pancreas	0	(0.0)	1	(1.1)
Skin Papilloma	1	(1.0)	0	(0.0)
Nervous System Disorders	15	(15.6)	9	(9.6)
Diabetic Neuropathy	4	(4.2)	2	(2.1)
Dizziness	2	(2.1)	0	(0.0)
Facial Palsy	1	(1.0)	0	(0.0)
Headache	4	(4.2)	4	(4.3)
Neuralgia	1	(1.0)	0	(0.0)
Paraesthesia	1	(1.0)	0	(0.0)
Post-Traumatic Headache	0	(0.0)	1	(1.1)
Presyncope	0	(0.0)	1	(1.1)
Sciatica	0	(0.0)	1	(1.1)
Sensory Disturbance	0	(0.0)	1	(1.1)
Syncope	1	(1.0)	0	(0.0)
Tension Headache	1	(1.0)	1	(1.1)
Psychiatric Disorders	3	(3.1)	1	(1.1)
Depression	1	(1.0)	1	(1.1)
Insomnia	1	(1.0)	0	(0.0)
Panic Disorder	1	(1.0)	0	(0.0)
Reproductive System And Breast Disorders	2	(2.1)	0	(0.0)
Erectile Dysfunction	2	(2.1)	0	(0.0)
Respiratory, Thoracic And Mediastinal Disorders	3	(3.1)	0	(0.0)
Cough	1	(1.0)	0	(0.0)
Rhinitis Allergic	1	(1.0)	0	(0.0)
Sleep Apnoea Syndrome	1	(1.0)	0	(0.0)
Skin And Subcutaneous Tissue Disorders	3	(3.1)	2	(2.1)
Dermatitis	0	(0.0)	1	(1.1)
Dermatitis Contact	1	(1.0)	0	(0.0)
Intertrigo	1	(1.0)	0	(0.0)
Petechiae	0	(0.0)	1	(1.1)
Urticaria	1	(1.0)	1	(1.1)
Vascular Disorders	2	(2.1)	4	(4.3)
Flushing	0	(0.0)	1	(1.1)
Hypertension	2	(2.1)	3	(3.2)
Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				

Source: P053 study report table 12-8

7.4.2 Laboratory Findings

Overview of Laboratory Testing in P053: Standard safety laboratory data were obtained in all studies at baseline, during the treatment period, and at study end. The frequency of laboratory evaluations was as follows:

- Site fingerstick HbA1c: Visit 1
- Site fingerstick glucose: Weeks 0
- Meal tolerance test: Weeks 0 and 18
- FPG: Visits 1 and 3, and 4 and weeks -2, 0, 6, 12, 18, 24, and 30
- HbA1c: Visits 1 and 3 and weeks -1, 0, 6, 12, 18, 24, 30
- Complete blood count/differential: Visit 1 and weeks 0, 6, 12, 18, 24, and 30
- Chemistry: Visit 1 and weeks 0, 6, 12, 18, 24, and 30
- Lipid panel: Visit 1 and week -2, 0, 18, and 30
- TSH: Visit 1
- Dipstick urinalysis: Visit 1 and weeks 0, 18, and 30
- Urine pregnancy (for women of child bearing potential): Visits 1 and 3 and weeks -2, 0, 6, 12, 18, and 30
- Blood sample for archive: Weeks 0 and 30
- Blood sample for genetic analysis (if consented): Week 0

Analysis of Mean Change from Baseline: The mean (SE) change from baseline was similar for the sitagliptin and placebo groups for most laboratory parameters, as shown in Table 25. Small mean differences were seen. However, the general trends in these laboratory parameters were similar between sitagliptin and placebo and are not felt to be clinically significant.

Table 25. P053: Mean change (SE) from baseline to week 30 in laboratory parameters by treatment group, excluding data after initiation of glycemic rescue

Laboratory test	Sitagliptin	Placebo
Chemistry		
Alkaline phosphatase (IU/L)	-6.5 (1.6)	-1.2 (1.8)
ALT (IU/L)	2.4 (1.5)	-0.8 (1.1)
AST (IU/L)	1.0 (0.9)	-0.3 (0.9)
BUN (mg/dl)	0.2 (0.4)	0.4 (0.5)
Albumin (gm/dL)	0.1 (0.0)	0.0 (0.0)
Bicarbonate (mEq/L)	-0.9 (0.4)	-0.1 (0.4)
Calcium (mg/dL)	0.2 (0.1)	0.2 (0.1)
Chloride (mEq/L)	2.0 (0.4)	0.9 (0.4)
Creatinine (mg/dL)	0.0 (0.0)	0.0 (0.0)
Phosphorus (mg/dL)	-0.0 (0.1)	0.1 (0.1)

Potassium (mEq/L)	0.1 (0.0)	0.2 (0.1)
Sodium (mEq/L)	2.0 (0.4)	0.9 (0.4)
Total bilirubin (mg/dL)	-0.0 (0.0)	-0.0 (0.0)
Protein (gm/dL)	0.1 (0.1)	0.2 (0.1)
Uric acid (mg/dL)	0.5 (0.1)	0.3 (0.1)
Hematology		
WBCs (cells/microL)	76.0 (178.1)	-160.0 (220.1)
Absolute neutrophil count (ANC, cells/microL)	165.1 (173.9)	-101.8 (185.7)
Basophils (cells/microL)	-2.9 (2.2)	-1.9 (2.3)
Eosinophils (cells/microL)	0.6 (21.0)	-35.1 (21.3)
Hematocrit (%)	-0.2 (0.3)	-0.2 (0.3)
Hemoglobin (gm/dL)	-0.1 (0.1)	-0.1 (0.1)
Lymphocytes (cells/microL)	-96.3 (64.0)	-13.6 (71.9)
Mean corpuscular volume (fL)	0.9 (0.3)	0.7 (0.3)
Mean corpuscular hemoglobin (gm/dL)	-0.2 (0.1)	-0.0 (0.1)
Monocytes (cells/microL)	4.8 (12.7)	-2.9 (18.1)
Platelets (10^3 /microL)	-2.9 (4.2)	-3.3 (4.1)
RBCs (10^6 /microL)	-0.1 (0.0)	-0.1 (0.0)

Source: P053 study report tables 12-14, 12-15, and 14-83 to 14-107

As shown in Figure 5, a decrease from baseline in alkaline phosphatase was seen in the sitagliptin group by week 6. It decreased further by week 12 and then remained relatively stable. This is consistent with prior sitagliptin clinical trial findings. No subjects had an AE related to decreased alkaline phosphatase.

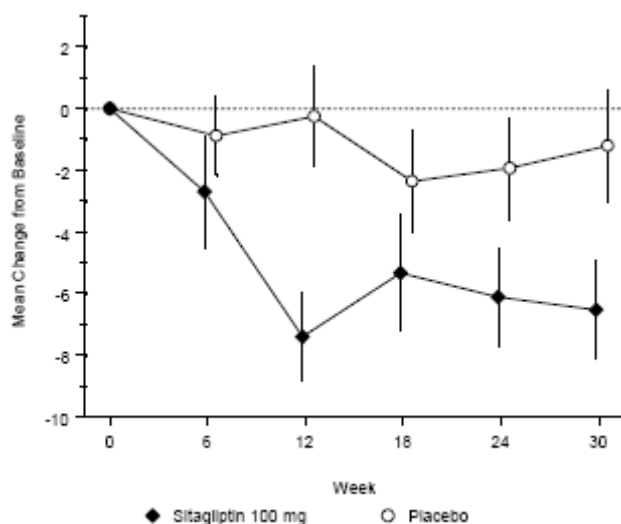


Figure 5. P053: Mean change from baseline in serum alkaline phosphatase (IU/L) by treatment group, excluding data after initiation of glycemic rescue

Source: P053 study report figure 12-2

As shown in Figure 6 and Figure 7 below, both mean ALT and AST increased from baseline in the sitagliptin group but decreased from baseline in the placebo group over the 30 week treatment period. ALT increased at week 12, peaked at week 18, and was then relatively stable until week 30. As the median changes were of a lesser magnitude (sitagliptin 1 IU/L, placebo 0 IU/L), the change from baseline in mean values is likely due to the following 5 outliers with ALT >100 IU/L. When these sitagliptin subjects were excluded, the mean change was smaller (0.5 IU/L). (See also Table 26. Note: The protocol exclude subjects with AST and/or ALT >2 times the upper limit of normal.)

- Subject 57172 (sitagliptin): At randomization, ALT was 76 IU/L with a normal AST. At week 12, ALT was 116 IU/L with AST 68 IU/L. At week 18, ALT was 91 IU/L and AST was 78 IU/L. At weeks 24 and 30, values returned to baseline. No cause was identified for the increase in ALT measurements.
- Subject 57146 (sitagliptin): At randomization, ALT was normal. At week 6, ALT was 43 IU/L with an unchanged AST. At week 18, ALT was 116 IU/L with AST 62 IU/L. Three days prior, the subject was diagnosed with malaria. The subject started carbamazepine on day 88 for diabetic neuropathy and chloroquine on day 135 for malaria. On day 157, ALT was 47 IU/L; it remained stable until study completion.
- Subject 57137 (sitagliptin): At randomization, ALT was 38 IU/L with normal AST. At week 18 when the subject was diagnosed with hepatic steatosis on ultrasound, ALT and AST were 92 and 66 IU/L, respectively. ALT and AST remained stable through week 24 and improved at week 30 (61 and 53 IU/L, respectively).
- Subject 57128 (sitagliptin): At randomization, ALT was 117 IU/L. It increased through the study and peaked at week 18 (162 IU/L), when the subject was discontinued. Hepatitis screening for CMV, hepatitis A and B were negative. After 19 days off medication, ALT was 119 IU/L, which was near baseline. The subject was treated with fluconazole from day -10 to 86 and from day 113 to 120 for mycosis.
- Subject 57242 (sitagliptin): At screening, ALT measurements were 99 and 88 IU/L. At randomization, ALT was 50 IU/L. At week 12, ALT was 118 IU/L with normal AST. The subject was then lost to follow up. No known cause for the ALT increases was reported.

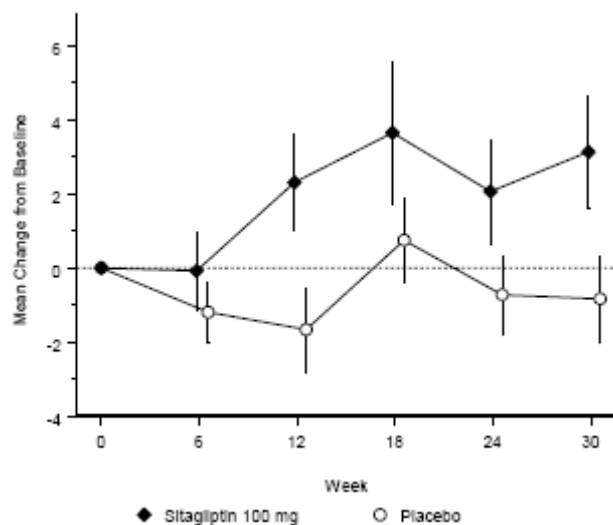


Figure 6. P053: Mean change from baseline in ALT (IU/L)

Source: P053 study report figure 12-3

Mean AST increased from at week 12, peaked at week 18, and then decreased at week 30. Unlike ALT though, the median and mean changes at weeks 18 and 30 were similar. Exclusion of the same 5 subjects resulted in a mean change from baseline in AST of 1.98 IU/L.

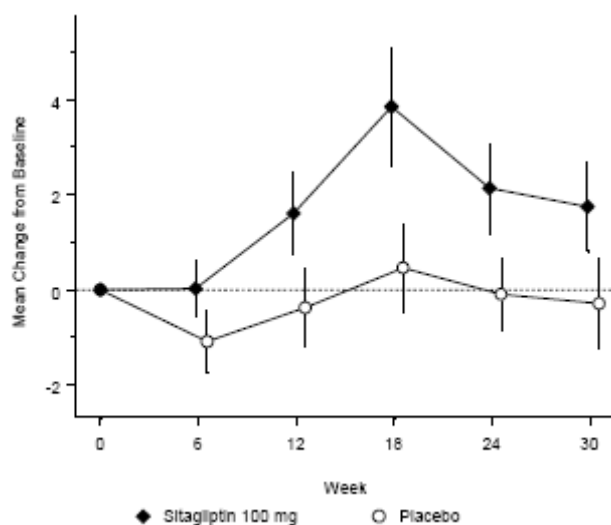


Figure 7. P053: Mean change from baseline AST (IU/L)

Source: P053 study report figure 12-4

Table 26. P053: Subjects with ALT >100 IU/L (repeat value[s])

Subject	Week	Screen	Random	6	12	18	24	30	Comment
	Visit	1	5	6	7	8	9	10	
57172	ALT	45	76	89	116	91	79	73	
	AST	29	39	52	68	78	41	33	
	T Bili	0.4	0.5	0.4	0.3	0.5	0.3	0.4	
57146	ALT	31	23	43	61	116 (47)	46	49	Malaria on day 129
	AST	29	25	26	48	62	41	46	
	T Bili	0.5	0.6	0.4	0.6	0.4	0.8	0.8	
57137	ALT	20	38	32	35	92	101	61	Hepatic steatosis wk 18
	AST	20	24	21	23	66	72	53	
	T Bili	0.4	0.3	0.3	0.4	0.4	0.3	0.3	
57128	ALT	45	117	86	131 (119)	147 (119-162)			Discontinued wk 18
	AST	19	44	36	43 (43)	61 (41-63)			
	T Bili	1.1	1.0	0.4	0.4	0.6 (0.6)			
57242	ALT	99 (88)	50	38	118				Lost to follow up Wk 12
	AST	44	22	22	42				
	T Bili	1.5 (1.0)	1.4	0.8	1.0				

An increase in WBC was observed in the sitagliptin group at week 6 and persisted to week 30, whereas a decrease in the placebo group was noted. No subjects had an AE related to increased absolute neutrophil count (ANC).

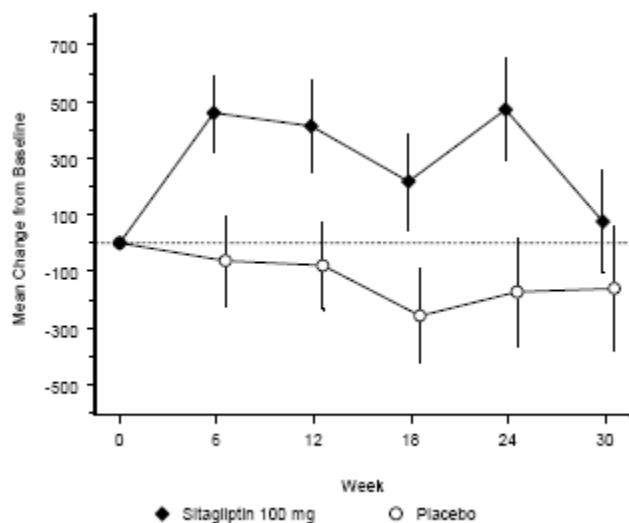


Figure 8. P053: Mean change from baseline in WBC (cells/microL)

Source: P053 study report figure 14-15.

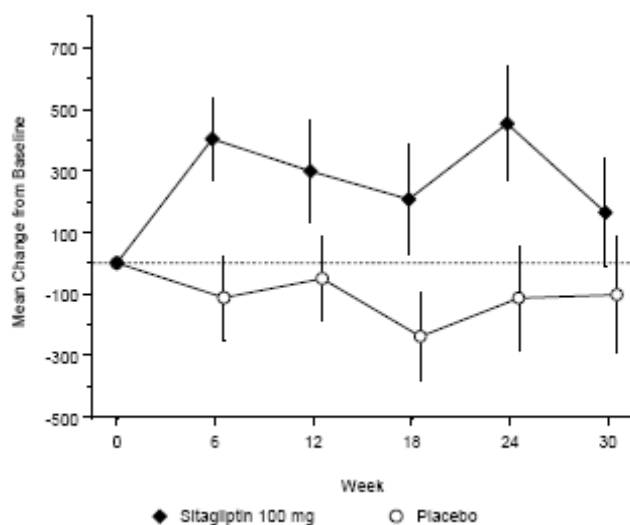


Figure 9. P053: Mean change from baseline in ANC (cells/microL)

Source: P053 study report figure 12-5.

The trends in eosinophils, lymphocytes, and monocytes were similar between sitagliptin and placebo and are felt to not be clinically significant.

Analysis using the Predefined Limits of Change: The PDLC from baseline and the number (%) of subjects who met the criteria, excluding data after initiation of glycemic therapy, are shown in Table 27. The sponsor's PDLC are acceptable.

Table 27. P053: Subjects meeting PDLC for selected laboratory parameters, excluding data after initiation of glycemic rescue

Lab Test	Predefined Limits of Change [†]	Treatment Group	n/N (%)	Difference with Placebo % (95% CI) [‡]
Hemoglobin (gm/dL)	Last value with a decrease ≥ 1.5 g/dL	Sitagliptin 100 mg Placebo	7/ 95 (7.4) 1/ 91 (1.1)	6.3 (0.1, 13.4)
WBC Count (10^3 /microL)	One value with a decrease $\geq 50\%$ and value $< LLN$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 2/ 91 (2.2)	-2.2
	One value with an increase $\geq 20\%$ and value $> ULN$	Sitagliptin 100 mg Placebo	3/ 95 (3.2) 0/ 91 (0.0)	3.2
	Last value with a decrease $\geq 50\%$ and value $< LLN$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 91 (0.0)	0.0
	Last value with an increase $\geq 20\%$ and value $> ULN$	Sitagliptin 100 mg Placebo	1/ 95 (1.1) 0/ 91 (0.0)	1.1
Platelet Count (10^3 /microL)	One value with a decrease $\geq 25\%$ and value $< LLN$	Sitagliptin 100 mg Placebo	1/ 95 (1.1) 0/ 91 (0.0)	1.1
	One value with an increase $\geq 100\%$ and value $> ULN$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 91 (0.0)	0.0
	Last value with a decrease $\geq 25\%$ and value $< LLN$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 91 (0.0)	0.0
	Last value with an increase $\geq 100\%$ and value $> ULN$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 91 (0.0)	0.0

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BUN (mg/dL)	Last value with an increase $\geq 50\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 1/ 92 (1.1)	-1.1
Serum Creatinine (mg/dL)	Last value with an increase $\geq 0.3 \text{ mg/dL}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0
Total Bilirubin (mg/dL)	One value with an increase $\geq 50\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	1/ 95 (1.1) 1/ 92 (1.1)	-0.0
	Last value with an increase $\geq 50\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 1/ 92 (1.1)	-1.1
AST (IU(aminotransferase)/L)	One value with an increase $> 100\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	5/ 95 (5.3) 1/ 92 (1.1)	4.2 (-1.5, 10.7)
	One value with an increase $> 200\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	2/ 95 (2.1) 0/ 92 (0.0)	2.1
	One value with an increase $> 400\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0
	Last value with an increase $> 100\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	2/ 95 (2.1) 1/ 92 (1.1)	1.0
	Last value with an increase $> 200\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	1/ 95 (1.1) 0/ 92 (0.0)	1.1
	Last value with an increase $> 400\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0
ALT (IU(aminotransferase)/L)	One value with an increase $> 100\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	9/ 95 (9.5) 2/ 92 (2.2)	7.3 (0.3, 15.0)
	One value with an increase $> 200\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	4/ 95 (4.2) 2/ 92 (2.2)	2.0 (-3.9, 8.4)
	One value with an increase $> 400\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	2/ 95 (2.1) 0/ 92 (0.0)	2.1
	Last value with an increase $> 100\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	5/ 95 (5.3) 1/ 92 (1.1)	4.2 (-1.5, 10.7)
	Last value with an increase $> 200\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	2/ 95 (2.1) 1/ 92 (1.1)	1.0
	Last value with an increase $> 400\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0

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AST or ALT	One value with an increase > 100% and value > ULN	Sitagliptin 100 mg Placebo	10/ 95 (10.5) 3/ 92 (3.3)	7.3 (-0.3, 15.3)
	One value with an increase > 200% and value > ULN	Sitagliptin 100 mg Placebo	4/ 95 (4.2) 2/ 92 (2.2)	2.0 (-3.9, 8.4)
	One value with an increase > 400% and value > ULN	Sitagliptin 100 mg Placebo	2/ 95 (2.1) 0/ 92 (0.0)	2.1
	Last value with an increase > 100% and value > ULN	Sitagliptin 100 mg Placebo	6/ 95 (6.3) 2/ 92 (2.2)	4.1 (-2.2, 11.1)
	Last value with an increase > 200% and value > ULN	Sitagliptin 100 mg Placebo	2/ 95 (2.1) 1/ 92 (1.1)	1.0
	Last value with an increase > 400% and value > ULN	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0
(AST or ALT) + Total Bilirubin	Consecutive or last value meeting (AST > 3*ULN or ALT > 3*ULN) with Bilirubin > 2*ULN	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0
	One value meeting (AST > 3*ULN or ALT > 3*ULN) with Bilirubin > 2*ULN	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0
Alkaline Phosphatase (mu/dL)	One value with an increase >= 50% and value > ULN	Sitagliptin 100 mg Placebo	4/ 95 (4.2) 1/ 92 (1.1)	3.1 (-2.3, 9.3)
	Last value with an increase >= 50% and value > ULN	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0
Serum Uric Acid (mg/dL)	One value with an increase >= 50% and value > ULN	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 1/ 92 (1.1)	-1.1
Serum Sodium (mEq(Na)/L)	Last value with a decrease >=10 mEq/L and value < LLN	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 1/ 92 (1.1)	-1.1
	Last value with an increase >= 10 mEq/L and value > ULN	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0
Serum Potassium (mEq(K)/L)	Last value with a decrease >= 1.0 mEq/L and value < LLN	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0
	Last value with an increase >= 1.0 mEq/L and value > ULN	Sitagliptin 100 mg Placebo	1/ 95 (1.1) 0/ 92 (0.0)	1.1
Serum Calcium (mg/dL)	Last value with a decrease >= 1.0 mg/dL and value < LLN	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 92 (0.0)	0.0
	Last value with an increase >= 1.0 mg/dL and value > ULN	Sitagliptin 100 mg Placebo	3/ 95 (3.2) 2/ 92 (2.2)	1.0

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Neutrophil Count ($10^3/\text{microL}$)	One value with a decrease $\geq 20\%$ and value $< \text{LLN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 1/ 91 (1.1)	-1.1
	One value with an increase $\geq 20\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	5/ 95 (5.3) 1/ 91 (1.1)	4.2 (-1.5, 10.7)
	Last value with a decrease $\geq 20\%$ and value $< \text{LLN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 91 (0.0)	0.0
	Last value with an increase $\geq 20\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	1/ 95 (1.1) 0/ 91 (0.0)	1.1
Lymphocyte Count ($10^3/\text{microL}$)	One value with a decrease $\geq 20\%$ and value $< \text{LLN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 91 (0.0)	0.0
	One value with an increase $\geq 20\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 91 (0.0)	0.0
	Last value with a decrease $\geq 20\%$ and value $< \text{LLN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 91 (0.0)	0.0
	Last value with an increase $\geq 20\%$ and value $> \text{ULN}$	Sitagliptin 100 mg Placebo	0/ 95 (0.0) 0/ 91 (0.0)	0.0
[†] Increases or decreases are relative to baseline; last value = last on-treatment value in the study. [§] CI = Confidence interval computed using the Wilson score method; 95% CI computed only for those criteria with 4% incidence in one or more treatment group. LLN = Lower limit of normal; ULN = Upper limit of normal.				

Source: P053 study report table 14-137

The percentage of subjects meeting the PDLC was similar between the sitagliptin and placebo groups, except in the following categories which had a between-group difference $\geq 3\%$:

- Hemoglobin: Last value with a decrease ≥ 1.5 g/dl (7.4% vs. 1.1%). The 6.3% difference was significant (95% CI 0.1, 13.4)
- WBC: One value with an increase $\geq 20\%$ and value $\geq$ ULD (3.2% vs. 0.0%)
- AST: One value with an increase $> 100\%$ and value $>$ ULN (5.3% vs. 1.1%)
- ALT
 - o One value with an increase $>100\%$ and value $>$ ULN (9.5% vs. 2.2%). The 7.3% difference was statistically significant (95% CI 0.3, 15.0).
 - o Last value with an increase $>100\%$ and value $>$ ULN (5.3% vs. 1.1%)
- AST or ALT:
 - o One value with an increase $>100\%$ and value $>$ ULN (10.5% vs. 3.3%)
 - o Last value with an increase $>100\%$ and value $>$ ULN (6.3% vs. 2.2%)
- Alkaline phosphatase: One value with an increase $\geq 50\%$ (4.2% vs. 1.1%)
- Neutrophil count: One value with an increase $\geq 20\%$ and value $>$ ULN (5.3% vs. 1.1%)

A statistically significant difference between treatment groups was seen with only two of the PDLC criteria (hemoglobin and ALT). A labeled safety risk of metformin is anemia. In the sitagliptin/metformin XR label, the sponsor proposes a warning to “measure hematologic parameters annually” consistent with the metformin PI. This recommendation is listed under Warnings in the Glumetza label. The PDLC for ALT was $>100\%$ and value $>$ ULN. However, a significant change in liver function tests (ALT or AST) was not seen with increases $>200\%$ or 400% . The sponsor proposes labeling which contains a warning against using Janumet XR in patients with hepatic disease and use of excessive alcohol intake, also consistent with the metformin PI. This is acceptable.

Laboratory Adverse Events: More sitagliptin subjects experienced laboratory AEs than placebo subjects (15.6% vs. 4.3%). All laboratory AEs occurred as single events in the sitagliptin group, except for hemoglobin decreased (n=4), blood triglycerides increased (n=2), and blood uric acid increased (n=2). In addition, the pre-specified analysis of 95% CI for the between-group differences in the incidence of specific laboratory AEs was negative (i.e. no between-group differences excluded zero).

Table 28. P053: Number (%) of subjects with specific laboratory AEs by laboratory test category, excluding data after initiation of glycemic rescue

	Sitagliptin 100 mg (N=96)		Placebo (N=94)	
	n/m	(%)	n/m	(%)
Patients with one or more adverse experiences	15/96	(15.6)	4/92	(4.3)
Patients with no adverse experiences	81/96	(84.4)	88/92	(95.7)
Blood Chemistry Test	8/96	(8.3)	3/92	(3.3)
Alanine aminotransferase increased	1/95	(1.1)	1/92	(1.1)
Blood bicarbonate decreased	1/95	(1.1)	0/92	(0.0)
Blood cholesterol increased	1/91	(1.1)	0/86	(0.0)
Blood creatinine increased	1/95	(1.1)	0/92	(0.0)
Blood sodium decreased	0/95	(0.0)	1/92	(1.1)
Blood triglycerides increased	2/91	(2.2)	1/86	(1.2)
Blood uric acid increased	2/95	(2.1)	0/92	(0.0)
Fasting blood glucose increased	0/96	(0.0)	2/92	(2.2)
Hematology Laboratory Test	6/95	(6.3)	0/91	(0.0)
Eosinophil count increased	1/95	(1.1)	0/91	(0.0)
Haemoglobin decreased	4/95	(4.2)	0/91	(0.0)
Platelet count increased	1/95	(1.1)	0/91	(0.0)
Urinalysis Test	1/41	(2.4)	1/35	(2.9)
Bacteria urine identified	1/22	(4.5)	0/17	(0.0)
Creatinine renal clearance decreased	0/1	(0.0)	1/4	(25.0)
† indicates there was no associated laboratory test or there were no patients for whom the laboratory test was recorded postbaseline.				
n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.				
Although a patient may have had two or more laboratory adverse experiences, the patient is counted only once in a category.				
The same patient may appear in different categories.				
This table was run using a "percent incidence". This means that a row will appear on this report only if one of the columns is greater than or equal to that percentage, after rounding				

Source: P053 study report table 12-9

Summary: Standard safety laboratory data were obtained at appropriate time points in study P053. The mean (SE) change from baseline were similar for the sitagliptin and placebo groups for most laboratory parameters, although small differences were seen as shown in Table 29.

Table 29. P053: Summary of key mean (SE) changes in laboratory data from baseline

Laboratory	Sitagliptin	Placebo
Alkaline phosphatase (IU/L)	-6.5 (1.6)	-1.2 (1.8)
ALT (IU/L)	2.4 (1.5)	-0.8 (1.1)
AST (IU/L)	1.0 (0.9)	-0.3 (0.9)
WBCs (cells/microL)	76.0 (178.1)	-160.0 (220.1)
Absolute neutrophil count (ANC, cells/microL)	165.1 (173.9)	-101.8 (185.7)
Eosinophils (cells/microL)	0.6 (21.0)	-35.1 (21.3)

Lymphocytes (cells/microL)	-96.3 (64.0)	-13.6 (71.9)
Monocytes (cells/microL)	4.8 (12.7)	-2.9 (18.1)

However, the general trends in these laboratory parameters were similar between sitagliptin and placebo and are felt to not be clinically significant.

The sponsor's PDLC were acceptable. The percentage of subjects meeting the PDLC was similar between the sitagliptin and placebo groups, except in the following categories which had a difference $\geq 3\%$: hemoglobin, WBC, AST, ALT, alkaline phosphatase, and neutrophil count. However, only two of the PDLC criteria's (hemoglobin and ALT) 95% CIs excluded zero. The sponsor proposes a warning to "measure hematologic parameters annually". The sponsor also proposes labeling which contains a warning against using Janumet XR in patients with hepatic disease and use of excessive alcohol intake. This is acceptable.

More sitagliptin subjects experienced laboratory AEs than placebo subjects (15.6% vs. 4.3%). All laboratory AEs occurred as single events in the sitagliptin group, except for hemoglobin decreased (n=4), blood triglycerides increased (n=2), and blood uric acid increased (n=2). In addition, the pre-specified analysis of 95% CI for the between-group differences in the incidence of specific laboratory AEs was negative (i.e. no between-group differences excluded zero).

7.4.3 Vital Signs

The mean changes from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were generally small and similar between the sitagliptin and placebo treatment groups (see Table 30). The largest change from baseline was the decrease in mean SBP from baseline in the placebo group (-3.2 mm Hg).

Table 30. P053: Change from baseline in mean blood pressure and heart rate at week 30

Vital sign	Sitagliptin	Placebo
Systolic blood pressure (mm Hg)	-0.7 (1.6)	-3.2 (2.3)
Diastolic blood pressure (mm Hg)	0.5 (0.9)	1.0 (1.5)
Heart rate (bpm)	0.1 (1.0)	-0.4 (1.6)

Source: P053 study report tables 12-20, 12-21, and 12-22

At this time, I do not believe the changes in SBP, DBP, and HR are clinically relevant. Furthermore, the sponsor 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 metformin. Its planned completion date is December 2014.

7.4.4 Electrocardiograms (ECGs)

Study P053: Subjects who had a clinically significant ECG abnormality, which in the opinion of the investigator exposed them to risk, were excluded from study P053. When the study report was searched with the terms “electrocardiogram” and “ECG”, four events were identified as secondary diagnoses in table 14-7 (i.e. events that were part of the past medical history and did not occur in study P053), but no ECG-events were observed during the study. Thus, there is no signal for ECG abnormalities in study P053.

Prior Thorough QT (tQT) Studies and Commitments: As described in Dr. Ilan Irony’s original review of sitagliptin NDA 21-995, in tQT study P032, 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.

As described in Dr. Irony’s review of sitagliptin/metformin IR FDC NDA 22-044, ECG assessments were conducted in studies P024 and P036. Review of these data supported the approval of sitagliptin/metformin IR FDC.

As 1) a negative tQT study was conducted with sitagliptin and 2) metformin XR’s C_{max} and T_{max} are lower and the AUC is comparable to metformin IR, a tQT study of sitagliptin/metformin XR FDC is not necessary to support the NDA.

Please also refer to my comments in the section above which pertain to the planned CV study TECOS.

7.4.5 Special Safety Studies/Clinical Trials

As there were no additional completed or ongoing studies of sitagliptin/metformin XR at the time the four-month safety update was submitted, the sponsor submitted the following three sitagliptin/metformin IR clinical study reports:

- Protocol 66: A Phase III Randomized, Active-Comparator (Pioglitazone) Controlled Clinical Trial to Study the Efficacy and Safety of MK-0431A (A Fixed-Dose Combination Tablet of Sitagliptin and Metformin) in Patients With Type 2 Diabetes Mellitus
- Protocol 68: A Phase III Randomized, Active-Comparator (Pioglitazone) Controlled Clinical Trial to Study the Efficacy and Safety of Sitagliptin and MK-0431A (A Fixed-Dose Combination Tablet of Sitagliptin and Metformin) in Patients With Type 2 Diabetes Mellitus
- Protocol 79: A Phase III Randomized, Active-Comparator (Metformin) Controlled, Clinical Trial to Study the Efficacy and Safety of MK-0431A in Patients with Type 2 Diabetes Mellitus

The adverse events described in the sitagliptin/metformin IR studies above are consistent with our current understanding of sitagliptin, metformin, and pioglitazone. Thus, the study reports did not change my assessment of the risk/benefit ratio of the sitagliptin/metformin XR FDC.

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 between treatment groups (sitagliptin 32.5% vs. placebo 28.7%).

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. In such cases, it is advised that the patient promptly stop sitagliptin, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. The sponsor proposes similar language in the sitagliptin/metformin XR FDA label, which is acceptable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Study P053 only evaluated sitagliptin 100 mg daily versus placebo when added to metformin monotherapy.

Previous clinical experience with metformin has shown that gastrointestinal AEs (e.g. nausea, abdominal pain, and diarrhea) are dose-proportional.

7.5.2 Time Dependency for Adverse Events

Please refer to section 7.4.2 Laboratory Findings for a discussion about time-related changes in laboratory parameters.

There was no time dependency for AEs in study P053.

7.5.3 Drug-Demographic Interactions

No difference in the rate of AEs in different demographic subgroups was detected during my review of study P053.

Consistent with the metformin label however, the sponsor proposes the following in the sitagliptin/metformin XR FDC label, *Treatment of the elderly should be accompanied by careful monitoring of renal function.* (b) (4)

[REDACTED]

7.5.4 Drug-Disease Interactions

Consistent with the diabetic population enrolled, the majority of subjects in P053 had concomitant hypertension, hyperlipidemia, and obesity. I detected no significant exacerbation of concomitant medical conditions during my review of study P053. However, as noted above, subjects with renal impairment are at higher risk for lactic acidosis when using metformin. Thus, the sponsor proposes the following appropriate contraindication: *Renal dysfunction (e.g. serum creatinine ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females], or abnormal creatinine clearance.*

7.5.5 Drug-Drug Interactions

Metformin and sitagliptin have not been shown to affect the PK of each other.

As shown in Table 31, all of the subjects in study P053 were on at least one concomitant medication. No trend toward increased AEs was noted with any specific drug group.

Table 31. P053: Number (%) of subjects with concomitant medications (incidence >5% in one or more treatment groups) including data after initiation of glycemic rescue

Drug class	Sitagliptin (n=96)	Placebo (n=94)
Subjects with ≥ 1 concomitant medications	96 (100)	94 (100)
Drugs for acid related disorders	17 (17.7)	11 (11.7)
Drugs used in diabetes	96 (100)	94 (100)
Vitamins	4 (4.2)	9 (9.6)
Antibacterials for systemic use	20 (20.8)	23 (24.5)
Antimycotics for systemic use	6 (6.3)	3 (3.2)
Antianemic preparations	6 (6.3)	1 (1.1)
Agents acting on the renin-angiotensin system	45 (46.9)	43 (45.7)
Antihypertensives	3 (3.1)	5 (5.3)

Beta blocking agents	11 (11.5)	13 (13.8)
Calcium channel blockers	6 (6.3)	8 (8.5)
Cardiac therapy	1 (1.0)	5 (5.3)
Lipid modifying agents	41 (42.7)	35 (37.2)
Urologicals	6 (6.3)	3 (3.2)
Anti-inflammatory and antirheumatic products	16 (16.7)	17 (18.1)
Analgesics	49 (49.0)	49 (50.0)
Antiepileptics	13 (13.5)	13 (13.8)
Psychoanaleptics	4 (4.2)	6 (6.4)
Antihistamines for systemic use	11 (11.5)	6 (6.4)
Cough and cold preparations	7 (7.3)	9 (9.6)
Corticosteroids for systemic use	5 (5.2)	2 (2.1)
Thyroid therapy	6 (6.3)	7 (7.4)

Source: P053 study report table 14-9

Please refer to the Janumet label for information on drug interactions. The sponsor proposes similar language for the sitagliptin/metformin XR FDC label.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No animal studies have been conducted with the combined products in sitagliptin/metformin XR FDC (Janumet XR) or sitagliptin/metformin IR FDC (Janumet) to evaluate carcinogenicity or mutagenesis. Please refer to the Janumet label for full details. The sponsor proposes similar language for the Janumet XR label, which is acceptable.

7.6.2 Human Reproduction and Pregnancy Data

No animal studies have been conducted with the combined products in sitagliptin/metformin XR FDC or sitagliptin/metformin IR FDC to evaluate impairment of fertility.

Sitagliptin/metformin IR FDC is pregnancy category B. There are no adequate and well-controlled studies in pregnant women or its individual components. Therefore, the safety of Janumet in pregnant women is not known. Similarly, there are no studies in lactating animals with the combined components, although both sitagliptin and metformin are individually secreted in the milk of lactating rats. It is not known if sitagliptin is excreted in human milk.

No pregnancies were reported during study P053. The sponsor proposes pregnancy and nursing mother labeling language that is similar to that for the sitagliptin/metformin IR FDC. This is acceptable.

7.6.3 Pediatrics and Assessment of Effects on Growth



Table 32. Relevant tablet sizes

Sitagliptin/Metformin XR FDC Tablet			
Strength (mg)	50/500	50/1000	100/1000
Size (mm)	20.5 x 10.2	21.9 x 11.0	22.2 x 11.2

Sitagliptin Tablet			
Strength (mg)	25	50	100
Size (mm)	6.12 x 2.74	7.87 x 3.30	9.78 x 4.15

Metformin XR Tablet	
Strength (mg)	500
Size (mm)	10 x 18

Source: December 23, 2010 submission

The sponsor is currently conducting pediatric studies of sitagliptin and sitagliptin/metformin IR FDC, which it plans to make available for pediatric patients. Please refer to my reviews of studies protocol 083 *A phase 3, multicenter, double blind, randomized, placebo and active controlled clinical trial to evaluate the safety and efficacy of sitagliptin in pediatric patients with T2DM and inadequate glycemic control* and protocol 170 *A phase 3, multicenter, double blind, randomized, placebo controlled clinical trial to evaluate the safety and efficacy of MK-0431A (a FDC tablet of sitagliptin and metformin) in pediatric patients with T2DM*, which were submitted in IND 65,495

serial document numbers (SDNs) 530, 536, and 544 and IND 70,934 SDNs 185, 187, and 191.

The Pediatric Review Committee (PeRC) recently reviewed another DPP-4 inhibitor/metformin XR FDC (i.e. saxagliptin/metformin XR FDC NDA 200-678) and decided to waive pediatric studies in subjects 0–9 years but to impose studies in subjects 10-16 years.

Given this precedent, and the possibility that Janumet XR will be used in children more often than Janumet immediate release, the same should be required of sitagliptin/metformin XR FDC. A request was sent to the sponsor in the 74 day letter to propose a pediatric study plan, which may incorporate ongoing studies P083 and P170.

On December 23, 2010, the sponsor submitted a revised pediatric development plan. It included a waiver for subjects aged 0-9 years because “necessary studies are impossible or highly impractical” (e.g. the number of patients is so small or the patients are geographically dispersed). The sponsor plans to defer studies in subjects aged 10-17 years until the safety and efficacy of Janumet has been established in this population. If the results of study P170 (expected in 2016) demonstrate that a FDC of sitagliptin/metformin is not appropriate for pediatric use, development of sitagliptin/metformin XR will not be initiated and labeling will be proposed to reflect this limitation of use.

(b) (4)



(b) (4)



(b) (4)

Although P170 will complete in 2016, submission of an sNDA for the use of Janumet in pediatric patients will not occur until P083 has completed because the longer term safety data from the Januvia study will also support the use of Janumet in this pediatric population. P083 is to complete in 4Q18. Thus, according to the sponsor, the swallowability and PK studies of sitagliptin/metformin XR can be initiated after the completion of P170 and still be completed by the time all of the data in pediatric T2DM subjects is to be submitted to FDA in 2Q19.

However, after lengthy discussions with Pediatric Planning Committee (PePC) in preparation for the June 8, 2011 PeRC meeting, I recommend the following two studies rather than the sponsor-proposed (b) (4), as they are consistent with other recent PREA-related PMRs and lessen the required bridging between NDAs.

- A single dose pharmacokinetic study of Janumet XR in pediatric patients 10 through 17 years (inclusive) of age with T2DM. As part of this study the sponsor will evaluate whether pediatric patients can safely swallow the Janumet XR tablets. At least 30% of randomized subjects will be 10-14 years.
- A (b) (4) week, randomized, double-blind placebo-controlled trial to evaluate the efficacy and safety of Janumet XR vs. metformin (immediate and/or extended release) in pediatric T2DM patients who are inadequately controlled. As part of this study, the sponsor must evaluate whether pediatric patients can safely swallow Janumet XR. At least 30% of randomized subjects will be 10-14 years. At least 1/3 and not more than 2/3 of the patients in either age subset (10-14, 15-17 years) will be female.

My proposal will be discussed with PeRC on June 8, 2011.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose was reported in study P053. In phase 1 studies, single sitagliptin doses of 800 mg or 10 days dosing with 600 mg daily were well tolerated in healthy volunteers. Please refer to the sitagliptin/metformin IR FDC label. The sponsor proposes similar language for this NDA, which is acceptable.

7.7 Additional Submissions / Safety Issues

The applicant proposed the trade name Janumet XR for this sitagliptin/metformin XR FDC tablet. Discussions are currently ongoing between the sponsor and the Division of

Medication Error and Prevention Analysis (DMEPA) regarding an acceptable trade name, given the related names of previously approved drug products.

8 Postmarket Experience

As described in section 2.3 Availability of Proposed Active Ingredient in the United States, sitagliptin and metformin XR have been available in the US since 2006 and 2000, respectively. The important safety issues associated with each drug are listed in section 2.4. The sponsor last submitted a Periodic Update Safety Report (PSUR) for related sitagliptin/metformin IR NDA 22044 on September 28, 2010.

On March 19, 2010, the sponsor submitted a safety labeling change supplement to the sitagliptin and sitagliptin/metformin NDAs 21-995 and 22-044. The sponsor proposed adding “worsening renal function, including acute renal failure (sometimes requiring dialysis)” in section 6.2 Postmarketing Experience and corresponding text in the MG. After discussions with the sponsor and OSE, a revised prescribing information (PI) and MG were submitted on February 4, 2011. It includes the following Highlights Warning and Precaution, *There have been postmarketing reports of acute renal failure, sometimes requiring dialysis. Before initiating JANUMET and at least annual thereafter, assess renal function and verify as normal.* Section 5.4 Assessment of Renal Function was also revised to include similar wording. The sponsor should align the Janumet XR PI and MG with the February 4, 2011 Janumet NDA 22-044 submission, as it will likely be accepted.

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

Please refer to the following sections of this review for my labeling recommendations:

- 7.4.2 Laboratory Findings
- 7.4.6 Immunogenicity
- 7.5.3 Drug-Demographic Interactions
- 7.5.4 Drug-Disease Interactions
- 7.5.5 Drug-Drug Interactions
- 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

At the time of review finalization, label negotiations were still ongoing with the applicant. As the RLD for this sitagliptin/metformin XR NDA is Glumetza (NDA 21-748) and this differs from the metformin IR used in Janumet NDA 22-044, the applicant was recently advised to submit sitagliptin/metformin XR labeling that is separate and independent of sitagliptin/metformin IR (Janumet).

9.3 Advisory Committee Meeting

Not applicable.

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
05/31/2011

ILAN IRONY
05/31/2011

I concur with Dr. Pratt's review. Please see the CDTL review.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Applicant: Merck

Stamp Date: 9-23-10

NDA/BLA Type: Standard

Sitagliptin/metformin XR

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.	x			
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	Only 1 new clinical study
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	Only 1 new clinical study
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?				505b2 – Sitagliptin & Glumetza
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)? Study Number: Study Title: Sample Size: Arms: Location in submission:	x			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:	x			Clinical study P053

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
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 arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	
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			Including postmarketing data.
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?		x		I could not locate this.
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			

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).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement (b) (4)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
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 (<i>e.g.</i> , 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			
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			
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			
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.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement (b) (4)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

1. Please state the location within the application where the coding dictionary used for mapping investigator verbatim terms to preferred terms is located. If it was not previously submitted, please submit it.
2. In tabular format, please clarify the metformin formulations used in each of the 7 clinical trials submitted. Please include whether or not the metformin was immediate or sustained release.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA 202-270: Sitagliptin/metformin XR FDC

Filing Meeting: November 3, 2010

Clinical Reviewer: Valerie Pratt, M.D.

Overview

Merck has submitted this new drug application (NDA) for the use of sitagliptin/extended release metformin fixed dose combination (sita/met XR FDC, MK-0431A XR) (Janumet® XR) as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). The sponsor has developed a FDC of sitagliptin and metformin XR in the following tablet strengths:

- 50/500 mg to be given as 2 tablets once daily (QD)
- 50/1000 mg to be given as 2 tablets QD
- 100/1000 mg to be given as 1 tablet QD

Important Safety Issues

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 metformin include the following:

- Risk of lactic acidosis, which increases with sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure
- Contraindication in patients with renal dysfunction (e.g. serum creatinine ≥ 1.5 mg/dl [males], ≥ 1.4 mg/dl [females] or abnormal creatinine clearance)
- Use with intravascular iodinated contrast materials or excessive alcohol intake, when hypoxic, and when undergoing surgery
- Hypersensitivity
- Decrease in vitamin B12 levels and associated anemia
- Hypoglycemia, especially in the elderly and debilitated patients when caloric intake is deficient or during concomitant use of other glucose-lowering agents (e.g. SU and insulin) or alcohol
- Hyperglycemia, during times of stress

Presubmission Regulatory Activities

The sita/met XR FDC IND 101,964 was opened May 2, 2008. The request for an end of phase 2 (EOP2) meeting was denied, although the sponsor's questions were answered via letter on March 5, 2009. The key points communicated were as follows:

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

- No additional preclinical studies with the XR formulation are required, although support for any differences in the impurity/degradant profile of the new formulation were requested
- The sponsor should provide metformin pharmacokinetic (PK) comparability or clinical equivalency data between sita/met XR FDC and Janumet
- The following clinical pharmacology components are required to support registration:
 - Completed FDC probe formulation biocomparison study-fed
 - Definitive bioequivalence (BE) study (treatment may be administered with morning meal)
 - Multiple dose safety, tolerability, and PK study with sita/met XR FDC tablets
 - Food-effect study with a high fat meal, using only the highest doses of each of the respective components (i.e. 100/2000 mg)
 - Sitagliptin/metformin drug-drug interaction study
 - Dosage form equivalence study comparing 2 tablets of 50/500 mg and 1 tablet of 100/1000 mg
 - Biowaiver request for the 50/1000 mg dose
 - Metformin PK comparability or clinical equivalency data described above
- Glumetza is the appropriate comparator for the BE study

The May 10, 2010 pre-NDA meeting was cancelled because our preliminary meeting comments adequately addressed the sponsor's questions. Key responses were as follows:

- The agency concurred that sufficient data are available to support bridging between Glumetza (a metformin reference for the sita/met XR FDC) and a generic metformin formulation (a metformin reference for Janumet)
- The agency concurred that the biowaiver requirements for the 50/1000 mg tablet strength was met.
- In addition to the phase 1 clinical pharmacology studies listed in the background package and the references to the Glumetza product label and Janumet NDA, the sponsor should address the dose-dumping potential of the XR formulation with alcohol. This may be evaluated *in vitro* and if necessary *in vivo*.
- The sponsor should include the (b) (4)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Table of Phase 2/3 Clinical Studies of Sitagliptin + Metformin IR

Study #	Study Design Primary Objective	Population & Treatment	Endpoints	Reviewer and date
P015	Randomized, double blind, placebo controlled, crossover study	28 T2DM subjects on sita 50 mg BID + met ≥ 1500 mg QD x 4 wk	24h weighted mean glucose FPG, fructosamine, SBGM Clinical evaluation & labs EKG	Dr. Ilan Irony 8/31/06
P020	Randomized, double blind, safety and efficacy study	464 T2DM subjects on sita 100 mg QD + met ≥ 1500 mg QD x 24 wk placebo-controlled period (& 80 wk active-controlled period)	HbA1c, FPG Meal tolerance test Clinical evaluation & labs EKG	Dr. Ilan Irony 8/31/06
P024	Randomized, double blind, safety and efficacy study of sita vs glipizide 5-20 mg	588 T2DM subjects on sita 100 mg QD + met ≥ 1500 mg QD x 104 wk (primary endpt wk 52)	HbA1c, FPG Meal tolerance test Clinical evaluation & labs EKG	Dr. Ilan Irony S-002 9/17/07
P035	Randomized, double blind, placebo controlled, safety and efficacy study	116 T2DM subjects on glimepiride ≥ 4 mg QD, met ≥ 1500 mg QD, & sita 100 mg QD x 24 wk (& 30 wk active-controlled period)	HbA1c, FPG, lipids Meal tolerance test Clinical evaluation & labs EKG	Dr. Ilan Irony S-002 9/17/07
P036	Randomized, double blind, factorial study	372 T2DM subjects on sita/met 50/500 or 50/1000 mg BID 117 T2DM subjects on open label sita/met 50/1000 mg BID 54 wk (primary endpt wk 24)	HbA1c, FPG, fructosamine Meal tolerance test Clinical evaluation & labs EKG	Dr. Ilan Irony S-003 9/17/07
P052	Randomized, placebo controlled, safety and efficacy study	170 T2DM subjects on met ≥ 1500 mg QD, rosiglitazone ≥ 4 mg QD, & sita 100 mg QD x 54 wk (primary endpt wk 18)	HbA1c, FPG Meal tolerance test Clinical evaluation & labs EKG	Hyon Kwon S-010 9/3/09
P053	Randomized, double blind, safety and efficacy study	96 T2DM subjects on sita 100 mg QD & met ≥ 1500 mg QD vs. T2DM subjects on placebo + met ≥ 1500 mg QD 30 wk (primary endpt wk 18)	HbA1c, FPG Meal tolerance test Clinical evaluation & labs EKG	Not previously reviewed

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Review Strategy

My review will focus on the one phase 2/3 clinical study that was not previously reviewed, study P053.

Study P053: A multicenter, double blind, randomized, study to evaluate the safety and efficacy of the addition of sitagliptin to patients with T2DM who have inadequate glycemic control on metformin monotherapy

Objectives:

Primary:

- After 18 weeks, to assess the effect of the addition of treatment with sitagliptin compared to placebo on HbA1c
- To assess the safety and tolerability of sitagliptin

Secondary:

- After 18 weeks, to assess the effect of the addition of treatment with sitagliptin compared to placebo on the post-meal glucose (e.g. 2 hour postprandial [PPG], glucose area under the concentration-time curve [AUC] after a meal tolerance test
- After 18 weeks, to assess the effect of the addition of treatment with sitagliptin compared to placebo on FPG
- After 30 weeks, to assess the effect of the addition of treatment with sitagliptin compared to placebo on HbA1c

Study design: This was a multicenter, double blind, randomized, parallel group, placebo controlled study that included the following (see Figure 1):

- 1 week screening period
- Up to 12 week metformin dose-titration/dose-stable and diet/exercise period
- 2 week, single blind, placebo run-in period
- 30 week double blind treatment period

Subjects were randomized (1:1) to sitagliptin 100 mg or placebo daily for this 30 week study. Subject who experienced hyperglycemia were rescued with glipizide.

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(b) (4)

Figure 1. P053 study design

Results:

Efficacy: Sitagliptin was superior to placebo in decreasing HbA_{1c} from baseline after 18 weeks of treatment (see below)

P053. Primary and secondary endpoints: Least squares means for change from baseline with 95% CI (FAS excluding data after initiation of glycemic rescue)

Treatment Group	Week 18			Week 30
	HbA _{1c} (%)	Fasting Plasma Glucose (mg/dL)	2-Hour Post-Prandial Glucose (mg/dL)	HbA _{1c} (%)
Sitagliptin 100 mg	-1.00 (-1.24, -0.75)	-32.0 (-40.6, -23.3)	-67.6 (-82.1, -53.2)	-0.98 (-1.25, -0.70)
Placebo	0.02 (-0.23, 0.27)	-6.5 (-15.1, 2.2)	-13.5 (-28.2, 1.2)	0.04 (-0.24, 0.31)
Difference from Placebo [†]				
Sitagliptin 100 mg vs. Placebo	-1.02 (-1.36, -0.67)	-25.5 (-37.7, -13.3)	-54.1 (-74.7, -33.6)	-1.01 (-1.4, -0.6)
[†] All comparisons vs. placebo had p < 0.001.				

Safety: No deaths or SAEs were reported in the sitagliptin group. The incidence of AEs was similar between treatment groups (57.3% vs. 58.5%), although there was a greater incidence of laboratory AEs with sitagliptin (15.6% vs. 4.3%). Discontinuation due to

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laboratory AEs (blood creatinine increased and ALT increased) occurred in 2 sitagliptin subjects but no placebo subjects.

Conclusions

- I recommend filing.
- Requests for inclusion in the 74-day letter:
 - Please state the location within the application where the coding dictionary used for mapping investigator verbatim terms to preferred terms is located. If it was not previously submitted, please submit it.
 - In tabular format, please clarify the metformin formulations used in each of the 7 clinical trials submitted. Please include whether or not the metformin was immediate or sustained release.
- As the pivotal studies for approval are clinical pharmacology studies, I do not recommend the Division of Scientific Investigations (DSI) investigate clinical study P053.

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
11/04/2010

ILAN IRONY
11/05/2010

I concur with Dr. Pratt that the NDA can be filed, and I concur with the requests for the 74-day letter.