

Study P036

In general, trends toward shorter QTc intervals were observed for subjects in the active treatment groups compared with those in the placebo group, with no clinically meaningful differences in QTc intervals between the treatment groups for subjects in either the Randomized Cohort or the OLC. In three subjects (all continuing in the study), QTc intervals >500 msec were observed following randomization (Table 55). One subject (in the sitagliptin monotherapy group) had a QTc interval of 519 msec on Day 106, compared with 497 msec at baseline. This subject had pre-randomization ECG abnormalities, including left bundle branch block (reported as an AE) and left atrial enlargement. Another subject (in the sitagliptin 50/metformin 1000 mg bid coadministration group) had a QTc interval of 507 msec at Week 24, compared with 417 msec at baseline. This subject had a pre-randomization ECG abnormality of right bundle branch block and a medical history of hypertension. The third subject (also in the sitagliptin 50/metformin 1000 mg bid coadministration group) had a QTc interval of 501 msec at Week 24 compared with 440 msec at baseline. This subject had a medical history of arrhythmia and non-specific ST-T changes. The subject's repeat QTc interval on Day 174 was 455 msec while the patient continued taking study drug.

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Table 55. Subjects exceeding pre-defined limits of change in QTc from baseline in Study P036

ECG parameter	Predefined Limits of Change	Treatment	n/N (%)	% Difference with Placebo % (95% CI)
QTc (milliseconds)	One value > 500 msec	Sita 100 mg qd	1/150 (0.7)	0.7
		Met 500 mg bid	0/159 (0.0)	0.0
		Met 1000 mg bid	0/152 (0.0)	0.0
		Sita 50 mg bid + Met 500 mg bid	0/168 (0.0)	0.0
		Sita 50 mg bid + Met 1000 mg bid	2/162 (1.2)	1.2
		Placebo	0/137 (0.0)	
		Sita 50 mg bid + Met 1000 mg bid OLC	0/99 (0.0)	
	One value with increase ≥ 30 msec	Sita 100 mg qd	10/145 (6.9)	-5.3 (-12.7, 1.7)
		Met 500 mg bid	7/158 (4.4)	-7.8 (-14.9, -1.4)
		Met 1000 mg bid	13/147 (8.8)	-3.4 (-11.0, 3.9)
		Sita 50 mg bid + Met 500 mg bid	11/164 (6.7)	-5.5 (-12.8, 1.2)
		Sita 50 mg bid + Met 1000 mg bid	10/155 (6.5)	-5.8 (-13.1, 1.0)
		Placebo	16/131 (12.2)	
		Sita 50 mg bid + Met 1000 mg bid OLC	8/99 (8.1)	
	One value with an increase ≥ 30 msec and > gender specific ULN (430 and 450 msec for males and females, respectively)	Sita 100 mg qd	5/145 (3.4)	-0.4 (-5.6, 4.5)
		Met 500 mg bid	1/158 (0.6)	-3.2 (-8.0, 0.4)
		Met 1000 mg bid	2/147 (1.4)	-2.5 (-7.4, 1.6)
		Sita 50 mg bid + Met 500 mg bid	5/164 (3.0)	-0.8 (-5.9, 3.7)
		Sita 50 mg bid + Met 1000 mg bid	5/155 (3.2)	-0.6 (-5.7, 4.1)
		Placebo	5/131 (3.8)	
		Sita 50 mg bid + Met 1000 mg bid OLC	3/99 (3.0)	
	One value with an increase ≥ 60 msec	Sita 100 mg qd	0/145 (0.0)	-0.8
		Met 500 mg bid	0/158 (0.0)	-0.8
		Met 1000 mg bid	0/147 (0.0)	-0.8
		Sita 50 mg bid + Met 500 mg bid	1/164 (0.6)	-0.2
		Sita 50 mg bid + Met 1000 mg bid	2/155 (1.3)	0.5
		Placebo	1/131 (0.8)	
		Sita 50 mg bid + Met 1000 mg bid OLC	0/99 (0.0)	
One value with an increase ≥ 60 msec and > gender specific ULN (430 and 450 msec for males and females, respectively)	Sita 100 mg qd	0/145 (0.0)	-0.8	
	Met 500 mg bid	0/158 (0.0)	-0.8	
	Met 1000 mg bid	0/147 (0.0)	-0.8	
	Sita 50 mg bid + Met 500 mg bid	0/164 (0.0)	-0.8	
	Sita 50 mg bid + Met 1000 mg bid	2/155 (1.3)	0.5	
	Placebo	1/131 (0.8)		
	Sita 50 mg bid + Met 1000 mg bid OLC	0/99 (0.0)		

Adapted from the applicant's Table 14-85, reference p036v1

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

There were no marked outliers or dropouts in either Study P024 or P036 due to ECG abnormalities.

7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

Sitagliptin, being a small molecule, is unlikely to generate an immune response. On the other hand, sitagliptin exerts its metabolic effect by inhibition of DPP4, which is identical to CD26, a

T lymphocyte surface glycoprotein. This fact prompted the applicant to be particularly vigilant to effects of sitagliptin on infections or other immune disorders in the clinical studies. No increased risk of infections or immune disorders has been observed.

7.1.11 Human Carcinogenicity

The review of the sitagliptin clinical studies did not reveal an increase risk of neoplasia. Please see Dr. Bourcier's toxicology review for a complete discussion of the applicant's carcinogenicity program. Sitagliptin was found to increase risk of hepatic neoplasia in rat toxicity studies, when exposed to a dose of 500 mg/kg/day, corresponding to 250 times the human dose and a 58-fold greater exposure than that achieved with the maximum recommended human dose. This dose was associated with hepatotoxicity in those animal studies. In addition, no evidence of genotoxicity or mutagenicity with sitagliptin was found and no trend to cause tumors was evident in mice studies with the MTD of 500 mg/kg/day for 2 years. From metformin labeling: "Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day."

7.1.12 Special Safety Studies

As discussed in Section 7.1.9.2 in this review document, the applicant has conducted a clinical study to assess effects of sitagliptin on the QT_c interval in healthy volunteers. That study did not demonstrate prolongation of the QT_c interval that would merit concerns for arrhythmias or Torsades.

Sitagliptin is the first representative of a new class of antidiabetic medications, first approved for marketing in the US only recently (October 16, 2006). Therefore, most of the experience with sitagliptin that has been reviewed comes from clinical studies reported in the present application, as well as those reported under NDA 21995. No special safety studies have been performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Based on the 2-week post study telephone contact and based on the direct follow up of subjects who had sitagliptin discontinued or held during the clinical studies, there is no indication of withdrawal or rebound symptoms.

The potential for abuse was not investigated in the sitagliptin development. No effect on the Central Nervous System was detected to suggest an abuse potential. Unlike Exenatide, which is a GLP1 analog that was shown to cause weight loss, sitagliptin has not demonstrated capacity to decrease weight, and therefore use (or abuse) for weight loss is not anticipated. There were no CNS AEs to suggest impairment of mental ability or ability to drive or operate machinery.

7.1.14 Human Reproduction and Pregnancy Data

Sitagliptin

The sitagliptin development did not provide evidence of effects on reproduction and pregnancy. Preclinical development and reproductive toxicity studies indicate that sitagliptin does not affect fertility in female or male rats at the limit dose of 1000 mg/kg/day but does slightly increase the incidence of rib abnormalities at this dose with a NOEL for developmental toxicity in rats of 250 mg/kg/day. There was no effect on fetal development in rabbits at 125 mg/kg/day. Sitagliptin is classified as a Pregnancy Category B drug.

Sitagliptin is secreted in the milk of lactating rats. It is not known whether sitagliptin is secreted in human milk. Therefore it should not be used by a woman who is nursing. Please see Dr. Bourcier's review for a complete discussion on the effects of sitagliptin on reproduction in animal studies.

Metformin

Metformin is a Pregnancy Category B drug. There are no adequate and well-controlled studies in pregnant women with metformin. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers.

7.1.15 Assessment of Effect on Growth

The youngest subjects enrolled in the Phase 3 studies were 18 years old, and therefore no effect of sitagliptin on linear growth can be inferred from these studies.

Diprotin A, another DPP4 inhibitor, was shown to inhibit the degradation of human growth hormone releasing hormone GRH (1-44)-NH₂ to GRH (3-44)-NH₂ in in-vitro experiments.² Metformin has been used widely in adolescents with T2DM and with insulin resistance associated with polycystic ovaries, and has not been shown to have direct effects on linear growth.

7.1.16 Overdose Experience

No overdose in excess of 400 mg occurred during the Phase 2 or Phase 3 studies with sitagliptin under NDA 21995. In Phase 1 studies, single doses of 800 mg or 10-day dosing with 600 mg daily of sitagliptin have been well tolerated in healthy volunteers. There has been more substantive experience with a dose of 200 mg daily, in healthy obese middle age volunteers during Phase 1 studies as well as in diabetics during Phase 3 studies, without dose-dependent events related to safety or tolerability.

² Frohman LA, Downs TR et al. Dipeptidylpeptidase IV and trypsin-like enzymatic degradation of human growth hormone-releasing hormone in plasma. J Clin Invest. 1989 May; 83(5): 1533-1540

Sitagliptin has a wide therapeutic margin; thus, the potential for toxicity as a result of overdose is limited. Since single doses up to 800 mg have been well-tolerated in Phase 1 studies, hence accidental exposure to doses of up to 800 mg are unlikely to result in clinical sequelae. There is no clinical experience with doses above 800 mg.

In the event of an overdose, the applicant proposes to employ usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3 to 4 hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

7.1.17 Postmarketing Experience

There has been little postmarketing experience with the use of sitagliptin reported and reviewed. No safety signals from the postmarketing experience are apparent that have not been detected in the original sitagliptin development controlled studies.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 2930 subjects have participated in the Phase 2 and Phase 3 studies in which sitagliptin 100 mg daily (either as 100 mg qd or 50 mg bid) and metformin (≥ 1500 mg/day in P015, P020, P024) were coadministered. In these studies 1569 subjects have been exposed to coadministered sitagliptin and metformin for between 1 to 404 days with a mean duration of exposure of 254.8 days (approximately 36 weeks).

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Clinical Review
 Ilan Irony, M.D.
 NDA 22044, Submission 000
 Janumet™ (Sitagliptin / metformin fixed-dose combination)

Table 56. Overall exposure to the coadministration of sitagliptin and metformin

Study and dose	<14 Days	≥14 to <42 Days	≥42 to <84 Days	≥84 to <126 Days	≥126 to <154 Days	≥154 to <180 Days	≥180 to <270 Days	≥270 to <360 Days	≥360 Days	Total	Range of Days on Drug	Mean Number of Days on Drug
P015												
ANY DOSE Sitagliptin	1	27	0	0	0	0	0	0	0	28	13 to 34	28.3
100 mg	1	27	0	0	0	0	0	0	0	28	13 to 34	27.6
P020												
ANY DOSE Sitagliptin	3	9	11	8	14	23	24	60	312	464	1 to 403	322.6
100 mg	3	9	11	8	14	23	24	60	312	464	1 to 403	323.3
P024												
ANY DOSE Sitagliptin	5	14	29	22	17	18	52	164	267	588	1 to 404	297.4
100 mg	5	14	29	22	17	18	52	168	263	588	1 to 404	297.1
P036 Randomized cohorts												
ANY DOSE (lower-dose coadministration)	5	5	7	9	9	155	0	0	0	190	1 to 202	152.4
Sitagliptin 100 mg + Metformin 1000 mg	5	3	7	8	8	158	0	0	0	189	3 to 192	153.1
ANY DOSE (higher-dose coadministration)	1	5	2	10	4	160	0	0	0	182	1 to 189	158.2
Sitagliptin 100 mg + Metformin 2000 mg	0	5	4	8	12	152	0	0	0	181	14 to 184	156.4
P036 OLC												
ANY DOSE	2	8	8	6	11	82	0	0	0	117	1 to 191	143.0
Sitagliptin 100 mg + Metformin 2000 mg	4	4	8	14	73	6	0	0	0	109	1 to 168	124.6
Total of all Studies												
ANY DOSE	17	67	57	50	54	445	76	224	579	1569	1 to 404	254.8

Adapted from the applicant's Table 2.7.4: 5, Reference Summary of Clinical Safety in the 4-Month Safety Update Report

The exposure is adequate for assessment of the safety of coadministration of sitagliptin and metformin, at doses that are being proposed for the FDC. In addition, experience with sitagliptin from other studies (not listed above) adding to approximately 2000 subjects has been reviewed under NDA 21995, and the experience with the use of metformin spans over 20 years in the US, being prescribed for millions of people worldwide.

7.2.1.1 Study type and design/patient enumeration

Table 57 is a comprehensive list of the clinical safety and efficacy studies conducted in the development of sitagliptin / metformin FDC. These studies are described in the new drug application.

Clinical Review
 Ilan Irony, M.D.
 NDA 22044, Submission 000
 Janumet™ (Sitagliptin / metformin fixed-dose combination)

Table 57. Listing of studies contributing data to support the safety of sitagliptin / metformin FDC

Study #	Study Population			Study Goal	Study Design
	M	F	Age range		
P015	10	18	38-71	Combination with metformin: safety / efficacy	DB, R, PC, crossover study with 50 mg bid (or PBO, random sequence) and metformin X 4 weeks per period
P020	301	400	19-78	Efficacy with metformin	Phase 3, MC, DB, R, PC, 100 mg (or PBO) with metformin ≥ 1500 mg X 24 wks
P024	694	478	22-79	Efficacy with metformin in non-inferiority to glipizide	Phase 3, MC, DB, AC (versus glipizide), X 104 wks on metformin ≥ 1500 mg randomized 1:1 to sitagliptin 100 mg or glipizide 5- 20 mg qd
P036	539	552	20-78	Efficacy with metformin for first line therapy	Phase 3, MC, DB, Factorial, R to 1 of 6 Rx groups: sita 100 qd, metformin 500 bid, metformin 1000 bid, sita 50 /met 500 bid, sita 50 / met 1000 bid, or placebo X 24 weeks with extension
P036 OLC	67	50	26-75	Efficacy in monotherapy for first line therapy	MC, OL, uncontrolled, sita 50 / metformin 1000 bid for subjects with HbA1c > 11% or FPG > 280 X 24 weeks

DB: double-blind; R: randomized; PC: placebo-controlled; AC: active-controlled; MC: multicenter; PBO: placebo

7.2.1.2 Demographics

Table 58 and Table 59 show the demographic characteristics (age, gender and race) of subjects who participated in Studies P024 and P036.

Table 58. Demographic characteristics of subjects in Study P024, by treatment group

Age (years)						
Treatment	N	Mean	SD	Median	Range	
Sitagliptin 100 mg	588	56.8	9.3	57.0	22.0 to 78.0	
Glipizide	584	56.6	9.8	57.0	23.0 to 79.0	
All	1172	56.7	9.6	57.0	22.0 to 79.0	
Gender						
Treatment	Male		Female		Total	
	N (%)		N (%)		N	
Sitagliptin 100 mg	336 (57.1)		252 (42.9)		588	
Glipizide	358 (61.3)		226 (38.7)		584	
All	694 (59.2)		478 (40.8)		1172	
Race						
Treatment	White	Black	Hispanic	Asian	Other	Total
	N (%)					
Sitagliptin 100 mg	432 (73.5)	41 (7.0)	43 (7.3)	50 (8.5)	22 (3.7)	588
Glipizide	434 (74.3)	35 (6.0)	46 (7.9)	49 (8.4)	20 (3.4)	584
All	866 (73.9)	76 (6.5)	89 (7.6)	99 (8.4)	42 (3.6)	1172

Table 59. Demographic characteristics of subjects in Study P036, by treatment group

Age (years)						
Treatment Group	N	Mean	SD	Median	Range	
Sitagliptin 100 mg qd	179	53.3	10.2	53.0	20.0 to 77.0	
Metformin 500 mg bid	182	53.4	10.2	55.0	28.0 to 77.0	
Metformin 1000 mg bid	182	53.2	9.6	53.0	25.0 to 78.0	
Sita 50 mg + Met 500 bid	190	54.1	10.0	54.0	30.0 to 77.0	
Sita 50 + Met 1000 bid	182	53.3	9.6	54.0	29.0 to 78.0	
Placebo	176	53.6	10.0	54.0	24.0 to 78.0	
All Randomized	1091	53.5	9.9	54.0	20.0 to 78.0	
Sita 50 + Met 1000 bid OLC	117	52.6	10.0	53.0	26.0 to 75.0	
Gender						
Treatment Group	Male		Female		Total	
	N (%)		N (%)		N	
Sitagliptin 100 mg qd	93 (52.0)		86 (48.0)		179	
Metformin 500 mg bid	89 (48.9)		93 (51.1)		182	
Metformin 1000 mg bid	82 (45.1)		100 (54.9)		182	
Sita 50 + Met 500 mg bid	105 (55.3)		85 (44.7)		190	
Sita 50 + Met 1000 bid	77 (42.3)		105 (57.7)		182	
Placebo	93 (52.8)		83 (47.2)		176	
All Randomized	539 (49.4)		552 (50.6)		1091	
Sita 50 + Met 1000 bid OLC	67 (57.3)		50 (42.7)		117	
Race						
Treatment Group	White	Black	Hispanic	Asian	Other	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N
Sitagliptin 100 mg qd	93 (52.0)	11 (6.1)	52 (29.1)	6 (3.4)	17 (9.5)	179
Metformin 500 mg bid	87 (47.8)	12 (6.6)	55 (30.2)	14 (7.7)	14 (7.7)	182
Metformin 1000 mg bid	106 (58.2)	9 (4.9)	39 (21.4)	10 (5.5)	18 (9.9)	182
Sita 50 + Met 500 bid	102 (53.7)	13 (6.8)	55 (28.9)	9 (4.7)	11 (5.8)	190
Sita 50 + Met 1000 bid	95 (52.2)	14 (7.7)	49 (26.9)	11 (6.0)	13 (7.1)	182
Placebo	81 (46.0)	17 (9.7)	47 (26.7)	12 (6.8)	19 (10.8)	176
All Randomized	564 (51.7)	76 (7.0)	297 (27.2)	62 (5.7)	92 (8.4)	1091
Sita 50 + Met 1000 bid OLC	44 (37.6)	9 (7.7)	54 (46.2)	1 (0.9)	9 (7.7)	117

Similar to the conclusions from the review of NDA 21995, the group of African Americans has been underrepresented as compared to the proportion of Type 2 diabetics in the United States Population who are African American.

7.2.1.3 Extent of exposure (dose/duration)

Only the dose of sitagliptin of 100 mg (either administered as a single dose or as 50 mg bid) coadministered with metformin at doses of either 500 mg bid or 1000 mg bid have been studied in this development program. Table 56 provides the overall exposure to these drugs in the studies described in this application.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary sources of clinical data were submitted for review. The clinical reviewer conducted a literature search for evidence of safety concerns with sitagliptin or other DPP4 inhibitors.

7.2.2.1 Other studies

There were no additional studies conducted with sitagliptin, other than the ones reported under this application. This clinical reviewer has enriched the review of sitagliptin by comparing the data from the clinical studies to the data obtained from clinical studies investigating safety of vildagliptin, a similar DPP4 inhibitor, used in combination with metformin.

7.2.2.2 Postmarketing experience

Sitagliptin has only recently been approved for marketing in the United States (October 16, 2006). Sitagliptin is the first DPP4 inhibitor approved for the treatment of T2DM.

7.2.2.3 Literature

The applicant has provided relevant references to the review of sitagliptin / metformin FDC. The clinical reviewer has also searched the medical literature for additional references to address specific issues of review.

7.2.3 Adequacy of Overall Clinical Experience

The clinical experience with the coadministration of sitagliptin and metformin at doses that are part of the fixed-dose combinations, regarding extent and duration of exposure needed to assess safety is adequate, according to the ICH E1 guidance. ICH E1 mentions a total exposure of about 1500 subjects, with 300-600 for 6 months and 100 for one year for products intended to treat chronic conditions. The Division of Metabolism and Endocrinology Products has traditionally requested more substantive safety experience in the development of products intended for the treatment of T2DM, for which the applicant generally complied with.

The design of studies intended to demonstrate the safety of sitagliptin in combination with metformin is adequate.

The applicant appropriately excluded subjects with renal impairment, as this is a contraindication for the use of metformin. The applicant has proposed labeling where use of the product in patients with chronic renal insufficiency is contraindicated.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see Dr. Bourcier's toxicology review for details of the adequacy of preclinical testing of sitagliptin. In general, preclinical testing for sitagliptin was adequate, and an important toxicity study in monkeys is still ongoing at the time of this review.

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing performed routinely in the studies was adequate to elicit adverse events and other clinical, electrocardiographic and laboratory parameters that could represent a safety concern.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see Dr. Jaya Vaidyanathan's Biopharmacology review for details on the adequacy of the sitagliptin PK evaluation program. The overall program is adequate to learn about the PK of sitagliptin and effects of meals and interactions with metformin (both in terms of PK as well as PD). However, there is no significant experience of the concomitant use of sitagliptin with insulin and insulin analogs, and a limited experience with oral insulin secretagogues. This is an important issue because sitagliptin indirectly stimulates endogenous insulin and although the risk of hypoglycemia is small when used in monotherapy or in combination with insulin sensitizing drugs, the risk of hypoglycemia with other insulin secretagogues (that do not stimulate insulin secretion in a glucose-dependent manner) is unknown. This deficiency is currently being addressed as a post-marketing commitment, under the original sitagliptin approval.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant has adequately collected data on potential adverse events that could be resulting from exposure to any new drug / drug class. For this purpose the applicant has conducted a QT interval study and studies in chronic renal insufficiency and chronic liver dysfunction, which were reviewed under NDA 21995. In addition, the applicant planned for and gathered information on AEs expected based on mechanism of action (such as hypoglycemia, for insulin secretagogues).

7.2.8 Assessment of Quality and Completeness of Data

The overall assessment of the application and study reports regarding the safety of sitagliptin in combination with metformin is that sufficient data to assess risk to benefit profile of sitagliptin have been provided. Data that are as complete and of good quality are available for review, and the applicant provided in the study reports important analyses of the safety data.

7.2.9 Additional Submissions, Including Safety Update

Most of the review of safety data in this document is based on the 4-Month Safety Update Report, submitted to FDA on October 19, 2006. The original submission contained only data on the OLC of Study P036 (117 subjects followed for a mean 66 days on sitagliptin 100 mg and metformin >1500 mg qd) and data from Studies P015 and P020 which had been previously reviewed under NDA 21995. The 4-Month Safety Update Report contained data from 24 weeks

of Study P036 (all randomized cohorts as well as the OLC), 52 weeks of data in Study P024 and an updated reporting of SAEs through Merck's Worldwide Adverse Event Reporting System.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

At each dose of metformin tested, the combination of sitagliptin and metformin was generally well tolerated and was comparable to either component of the combination when given alone. One general concern in the review of products to treat T2DM is the incidence of hypoglycemia. In addition, since sitagliptin in monotherapy has been noted to cause small increases in gastrointestinal AEs compared to placebo (specifically abdominal pain, nausea and diarrhea) and since metformin also is known to cause dose-dependent gastrointestinal AEs (specifically abdominal pain, nausea, and diarrhea) the studies of the combination of sitagliptin and metformin were planned and powered to focus on this issue. The review of the sitagliptin NDA has also revealed some consistent laboratory findings, none of them raising specific clinical concerns except for a small mean increase in serum creatinine, particularly in subjects with mild to moderate renal failure. Because renal failure is a contraindication for the use of metformin, patients with such condition were appropriately excluded from Studies P024 and P036. Below the reviewer presents a brief summary of the findings addressing these concerns in the NDA 22044.

Hypoglycemia

Table 32 shows a summary of the hypoglycemic events reported in Study P036, in terms of number of subjects reporting the AE and number of episodes occurring in each treatment cohort. Hypoglycemia occurred infrequently (11 subjects out of 1091 randomized and 2 subjects out of 117 in the OLC), with symptoms being mild to moderate, none requiring medical assistance, and the majority of these not confirmed with concurrent fingerstick blood glucose.

Table 33 shows the summary of hypoglycemic events in Study P024; as compared to the combination of metformin and glipizide, subjects randomized to metformin and sitagliptin had few events and milder events (4.9 % for sitagliptin / metformin combination versus 32 % for the glipizide/metformin combination).

Gastrointestinal Events

From Table 34, there is a metformin dose-proportional increase in nausea and diarrhea. Sitagliptin, on the other hand, tends to increase constipation. There were no clinically meaningful differences in the incidences of diarrhea, nausea and vomiting in the group receiving coadministered sitagliptin and metformin compared to the group receiving metformin alone, when properly comparing the groups according to the metformin dose (500 mg bid versus 1000 mg bid) received. In summary, the gastrointestinal AEs were mostly driven by the metformin dose used.

In Study P024, pre-specified gastrointestinal AEs (abdominal pain, diarrhea, nausea and vomiting) occurred with similar rates among the sitagliptin-treated and the glipizide-treated subjects.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

There were 2 new Phase 3 studies reported in this NDA (Studies P024 and P036). The studies had different goals and designs. However, when considering all subjects exposed to the combination of sitagliptin and metformin, the incidence of specific AEs, SAEs, and laboratory abnormalities remain low and generally well tolerated.

7.4.1.2 Combining data

Combining data from the 2 new studies reported in this NDA does not change the overall rates of these specific AEs (such as hypoglycemia or gastrointestinal events), and does not raise new concerns about particular clusters of AEs the applicant had considered of special interest at the time of submission of the sitagliptin NDA, such as infections, and neurologic and skeletal muscle-related AEs). The new laboratory data reported in these 2 new studies have not raise any new concerns regarding the combination of sitagliptin and metformin. In particular, anemia was investigated in the separate studies and with the data combined, and no concerns emerged from the review.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The only dose of sitagliptin proposed for marketing in the sitagliptin / metformin FDC is 100 mg daily dose, the same dose that has been extensively studied in the sitagliptin NDA. From Study P036, it is clear that gastrointestinal adverse findings are proportional to the dose of metformin, as there were more events of nausea, abdominal pain and diarrhea in the groups treated with sitagliptin 50 mg / metformin 1000 mg bid as compared to the group treated with sitagliptin 50 mg / metformin 500 mg bid, in similar proportions as occurred in the metformin 500 mg bid and 1000 mg bid alone. NO other AEs had dose dependency.

7.4.2.2 Explorations for time dependency for adverse findings

There was no time dependency for adverse findings in the studies reviewed in this NDA.

7.4.2.3 Explorations for drug-demographic interactions

There were similar rates of AEs and types of AEs across genders and racial groups among the different treatment groups. Also there were similar rates of AEs in different age categories, although it is worth emphasizing here that metformin should be prescribed with caution to elderly patients (those older than 80 years) only after documentation of normal renal function. Even in those patients with normal renal function, the sitagliptin / metformin FDC label recommends appropriately yearly assessment of renal function.

7.4.2.4 Explorations for drug-disease interactions

A wide range of diseases and conditions affecting many organs and systems were represented in the study population at baseline. There were no apparent interactions between treatment and AEs. The most common conditions present at baseline were hypertension, hyperlipidemia, obesity, drug hypersensitivity and allergies, GERD, depression, and back pain, and there appears to be no significant exacerbation of these conditions in any of the treatment groups. It is important to point out again that metformin is contraindicated in patients with renal dysfunction and other patients with conditions that put them at higher risk for lactic acidosis.

7.4.2.5 Explorations for drug-drug interactions

Metformin and sitagliptin administered in combination have not been shown to exert effects on the individual pharmacokinetic characteristics of each other.

Sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: rosiglitazone, glyburide, simvastatin, warfarin or the ethinyl estradiol/norethindrone oral contraceptive combination. Sitagliptin did not inhibit any of the CYP isozymes, and 100 mg doses of sitagliptin increased digoxin AUC by 11 % and C_{max} by 18 %, without an effect on digoxin clearance.

In single-dose drug interactions studies of metformin, the following conclusions were obtained:

- With glyburide: metformin decreased glyburide AUC and C_{max} , but glyburide did not change metformin PK;
- With furosemide: furosemide increased metformin plasma and blood AUC by 15 % and C_{max} by 22 %, while metformin decreased furosemide AUC by 12 % and C_{max} by 31 %.
- With nifedipine: nifedipine increased plasma metformin AUC by 9% and C_{max} by 20 %, while metformin had minimal effects on nifedipine PK.
- Cationic drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in metformin C_{max} and a 40% increase in metformin AUC. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of sitagliptin/metformin FDC and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

7.4.3 Causality Determination

The group of AEs most likely to have been caused by the coadministration of sitagliptin and metformin is related to gastrointestinal effects, mainly abdominal pain, nausea and diarrhea. As seen in this review document, the incidence of these AEs was proportional to the dose of metformin administered, with rates similar to those found when patients are treated with metformin alone.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The only dose of sitagliptin investigated in this NDA is the 100 mg daily dose. Because of the pharmacokinetic characteristics of metformin, the dose of sitagliptin was divided in 2 doses (bid administration). The doses of metformin as part of the FDC tablet are the doses used by more than 93 % of the diabetic population who uses this medication in the US, namely 500 or 1000 mg bid. The studies reviewed under NDA 21995 (P015 and P020) and the new data under this application support the safety of coadministration of sitagliptin 50 mg with metformin at either 500 or 1000 mg bid. Study P036 provides evidence of a dose-response in the metformin in reducing HbA_{1c} in subjects treated with the combination of metformin and sitagliptin, with effect more prominent with each dose in combination compared to the same metformin dose alone.

Daily doses of 50 mg and 25 mg of sitagliptin have been approved for use in diabetic patients with moderate or with severe renal insufficiency, respectively. Since any degree of renal insufficiency constitutes a contraindication for the use of metformin, these lower sitagliptin doses cannot be part of fixed-dose combination tablets for patients with renal dysfunction. It is recommended that the starting dose of metformin be low, at 500 mg qd or bid, with weekly titration of the dose to target glycemic goals. This regimen was found to decrease the severity of gastrointestinal effects and increase adherence to treatment.

8.2 Drug-Drug Interactions

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

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

Sitagliptin is well absorbed with an absolute bioavailability of 87 %, which does not change substantially when dosing follows a high fat meal. Sitagliptin is eliminated by the kidneys as

unchanged drug, with minor metabolism mediated by CYP3A4. Sitagliptin is not an inducer of CYP3A4. The renal clearance is approximately 350 mL/min, suggesting that active tubular secretion is involved in the renal elimination of sitagliptin, possibly by the organic anionic transporter-3. Sitagliptin is a substrate for p-glycoprotein, but cyclosporin A, a potent probe p-glycoprotein inhibitor did not affect absorption and excretion of sitagliptin. In clinical studies sitagliptin did not meaningfully alter the pharmacokinetics of metformin, simvastatin, warfarin, oral contraceptives, rosiglitazone or glyburide, therefore suggesting low probability of drug-drug interactions with organic anion transporter, CYP3A4, CYP2C8 and CYP2C9.

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

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

The risk of hypoglycemic AEs in patients treated with insulin or insulin secretagogues, for whom the combination of sitagliptin and metformin are added to the therapeutic regimen, is unknown. The applicant has conducted studies investigating effects of sitagliptin in combination with sulfonylureas, but plans to submit these data in a future supplement. At the time of approval of sitagliptin, the applicant committed to conduct studies to assess the safety of the concomitant use of sitagliptin and insulin, specifically addressing the risk of hypoglycemia.

One-half (in Study P024) and three quarters (Study P036) of the study population had been treated with medications other than antidiabetic agents; in particular medications affecting the renin-angiotensin system, analgesics and anti-lipid agents were the most commonly used medications. No particular safety signals were identified with the concomitant use of these medications.

8.3 Special Populations

The clinical studies reported in this NDA enrolled subjects that constitute a representative sample of the intended patient population, regarding all demographic aspects. The oldest subject in these studies was 78 years old and 15.5 % of subjects in Study P020 and 12 % of subjects in

8.6 Literature Review

A literature review was conducted and relevant findings were summarized in Section 2.6 and in specific discussion of issues throughout this document.

8.7 Postmarketing Risk Management Plan

The applicant will continue to monitor the safety of sitagliptin in ongoing nonclinical studies, clinical trials and through routine pharmacovigilance.

Action Plan for Safety Concerns

Potential for sitagliptin to cause necrotic skin lesions in monkeys

Studies in monkeys are ongoing, but at least preliminary findings suggest that the necrotic skin lesions are not present in sitagliptin-treated monkeys and are present in less specific DPP4 inhibitors that have non-selective inhibition of DPP-8 and DPP-9.

AEs of special interest

The AEs of special interest, hypoglycemia and selected gastrointestinal events, and the selected laboratory findings, uric acid, alkaline phosphatase, and absolute neutrophil count, will be followed by routine post-marketing surveillance. Routine surveillance is appropriate for these laboratory findings because there were no recognized associated clinical sequelae in the clinical trials. Also, the applicant plans to monitor these AEs of special interest in ongoing and planned clinical trials.

Exposure during pregnancy

Sitagliptin and metformin are used in women of childbearing potential with the possibility of exposure to a developing fetus. In order to develop a better assessment of the safety profile of sitagliptin in pregnant women, the applicant proposes that pregnancy exposure to sitagliptin and sitagliptin/metformin FDC be followed through routine pharmacovigilance practices and via the establishment of a pregnancy registry for more intensified follow-up of pregnancy exposures. A report summarizing the cumulative outcomes of pregnancy and congenital anomaly reports received by the applicant is written at product launch and updated annually. An outside expert in teratology is available to review data from the registry, as needed.

The pregnancy registry for sitagliptin will be operational in the United States. The data will be analyzed continually as it is received and will be compiled on an annual basis.

Unanticipated Safety Signals

Data from clinical trials cannot always predict rare AEs which may only become evident after being used in a larger number of patients with a greater range of comorbid conditions.

Unanticipated safety signals will be monitored through routine pharmacovigilance.

Ongoing and Planned Trials Yielding Additional Safety Information

Risk minimization is primarily accomplished with the use of risk communication, through prescriber information for the health care professional and the patient package insert for the consumer.

8.8 Other Relevant Materials

Not applicable

9 OVERALL ASSESSMENT

9.1 Conclusions

The efficacy of coadministration of sitagliptin and metformin in the improvement of glycemic control has been reported and reviewed under NDA 21995, primarily through the Phase 3 study P020, in which subjects who did not achieve adequate glycemic control with metformin at doses ≥ 1500 mg qd were randomized to sitagliptin 100 mg qd or placebo, and experienced placebo-subtracted LS mean (90 % CI) reductions in HbA1c over a 24-week treatment period of **-0.65 %** (-0.8, -0.5). The review of safety of the coadministration of sitagliptin and metformin in that study was unremarkable, covering not only the initial 24 weeks of placebo-controlled Phase A study, but the 30 weeks of a Phase B, active-controlled extension. Based on the findings from that study, the applicant obtained an indication for use of sitagliptin in combination with metformin, when patients on metformin were not being adequately controlled.

The applicant developed a fixed-dose combination of sitagliptin and metformin, using the metformin dose strengths that are most commonly used in the United States market, and that were used in Study P020. The demonstration of bioequivalence between the FDC and the coadministered sitagliptin and metformin components is the main issue for approval of the sitagliptin / metformin FDC.

In addition to the bioequivalence study, FDA had requested additional data on subjects exposed to the combination of sitagliptin and metformin in the Open Label Cohort of Study P036. That study is a factorial design trial investigating effects of the coadministration of sitagliptin with a higher and lower dose of metformin (1000 mg bid and 500 mg bid, respectively), as compared to placebo and to each component alone during a 24-week study. In addition to these randomized cohorts, the applicant included a cohort of subjects who were too hyperglycemic to risk randomization to placebo for 24 weeks, by having HbA1c > 11 % or fasting plasma glucose > 280 mg /dL at the time of screening. At the time of the original submission of the present NDA, the interim analysis of safety included data from the 117 subjects in the OLC having been exposed to the coadministration of sitagliptin and metformin for a mean 75 days.

Both efficacy and safety data from Study P036 were described in the 4-Month Safety Update Report for the randomized cohorts through week 24, and updated for the OLC.

The 4-Month Safety Update Report also included 52 weeks of safety data from Study P024, a study primarily designed to investigate the comparative efficacy of sitagliptin and glipizide, when each drug is added to a regimen of metformin at doses ≥ 1500 mg qd. As these data from

Studies P036 and P024 constituted a substantial increase in the safety database for review, they were thoroughly reviewed in this document.

Bioequivalence between the FDC dose strengths and the coadministered equivalent doses of sitagliptin and metformin was demonstrated in Study P048. In addition, the additional safety data provided by both Studies P024 and P036 did not reveal any new concerns or signals, beyond the profile already described in both the sitagliptin and metformin labeling.

9.2 Recommendation on Regulatory Action

This clinical reviewer recommends the approval of sitagliptin 50 mg / metformin 500 mg bid and of sitagliptin 50 mg / metformin 1000 mg bid for patients that have achieved adequate glycemic control with the separate components of the FDC or for patients whose glycemia is not adequately controlled despite treatment with a single agent, diet and exercise.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The applicant plans for _____ the proposed pregnancy registry are adequate. _____

_____ during pregnancy, with automatic pregnancy outcome questionnaire being sent. The pregnancy registry is established by the applicant to be used for sitagliptin and sitagliptin / metformin FDC. The applicant actively seeks information on AEs during pregnancy and outcomes, and _____

9.3.2 Required Phase 4 Commitments

FDA has waived the pediatric study requirement for sitagliptin to be conducted in patients ages birth to 10 years, inclusive, and deferring pediatric studies for ages 11 to 16 years, inclusive. The deferred pediatric study is considered a required postmarketing study commitment. In addition, at the time of sitagliptin approval the applicant committed to conduct studies to establish the safety and efficacy of sitagliptin in combination with insulin, for which a protocol has been submitted for review, and in combination with sulfonylureas, for which an efficacy supplement has been submitted in December 2006.

No additional Phase 4 commitments are deemed required for the combination of sitagliptin and metformin, either as coadministered medications or as FDC tablet.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

At the time of filing of this review document, the Division of Medication Errors and Technical Support (DMETS) is reviewing the proposed trade name Janumet. DMETS has not provided a recommendation regarding the proposed trade name.

The Office of Surveillance and Epidemiology is currently reviewing the Patient Package Information. No comments or recommendations have been conveyed to this reviewer at the time of filing of this review document.

This reviewer recommends small changes in labeling regarding _____

The labeling review has not been discussed with the applicant, so the recommendations described here are to be viewed as interim proposals.

9.5 Comments to Applicant

None.

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10 APPENDICES

10.1 Review of Individual Study Reports

Studies reported under NDA 21995

The studies that supported approval of sitagliptin in combination with metformin were reviewed under NDA 21995. The Phase 2 Study P015 and the Phase 3 Study P020 enrolled subjects already on metformin at doses ≥ 1500 mg daily and randomized them to placebo or to sitagliptin as an add-on treatment, in a crossover or parallel group design, respectively. The data from these studies have been summarized in this review; please refer to the review of NDA 21995 for details and additional information.

Studies reported under NDA 22044

Study P036

As requested by the FDA, the applicant submitted additional data on the safety of the combination of sitagliptin and metformin, generated from 117 treatment-naïve subjects with HbA1c > 11 % who were treated with both metformin and sitagliptin for a mean of 75 days (the Open Label Cohort, or OLC) in Study P036.

On October 19, 2006, with the 4-Month Safety Update Report, the applicant submitted data on the other 1091 subjects that participated in Study P036 in the randomized cohorts. Due to the large number of subjects included in the study, with the potential to influence the conclusions on the safety of the coadministration of sitagliptin and metformin, a thorough review of the Study P036 safety data from the 4-Month Safety Update Report was conducted and included in this review document. These data were reviewed throughout Section 7 of this document. Under the same 4-Months Safety Update Report, the applicant also submitted efficacy data from Study P036, namely the observations regarding changes in HbA1c, fasting plasma glucose and other study endpoints. These data were not thoroughly reviewed under this application:

Only a summary of the efficacy data has been included in this review and no labeling changes are proposed based on these study results.

The adverse events of sitagliptin in combination with a low dose of metformin (500 mg bid) or a high dose of metformin (1000 mg bid) occurred in similar organ system categories at similar rates as those occurring in each of the components of the combination alone. The gastrointestinal AEs, in particular, occurred at rates similar in the sitagliptin 50 mg / metformin 500 mg bid as the metformin 500 mg bid alone, and at rates similar in the sitagliptin 50 mg / metformin 1000 mg bid, as the metformin 1000 mg bid alone.

Study P024

Clinical Review
Ilan Irony, M.D.
NDA 22044, Submission 000
Janumet™ (Sitagliptin / metformin fixed-dose combination)

This study was not included in the FDA – Merck pre-NDA meeting and the study report was not expected or needed in order to support the sitagliptin / metformin FDC application. The study report was included in the 4-Month Safety Update Report. Similar to our approach to the randomized cohorts in Study P036, this reviewer elected to undertake a thorough review of safety in Study P024, as there were 1172 subjects in that study, 588 of whom received the combination of metformin and sitagliptin. As seen with the data from Study P036, the additional AEs, SAEs and laboratory data reviewed did not change the overall conclusion on the safety of coadministration of sitagliptin and metformin.

10.2 Line-by-Line Labeling Review

The changes we propose have not been discussed with the applicant at the time of this review, so they must be considered preliminary.



2 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

REFERENCES

All references used, in addition to the applicant's NDA submission, are mentioned in relevant sections of the review document.

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MEDICAL OFFICER

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