Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Sitagliptin (as phosphate monohydrate)

Proprietary Product Name: Januvia

Sponsor: MSD (Australia) Pty Limited

December 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	Extension of indications
Decision:	Approved

Date of Decision:	13 September 2012
Active ingredient(s):	Sitagliptin (as phosphate monohydrate)
Product Name(s):	Januvia
Sponsor's Name	MSD (Australia) Pty Limited 66 Waterloo Rd, North Ryde NSW 2113
Dose form(s):	Film coated tablets
Strength(s):	25 mg, 50 mg, 100 mg
Container(s):	Blister pack
Pack size(s):	Pack containing 28 tablets
Approved Therapeutic use:	Januvia is indicated for the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise; • as monotherapy, as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus, when metformin cannot be used. • as dual combination therapy, with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.
Route(s) of administration:	Oral
Dosage:	100 mg once daily. Dosage adjustment with moderate and severe renal impairment.
ARTG Number (s)	AUST R 133188, AUST R 133187 and AUST R 133182

Product background

This AusPAR describes the application by the sponsor for an extension of the registered indications of Januvia to include monotherapy and initial combination therapy with metformin, without limitations. The initially proposed new indications/subheadings are shown in *italicised* text below:

Proposed Indications

Monotherapy

Januvia is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus.

Individual Combination Therapy with metformin

Januvia is indicated in patients with Type 2 diabetes mellitus to improve glycaemic control in combination with metformin as initial therapy.

Add-on combination Therapy with Antihyperglycemic agents

For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

The recommended dose of Januvia (sitagliptin) is 100 mg once daily for patients with normal renal function or mild renal insufficiency. Januvia is administered orally.

Januvia was first considered by the Australian Drug Evaluation Committee (ADEC) now called Advisory Committee on Prescription Medicines (ACPM) at its 254th Meeting held on the 4 and 5 October 2007.

The proposed indications were:

> *Monotherapy: as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus.*
>
> *Dual Combination Therapy: in patients with Type 2 diabetes mellitus to improve glycaemic control in combination with metformin, a sulfonylurea, or a PPARγ agonist (e.g., thiazolidinediones) when diet and exercise, plus the single agent do not provide adequate glycaemic control.*
>
> *Triple Combination Therapy: in patients with Type 2 diabetes mellitus to improve glycaemic control in combination with both metformin and a sulfonylurea when diet and exercise, plus both agents do not provide adequate glycaemic control.*

Initial combination therapy with metformin was not a feature of the previous application.

As previously noted by the ADEC:

"The studies used intermediate endpoints such as HbA1c but no long term morbidity or mortality studies were submitted. Sitagliptin was significantly more efficacious in all studies than placebo in reducing HbA1c over 24-52 weeks in adult patients with Type 2 diabetes mellitus."

The clinical evaluator recommended limited registration of sitagliptin as monotherapy and as dual combination therapy with metformin or with a PPARγ agonist. The evaluator considered that there was insufficient duration of experience to recommend the combination with sulphonylureas."

"In the Delegate's view sitagliptin appears to offer some effects in early diabetes Type 2. The placebo controlled studies in monotherapy showed that sitagliptin is better than placebo over 24 weeks. The phase 3 efficacy studies appear to have been well designed, with appropriate run-in periods and primary efficacy endpoints. However, failure to conduct a direct monotherapy comparison with metformin is a serious problem at least as far as assessing the place of sitagliptin in the Australian context. No information is available on the combination of sitagliptin with orlistat or acarbose, both of which might be used in early diabetes Type 2. In principle, sitagliptin might offer most benefit to patients with obesity and insulin resistance, making it likely to be used with metformin and in earlier stages of the disease when weight loss is still a possibility. The combination of sitagliptin with a thiazolidinedione would not ameliorate the adverse effects of the latter and the benefit of sitagliptin, lack of weight gain, would be lost. The current data set supports some role of sitagliptin in monotherapy but the durability of its effect is not known."

"The ADEC considered that although efficacy had been demonstrated there were insufficient safety data, especially long term, to recommend approval of sitagliptin for monotherapy. Clinical experience with sitagliptin in triple treatment with metformin and sulfonylureas was considered inadequate. However, data were adequate to recommend approval for sitagliptin as add-on therapy with metformin a sulfonylurea or with a thiazolidinedione." Durability of efficacy was of some concern.

The current application (detailed in this AusPAR) comprised clinical data only. There is a new Phase III non-inferiority study (P049) to test the glycaemic efficacy of sitagliptin against that of metformin.

There were also extension studies of previously evaluated studies:

- P010 : additional 54 weeks; total 106 weeks
- P014 : additional 54 weeks; total 106 weeks [combined with P010 as Study 010-C2]
- P021 : additional 80 weeks; total 104 weeks
- P023 : additional 36 weeks; total 54 weeks
- P036 : additional 80 weeks; total 104 weeks

Regulatory status

Table 1 summarises the current international regulatory status of Januvia.

Table 1. International regulatory status. Table continued across two pages.

COUNTRY	FILING DATE	APPROVAL DATE	INDICATION
United States	06 Dec 2005	16 Oct 2006	JANUVIA is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1)
European Union	06 Jan 2008	29 Jul 2009	*For adult patients with type 2 diabetes mellitus, Januvia is indicated to improve glycaemic control:* **as monotherapy** • in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. **as dual oral therapy in combination with** • metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control. • a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance. • a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

Table 1. International regulatory status. Continued

COUNTRY	FILING DATE	APPROVAL DATE	INDICATION
			as triple oral therapy in combination with • a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. • a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Januvia is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.
Canada	22 Dec 2008	16 Dec 2009	Monotherapy JANUVIA® (sitagliptin) is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus and for whom metformin is inappropriate due to contraindications or intolerance.
			Combination with Metformin JANUVIA® is indicated in combination with metformin in adult patients with type 2 diabetes mellitus to improve glycaemic control when diet and exercise, plus metformin do not provide adequate glycemic control. Combination with Metformin and a Sulfonylurea JANUVIA® is indicated in combination with metformin and a sulfonylurea in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise, and dual therapy with these agents, do not provide adequate glycemic control.
Switzerland	28 Feb 2011	2 Nov 2011 *Fast Track Review*	Type 2 diabetes mellitus If the blood glucose level is insufficiently controlled by diet and exercise - as monotherapy - in combination with metformin or a sulfonylurea in patients where no adequate glycemic control is achieved with metformin or any other oral antidiabetic agent. - in combination with metformin and a sulfonylurea when therapy with these two agents does not provide adequate glycemic control. If the blood glucose level is insufficiently controlled by diet and exercise and insulin - in combination with insulin (with or without metformin).

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

List of abbreviations used in this AusPAR

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
CI	confidence interval
CPK	creatinine phosphokinase
DAE	discontinuation due to adverse event
DPP-4	dipeptidyl-peptidase-4
ECG	electrocardiogram
FPG	fasting plasma glucose
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide 1
HbA1c	haemoglobin A1c (glycosylated haemoglobin)
HDL-C	high density lipoprotein cholesterol
HOMA-β	homeostasis model assessment – β-cell function
HOMA-IR	homeostasis model assessment – insulin resistance
hr	hour
LDL-C	low density lipoprotein cholesterol
LS	least squares
QUICKI	quantitative insulin sensitivity check index
SAE	serious adverse event
TG	triglyceride
TSH	thyroid stimulating hormone
TZD	thiazolidinedione
ULN	upper limit of normal

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Introduction

Januvia (sitagliptin) is currently registered as dual therapy. The sponsor has provided additional data in support of the current application to include initial therapy and monotherapy.

Formulation

No changes are proposed to the currently registered formulations.

Scope of the sponsor's clinical submission

The submission contained the following clinical information:

- Three pivotal extension studies in support of efficacy and safety: Study P021, Study P023 and Study P036X1
- One randomised controlled study in comparison with metformin: Study P049
- One supportive extension study in support of efficacy and safety: Study 010-C2

Good clinical practice

The studies presented in the submission were conducted according to Good Clinical Practice.

Pharmacokinetics

No new data were submitted.

Pharmacodynamics

No new data submitted.

Efficacy

Initial Therapy and Monotherapy

Pivotal efficacy studies

Study P021

Study design, objectives, locations and dates

Study P021 was an extension of a multinational, multicentre, randomised, parallel group, two dose level, placebo controlled study of sitagliptin as monotherapy. The extension had two treatment groups (sitagliptin 100 mg and 200 mg) and was double blind, with randomisation of the placebo group to either active treatment at the commencement of the extension study. The study was conducted at 111 sites, including 56 in the US and Puerto Rico, from 2004 to 2007.

Inclusion and exclusion criteria

The study included subjects with Type 2 diabetes mellitus, aged ≥18 and ≤75 years of age; and either not on anti hyperglycemic medication or on a single anti hyperglycemic agent

or on a low dose (at ≤50% of maximal dose of both components) dual oral combination agent therapy. In addition, subjects were required to have an HbA1c ≥7% and ≤10% at or within the 2 weeks prior to Visit 3/Week -2.

Study treatments

The study treatments were:

1. Sitagliptin 100 mg, once daily
2. Sitagliptin 200 mg, once daily

The extension was of 80 weeks duration (following on from the initial 24 week placebo controlled phase) to give a total treatment duration of up to 104 weeks.

Efficacy variables and outcomes

The primary efficacy outcome measure was change from baseline in glycosylated haemoglobin (HbA1c). The secondary efficacy outcome measures were; fasting plasma glucose (FPG); fructosamine; glucose; insulin; and C-peptide measured immediately prior to and at 60 and 120 minutes after a standard meal; fasting proinsulin and lipid panel; urinary micro albumin/creatinine ratio; global assessment of appetite; and other glycemic endpoints. In subsets of subjects who were willing to undergo more extensive blood sampling, glucose, insulin and C-peptide profiles were obtained after the standard meal and following an intravenous glucose challenge.

Randomisation and blinding methods

Subjects who had been treated with placebo during the initial 24 week phase of the study were re-randomised to sitagliptin 100 mg or 200 mg in a 1:1 ratio.

Statistical methods

The intra-group comparisons with baseline were performed using analysis of covariance (ANCOVA). Between group comparisons were not performed because of different rates of dropout between the treatment groups. The sample size calculations were not performed for the extension phase.

Participant flow and baseline data

A total of 1066 subjects were screened and 741 subjects were randomised: 238 to 100 mg, 250 to 200 mg and 253 to placebo. There were 384 (51.8%) males, 357 (48.2%) females and the age range was 18 to 75 years. A total of 555 (74.9%) subjects entered the extension but only 229 (30.9%) subjects completed the study. Of the 229 completers for Phase B there were 77 in the 100 mg group, 33 in the placebo/100 mg group, 81 in the 200 mg group and 38 in the placebo/200 mg group. The most frequent reason for discontinuation was lack of efficacy; 230 (31.0%) subjects. Only 27 (3.6%) subjects discontinued because of AEs. Of the subjects that entered the extension, 547 (98.6%) were included in the all patients treated analysis. At entry into the extension, the study groups had similar demographic characteristics but glycaemic control was worse in the 200 mg group.[1]

Results for the primary efficacy outcome

For all four treatment groups there was a significant decrease in HbA1c from baseline (Table 2). For the 100 mg group the mean (95% CI) change from baseline was -0.27 (-0.41 to -0.13) % and for 200 mg -0.40 (-0.53 to -0.26) %. However the magnitude of the

[1] Sponsor comment: "Table 2 (in which the 200/200 mg sitagliptin group had the highest mean HbA1c value) is showing the baseline (randomisation visit) not entry into the extension (Week 24) for the patients who entered the extension."

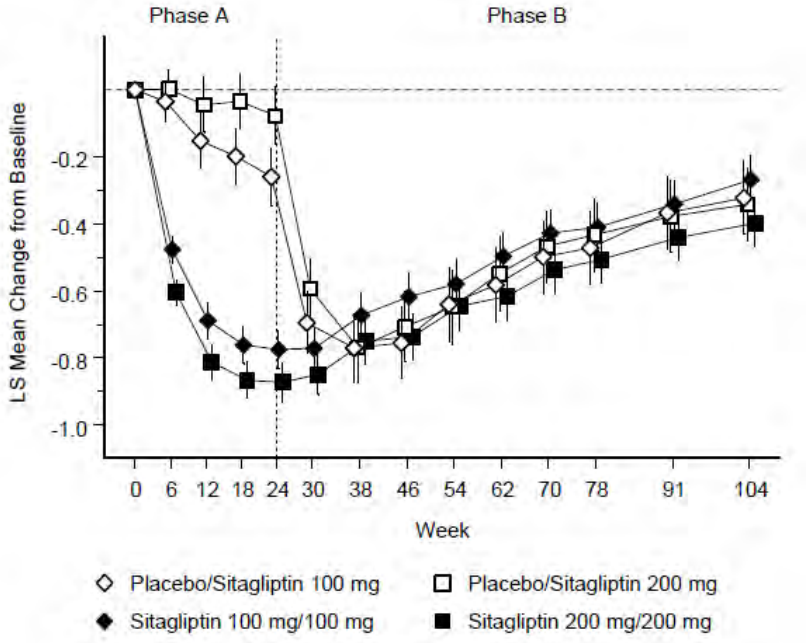
improvement decreased over the two year treatment period (Figure 1)[2]. The coefficient of durability (95% CI) was 0.007 (0.005 to 0.008) for 100 mg and 0.006 (0.005 to 0.008) for 200 mg. The proportion of subjects with HbA1c <7% at Week 104 was 44 (23.4%) subjects in the 100 mg group and 67 (34.4%) in the 200 mg.

Table 2. Analysis of Change from Baseline in HbA1c (%) at Week 104 All-Patients-Treated Population. Study P021.

		Mean (SD)		Change from Baseline		
Treatment	N	Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sitagliptin 100 mg/100 mg	188	7.90 (0.85)	7.62 (0.95)	-0.28 (0.08)	-0.27 (0.07)	(-0.41, -0.13)
Sitagliptin 200 mg/200 mg	195	8.03 (0.88)	7.57 (1.14)	-0.46 (0.08)	-0.40 (0.07)	(-0.53, -0.26)
Placebo/Sitagliptin 100 mg	81	7.87 (0.74)	7.54 (1.07)	-0.33 (0.12)	-0.32 (0.11)	(-0.53, -0.11)
Placebo/Sitagliptin 200 mg	83	7.81 (0.71)	7.51 (1.03)	-0.30 (0.11)	-0.34 (0.11)	(-0.55, -0.13)

Between Treatment Difference	Difference in LS Means (95% CI)
Placebo/Sitagliptin 200 mg vs. Placebo/Sitagliptin 100 mg	-0.02 (-0.32, 0.28)
Sitagliptin 200 mg/200 mg vs. Sitagliptin 100 mg/100 mg	-0.13 (-0.32, 0.06)
Root Mean Square Error of Change =0.97	
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.	

Figure 1. LS Mean Change From Baseline in HbA1c (%) Over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated Population.



Results for other efficacy outcomes

There was an initial decrease in FPG but the magnitude of this effect decreased over the two year treatment period (Figure 2). Two hour post meal glucose decreased from baseline for both doses: LS mean (95% CI) -30.5 (-40.1 to -21.0) mg/dL for 100 mg and -41.5 (-51.0 to -32.1) mg/dL for 200 mg (Table 3).

[2] Sponsor comment: "The durability of effect was evaluated by computing a 'coefficient of durability' (COD). The COD was calculated as follows: The A1C at Week 24 or 25 was considered as the lowest point reached (nadir) A1c; the LS means for A1C at each subsequent time point were then treated as individual values in a simple linear regression. The COD is the slope of the regression line fit to the LS means. A COD of 0.005 for example, implies that the A1C increases (on average) 0.005% per week after reaching its nadir at Week 24 or 25. Higher (more positive) values for the COD suggest a less durable response."

Figure 2. LS Mean Change from Baseline in Fasting Plasma Glucose (mg/dL) Over Time (LS Mean ± SE) by Treatment Group (All-Patients-Treated Population)

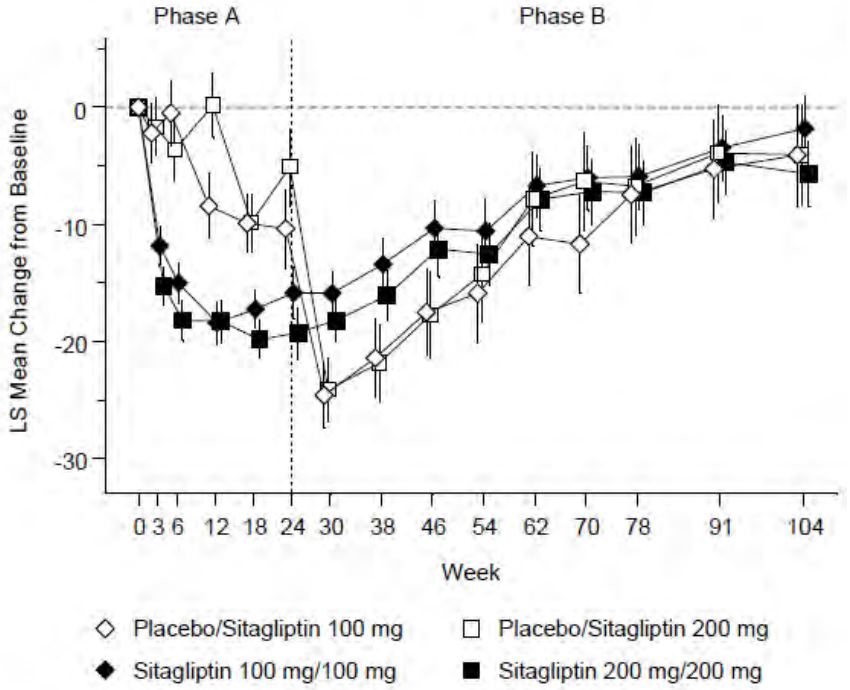


Table 3. Analysis of Change From Baseline in 2-Hour Post-Meal Glucose (mg/dL) at Week 104 (All-Patients-Treated Population) Study P021

Treatment	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sitagliptin 100 mg/100 mg	165	247.1 (68.4)	219.8 (59.6)	-27.3 (5.7)	-30.5 (4.9)	(-40.1, -21.0)
Sitagliptin 200 mg/200 mg	168	260.3 (76.3)	214.2 (75.8)	-46.1 (6.0)	-41.5 (4.8)	(-51.0, -32.1)
Placebo/Sitagliptin 100 mg	68	257.0 (60.2)	215.7 (69.9)	-41.3 (10.2)	-38.3 (7.6)	(-53.2, -23.4)
Placebo/Sitagliptin 200 mg	63	244.4 (72.9)	213.9 (64.6)	-30.6 (7.8)	-35.5 (7.8)	(-50.9, -20.1)

Between Treatment Difference	Difference in LS Means (95% CI)
Placebo/Sitagliptin 200 mg vs. Placebo/Sitagliptin 100 mg	2.8 (-18.6, 24.2)
Sitagliptin 200 mg/200 mg vs. Sitagliptin 100 mg/100 mg	-11.0 (-24.4, 2.4)
Root Mean Square Error of Change =62.0	

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.

Fasting serum insulin concentrations increased in the 100 mg group: mean (95% CI) change 1.3 (0.2 to 2.4) µIU/mL. Fasting serum proinsulin concentrations increased in the 100 mg group: LS mean (95% CI) from baseline 4.1 (0.5 to 7.7) pmol/L. There was no significant change in pancreatic B-cell function (HOMA[3]-β) but insulin resistance (HOMA-IR) decreased in the 100 mg group: LS mean (95% CI) change from baseline 0.7 (0.1 to 1.2). There was no significant change in quantitative insulin-sensitivity check index (QUICKI). There was a significant decrease in 2 hr post meal serum insulin concentration in the 200 mg group: LS mean change from baseline (95% CI) -15.7 (-21.9 to -9.5) µIU/mL. There was a decrease from baseline in post meal plasma glucose area under the plasma concentration effect curve (AUC) for all four treatment groups (Table 4) and in insulin AUC (Table 5) but no significant change in C-peptide AUC.

[3] The homeostatic model assessment (HOMA) is a method used to quantify insulin resistance and beta-cell function.

Table 4. Analysis of Change from Baseline in Glucose Total AUC (mg*h/dL) at Week 104 (All-Patients-Treated Population) Study P021.

Treatment	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sitagliptin 100 mg/100 mg	163	458.0 (102.4)	424.0 (93.6)	-34.0 (8.2)	-38.7 (7.5)	(-53.4, -24.1)
Sitagliptin 200 mg/200 mg	167	477.9 (112.5)	406.7 (114.4)	-71.2 (9.0)	-64.2 (7.4)	(-78.7, -49.8)
Placebo/Sitagliptin 100 mg	68	477.6 (91.2)	408.5 (107.9)	-69.1 (16.9)	-61.4 (11.6)	(-84.1, -38.6)
Placebo/Sitagliptin 200 mg	62	449.1 (113.5)	403.4 (92.7)	-45.8 (12.5)	-56.0 (12.1)	(-79.7, -32.3)

Between Treatment Difference	Difference in LS Means (95% CI)
Placebo/Sitagliptin 200 mg vs. Placebo/Sitagliptin 100 mg	5.4 (-27.4, 38.2)
Sitagliptin 200 mg/200 mg vs. Sitagliptin 100 mg/100 mg	-25.5 (-46.0, -4.9)
Root Mean Square Error of Change =94.7	

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.

Table 5. Analysis of Change from Baseline in Insulin Total AUC (microIU*h/mL) at Week 104 (All-Patients-Treated Population) Study P021

Treatment	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sitagliptin 100 mg/100 mg	153	127.0 (84.0)	122.2 (75.5)	-4.8 (4.7)	-3.4 (3.7)	(-10.8, 3.9)
Sitagliptin 200 mg/200 mg	155	119.6 (80.0)	112.9 (65.6)	-6.7 (4.0)	-7.9 (3.7)	(-15.1, -0.6)
Placebo/Sitagliptin 100 mg	59	139.3 (84.9)	120.2 (76.3)	-19.2 (6.3)	-13.7 (6.0)	(-25.5, -1.8)
Placebo/Sitagliptin 200 mg	60	107.8 (67.5)	112.1 (67.2)	4.3 (6.9)	-0.6 (6.0)	(-12.3, 11.1)

Between Treatment Difference	Difference in LS Means (95% CI)
Placebo/Sitagliptin 200 mg vs. Placebo/Sitagliptin 100 mg	13.1 (-3.5, 29.8)
Sitagliptin 200 mg/200 mg vs. Sitagliptin 100 mg/100 mg	-4.4 (-14.7, 5.9)
Root Mean Square Error of Change =45.9	

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.

Total serum cholesterol concentrations increased from baseline for both dose levels: least squares (LS) mean change from baseline (95% CI) 3.9 (1.6 to 6.3) mg/dL for 100 mg and 2.7 (0.4 to 5.1) mg/dL for 200 mg. Total serum triglyceride concentrations increased from baseline for both dose levels: LS mean change from baseline (95% CI) 8.9 (1.6 to 16.1) mg/dL for 100 mg and 12.3 (5.0 to 19.5) mg/dL for 200 mg. High density lipoprotein cholesterol (HDL-C) increased in the 100 mg group: LS mean change (95% CI) 3.2 (1.2 to 5.2) mg/dL. high density lipoprotein cholesterol (LDL-C) increased in the 100 mg group: LS mean change (95% CI) 5.4 (1.5 to 9.3) mg/dL. There was no significant change in urine micro albumin to creatinine ratios. There was no significant change in appetite.

Study P023

Study design, objectives, locations and dates

Study P023 (was a 36 week extension study of a 18 week multicentre, randomised, double blind, parallel group, placebo controlled study in subjects with Type 2 diabetes mellitus with inadequate glycaemic control. The study was conducted at 114 sites including 60 in the US from 2004 to 2006. The study duration was for 36 weeks (following on from an initial 18 week treatment phase).

Inclusion and exclusion criteria

The study included subjects with Type 2 diabetes mellitus, aged ≥18 and ≤75 years and either: (1) not on anti hyperglycemic agent (off for ≥8 weeks); or (2) on a single anti hyperglycemic agent; or (3) on low doses of dual oral combination agent therapy (at ≤50% of maximal dose of both components). In addition, patients were required to have an HbA1c ≥7% and ≤10% to qualify for randomization.

Study treatments

The treatment groups were:

1. Sitagliptin 100 mg, once daily orally
2. Sitagliptin 200 mg, administered as two 100 mg tablets, once daily orally
3. Placebo for the first 18 weeks, then pioglitazone 30 mg once daily for the remaining 36 weeks

Subjects were initially randomised 2:2:1 for 100 mg: 200 mg: placebo. Subjects not meeting glycaemic goals were to have rescue therapy with metformin.

Efficacy variables and outcomes

The primary efficacy outcome measures were the time profile plot of mean change from baseline in HbA1c and FPG. Secondary efficacy outcome measures were:

- Proportion of subjects meeting HbA1c goals at Week 54
- Fasting proinsulin and insulin
- HOMA-β
- HOMA-IR
- QUICKI
- In a subset of subjects undergoing a meal tolerance test: indices of insulin secretion derived from the C-peptide, insulin, and glucose profiles

The safety outcome measures were: adverse events (AEs), laboratory safety parameters, body weight, vital signs and electrocardiogram (ECG).

Sample size

The sample size calculation was not performed for the extension study.

Statistical methods

Within group comparisons were performed using ANCOVA models. Formal hypothesis tests between treatment groups were not performed for the extension study.

Participant flow and baseline data

A total of 1387 subjects were screened and 521 were randomised to treatment: 205 to 100 mg, 206 to 200 mg and 110 to placebo/pioglitazone. There were 283 (54.3%) males, 238 females and the age range was 27 to 76 years. At entry into the extension phase there were 162 subjects in the 100 mg group, 162 in the 200 mg group and 74 in the placebo/pioglitazone. There were 152 (74.1%) subjects in the 100 mg, 144 (69.9%) in the 200mg and 80 (72.7%) in the placebo/pioglitazone group that completed the study. In the all patients treated analysis there were 156 subjects in the 100 mg group, 158 in the 200 mg and 68 in the placebo/pioglitazone. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline efficacy variables and disease characteristics.

Results for the primary efficacy outcome

The time profile of HbA1c (Figure 3) appeared to be more favourable for pioglitazone than for either sitagliptin group, .[4] Effect for either sitagliptin group diminished over time but

[4] Sponsor comment: "Although there was a difference in the timing of the initiation of the treatments and inherent differences in the populations due to discontinuation/ rescue in some placebo patients prior to pioglitazone initiation. Therefore, it is difficult to make comparisons between the sitagliptin groups and pioglitazone group at Week 54."

was still apparent at Week 54. The LS mean (95% CI) change from baseline in HbA1c was -0.28 (-0.42, to -0.14) % for sitagliptin 100 mg, -0.19 (-0.33 to -0.05) % for sitagliptin 200 mg and -0.87 (-1.08 to -0.66) % for placebo/pioglitazone. The time profile for FPG also appeared to be more favourable for pioglitazone than for either sitagliptin group (Figure 4). Effect for either sitagliptin group diminished over time and was not apparent at Week 54. The LS mean (95% CI) change from baseline in FPG was -5.5 (-11.5 to 0.5) mg/dL for sitagliptin 100 mg, -0.7 (-6.7 to 5.3) mg/dL for sitagliptin 200 mg and -28.0 (-37.1 to -18.9) mg/dL for placebo/pioglitazone.

Figure 3. LS Mean Change from Baseline in HbA1c (%) Over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated Population.

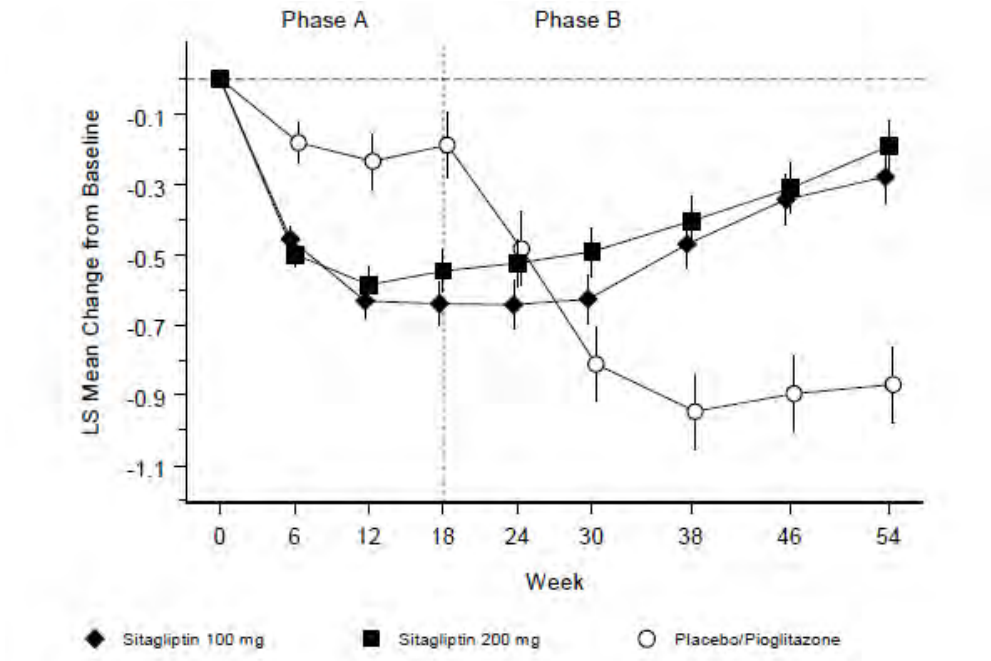
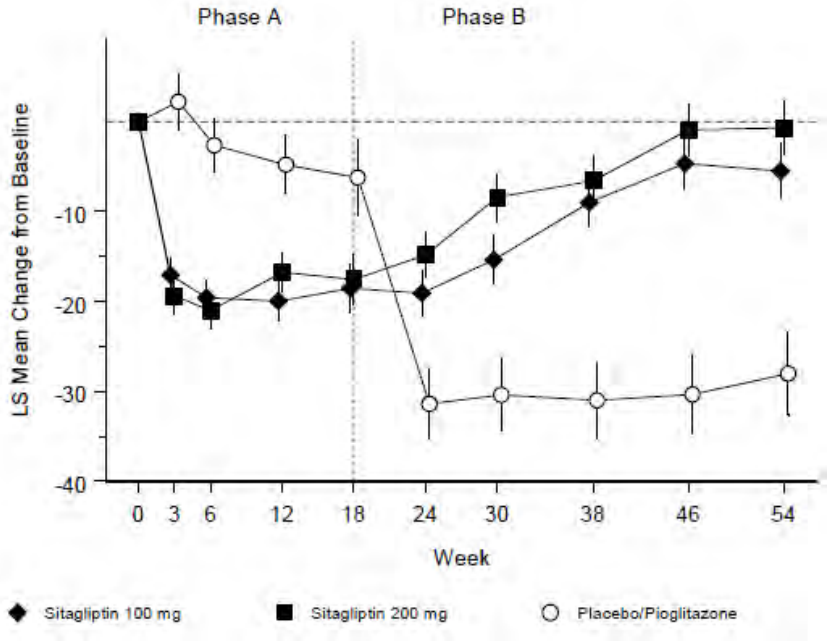


Figure 4. LS Mean Change from Baseline in Fasting Plasma Glucose (mg/dL) Over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated Population.



Results for other efficacy outcomes

The proportion of subjects with HbA1c <7% at Week 54 was 40 (25.6%) subjects in the sitagliptin 100 mg group and 36 (22.8%) in the sitagliptin 200 mg group. The fasting serum insulin concentration increased from baseline in the sitagliptin 100 mg group but decreased in the placebo/pioglitazone group (Table 6).

Table 6. Analysis of Change from Baseline in Fasting Serum Insulin (microIU/mL) at Week 54 All-Patients-Treated Population.

		Mean (SD)		Change from Baseline		
Treatment	N	Baseline	Week 54	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sitagliptin 100 mg	147	14.5 (8.8)	17.6 (13.1)	3.2 (0.8)	3.4 (1.5)	(0.6, 6.3)
Sitagliptin 200 mg	153	15.6 (12.1)	18.0 (30.9)	2.4 (2.0)	2.4 (1.4)	(-0.4, 5.2)
Placebo/Pioglitazone	65	17.7 (12.6)	13.9 (11.1)	-3.8 (1.0)	-4.3 (2.2)	(-8.7, -0.0)
Between Treatment Difference				Difference in LS Means (95% CI)		
Sitagliptin 200 mg vs. Sitagliptin 100 mg				-1.1 (-5.0, 2.9)		
Root Mean Square Error of Change =17.6						
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error						

There was no significant change in fasting serum proinsulin in the sitagliptin groups but there was a decrease in the placebo/pioglitazone group (Table 7).

Table 7. Analysis of Change from Baseline in Fasting Serum Proinsulin (pmol/L) at Week 54 All-Patients-Treated Population.

		Mean (SD)		Change from Baseline		
Treatment	N	Baseline	Week 54	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sitagliptin 100 mg	148	35.7 (28.9)	38.8 (42.7)	3.0 (2.5)	3.3 (3.1)	(-2.9, 9.5)
Sitagliptin 200 mg	145	36.0 (30.7)	41.1 (64.6)	5.1 (4.0)	5.5 (3.2)	(-0.7, 11.8)
Placebo/Pioglitazone	64	41.5 (36.8)	25.1 (21.0)	-16.4 (3.7)	-15.9 (4.8)	(-25.4, -6.4)
Between Treatment Difference				Difference in LS Means (95% CI)		
Sitagliptin 200 mg vs. Sitagliptin 100 mg				2.3 (-6.5, 11.0)		
Root Mean Square Error of Change =38.2						
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error						

There was a significant increase in HOMA-β in the sitagliptin 100 mg group, but no significant change in the other two groups (Table 8). There was no significant change in HOMA-IR for any of the treatment groups.

Table 8. Analysis of Change from Baseline in HOMA-β at Week 54 All-Patients-Treated Population.

		Mean (SD)		Change from Baseline		
Treatment	N	Baseline	Week 54	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sitagliptin 100 mg	146	54.8 (42.0)	68.6 (54.9)	13.8 (3.0)	13.3 (3.7)	(6.0, 20.7)
Sitagliptin 200 mg	153	58.5 (60.5)	65.3 (76.4)	6.8 (4.3)	6.4 (3.7)	(-0.8, 13.6)
Placebo/Pioglitazone	65	69.2 (55.6)	74.7 (63.3)	5.4 (5.3)	5.8 (5.7)	(-5.4, 16.9)
Between Treatment Difference				Difference in LS Means (95% CI)		
Sitagliptin 200 mg vs. Sitagliptin 100 mg				-6.9 (-17.2, 3.4)		
Root Mean Square Error of Change =45.1						
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error						

There was no significant change in QUICKI. There was no significant change for any of the treatment groups in 3 hour post meal glucose AUC, C-peptide AUC or insulin AUC (Tables 9-11). There was no significant change in appetite in any of the treatment groups. In the placebo/pioglitazone group there was a significant increase from baseline in HDL-C: mean (95% CI) 13.2 (9.5 to 16.9) mg/dL; and in LDL-C: 10.8 (4.0 to 17.6) mg/dL. In the sitagliptin 100 mg group there was an increase from baseline in LDL-C: mean (95% CI) 6.8 (2.3 to 11.3) mg/dL. There were no other significant changes in fasting plasma lipids.

Table 9. Summary Statistics Over Time for Change from Baseline in Glucose 3-Hour Total AUC (mg*hr/dL) All-Patients-Treated Population.

			Baseline	On Treatment	Change from Baseline		
Week	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Median	Range
18	Sitagliptin 100 mg	45	699.7 (178.1)	575.3 (147.8)	-124.4 (25.8)	-110.1	-564.3 to 289.6
	Sitagliptin 200 mg	40	793.2 (190.9)	646.1 (161.3)	-147.1 (22.7)	-141.4	-478.0 to 88.8
	Placebo/Pioglitazone	16	675.0 (130.4)	644.3 (152.5)	-30.7 (35.4)	-24.4	-279.7 to 327.8
54	Sitagliptin 100 mg	46	700.2 (176.1)	667.8 (159.4)	-32.4 (24.9)	-23.2	-504.8 to 253.7
	Sitagliptin 200 mg	40	793.2 (190.9)	726.3 (190.3)	-66.9 (30.1)	-87.9	-496.7 to 291.5
	Placebo/Pioglitazone	17	708.9 (188.4)	589.6 (196.0)	-119.3 (22.3)	-98.3	-334.8 to 1.6

Table 10. Summary Statistics Over Time for Change from Baseline in Insulin 3-Hour Total AUC (µIU.hr/mL) All-Patients-Treated Population.

			Baseline	On Treatment	Change from Baseline		
Week	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Median	Range
18	Sitagliptin 100 mg	37	160.5 (92.6)	166.0 (105.9)	5.5 (12.7)	6.8	-243.7 to 300.1
	Sitagliptin 200 mg	32	136.1 (60.8)	135.3 (58.5)	-0.8 (8.3)	-1.0	-89.5 to 100.2
	Placebo/Pioglitazone	16	280.9 (263.3)	217.4 (224.9)	-63.5 (20.5)	-22.6	-245.7 to 4.8
54	Sitagliptin 100 mg	43	156.9 (90.5)	172.5 (114.2)	15.6 (12.7)	2.2	-140.7 to 370.9
	Sitagliptin 200 mg	35	133.3 (62.1)	136.3 (66.1)	3.0 (8.7)	4.1	-108.5 to 149.8
	Placebo/Pioglitazone	17	268.2 (260.3)	214.8 (224.6)	-53.4 (24.5)	-22.0	-253.9 to 99.6

Table 11. Summary Statistics Over Time for Change from Baseline in C-peptide 3-Hour Total AUC (ng.hr/mL) All-Patients-Treated Population.

			Baseline	On Treatment	Change from Baseline		
Week	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Median	Range
18	Sitagliptin 100 mg	43	19.1 (6.2)	20.1 (6.8)	1.1 (0.7)	0.8	-10.0 to 15.9
	Sitagliptin 200 mg	40	17.1 (5.5)	19.1 (6.7)	2.0 (0.7)	2.0	-6.7 to 13.2
	Placebo/Pioglitazone	16	23.0 (10.6)	21.2 (9.6)	-1.7 (1.0)	-1.0	-10.0 to 3.8
54	Sitagliptin 100 mg	46	19.2 (6.1)	20.4 (6.4)	1.2 (0.7)	0.4	-11.8 to 16.9
	Sitagliptin 200 mg	40	17.1 (5.5)	19.0 (6.0)	1.9 (0.7)	1.2	-4.9 to 16.5
	Placebo/Pioglitazone	17	22.4 (10.5)	19.6 (8.5)	-2.8 (1.4)	-2.6	-15.9 to 5.5

Study P036X1

Study design, objectives, locations and dates

Study P036X1 was a 50 week extension to a multicentre randomised, double blind factorial study of the co-administration of sitagliptin and metformin in subjects with Type 2 diabetes mellitus who have inadequate glycaemic control. The study was conducted at 117 sites, 71 in the US and Puerto Rico, from May 2006 to Feb 2008.

Inclusion and exclusion criteria

The study enrolled subjects in the 54 week base study with Type 2 diabetes mellitus, aged 18 to 78 years inclusive, with inadequate glycaemic control (HbA1c ≥7.5% and ≤11%) on diet and exercise alone. Patients who completed the base study and who demonstrated adequate compliance (≥75%) with double-blind study medication were eligible to participate in the 50 week extension study. Patients who initiated rescue therapy during the base study were also eligible to participate in the extension study.

Study treatments

The treatment groups were:

1. Sitagliptin 100 mg once daily
2. Sitagliptin 50 mg twice daily/metformin 500 mg twice daily
3. Sitagliptin 50 mg twice daily/metformin 1000 mg twice daily
4. Metformin 500 mg twice daily
5. Metformin 1000 mg twice daily
6. Placebo for 24 weeks, then metformin

Rescue therapy was with open-label glyburide or glibenclamide.

Efficacy variables and outcomes

The primary efficacy outcome measure was the change from baseline in HbA1c. The secondary efficacy outcome measures were:

- Change from baseline in FPG
- Change from baseline in 2-hour post-meal glucose

Other outcome measures were:

- Fasting proinsulin
- Fasting insulin
- Proinsulin/insulin ratio
- C-peptide
- HOMA-β
- HOMA-IR
- QUICKI
- 2 hr post-meal insulin
- 2 hr post-meal C-peptide
- 2 hr incremental (above the fasting level) post-meal glucose
- Incremental AUC glucose, insulin and C-peptide
- HbA1c goals (<6.5%, <7.0% and <7.5%)
- Body weight
- Waist circumference
- Lipid panel endpoints

The safety outcome measures were: AEs, laboratory values, vital signs and ECG data.

Randomisation and blinding methods

Randomisation was in the ratio of 1:1:1:1:1:1 at the beginning of the study. There was no randomisation into the study extension.

Analysis populations

The analysis was performed on the all patients treated population.

Sample size

The sample size for the base study does not appear to have taken the extension study into account. However, estimates of the study population for the extension study were performed (50% to 70% of the base study) and the expected precision from this population (90 to 130 subjects per group) were determined.

Statistical methods

There were no formal hypothesis tests defined in the study protocol. Within group changes from baseline were analysed using ANCOVA and some between group differences were also analysed.

Participant flow

A total of 685 subjects entered the study: 103 sitagliptin 100 mg, 134 sitagliptin 50 mg/metformin twice daily (b.i.d.) 500 mg, 122 sitagliptin 50 mg/metformin 1000 mg b.i.d.; 107 metformin 500 mg b.i.d., 121 metformin 1000 mg b.i.d., and 98 placebo/metformin. There were 325 (47.4%) males, 360 (52.6%) females, and the age range was 20 to 78 years. A total of 517 subjects completed. Overall 86 (12.6%) subjects discontinued because of lack of efficacy but a higher proportion of subjects in the sitagliptin 100 mg group discontinued due to lack of efficacy: 26 (25.2%).

Relatively few of the subjects that were entered into the extension were included in the all patients treated analysis: 50 (48.5%) in the sitagliptin 100 mg group; 96 (71.6%) in the sitagliptin/metformin 500 mg b.i.d., 105 (86.1%) in the sitagliptin/metformin 1000 mg b.i.d., 64 (59.8%) in the metformin 500 mg b.i.d., 87 (71.9%) in the metformin 1000 mg b.i.d. and 42 (42.9%) in the placebo/metformin. The primary reason for this was lack of on-treatment data.

Baseline data

The treatment groups were similar in demographic characteristics apart from a lower proportion of females in the sitagliptin group and a higher proportion in the sitagliptin/metformin 1000 mg b.i.d. Baseline HbA1c and FPG were lowest in the placebo/metformin group and fasting insulin was highest in that group. Other than this the baseline disease severity was similar for the treatment groups.

Results for the primary efficacy outcome

In the sitagliptin 100 mg group there was a significant decrease in HbA1c from baseline to end of study: LS mean (95% CI) -1.15 (-1.37 to -0.92) % (Table 12). However, the largest effect size was for sitagliptin/metformin 1000 mg b.i.d. (-1.66 [-1.81 to -1.50] %) and there was a greater effect size for metformin 1000 mg b.i.d. (-1.34 [-1.51 to -1.17] %) than for sitagliptin alone. For all the treatment groups the effect diminished over time (over 104 weeks) (Figure 5).

Table 12. Analysis of Change from Baseline in HbA1c (%) at Week 104 All-Patients-Treated in the Extension Phase.

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	50	8.50 (0.94)	7.35 (0.71)	-1.15 (0.14)	-1.15 (0.11)	(-1.37, -0.92)
Met 500 mg b.i.d.	64	8.57 (0.87)	7.46 (0.73)	-1.11 (0.12)	-1.06 (0.10)	(-1.26, -0.87)
Met 1000 mg b.i.d.	87	8.50 (0.84)	7.19 (0.92)	-1.31 (0.11)	-1.34 (0.09)	(-1.51, -1.17)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	96	8.65 (0.94)	7.16 (0.83)	-1.49 (0.11)	-1.39 (0.08)	(-1.55, -1.22)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	105	8.63 (0.96)	6.91 (0.87)	-1.73 (0.11)	-1.66 (0.08)	(-1.81, -1.50)
Placebo/Met 1000 mg b.i.d.	42	8.09 (0.69)	7.03 (0.78)	-1.07 (0.17)	-1.39 (0.12)	(-1.63, -1.15)

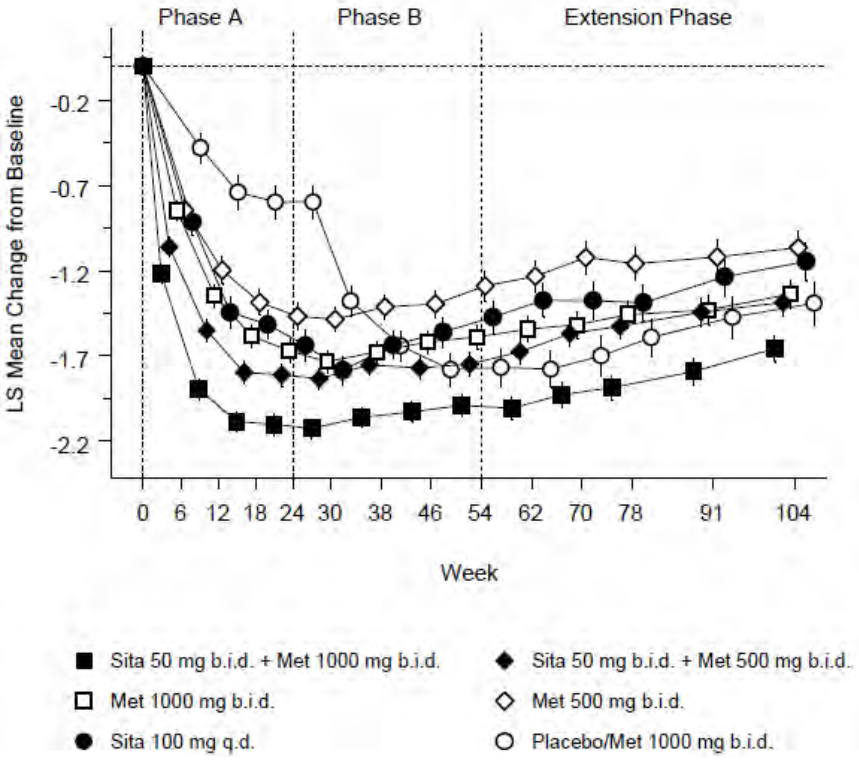
Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-0.32 (-0.57, -0.07)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.24 (-0.51, 0.03)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-0.32 (-0.55, -0.09)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-0.51 (-0.78, -0.24)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences[†]: Sita + Met vs. Met	-0.32 (-0.49, -0.15)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-0.05 (-0.28, 0.19)
Root Mean Square Error of Change = 0.80	

[†]LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

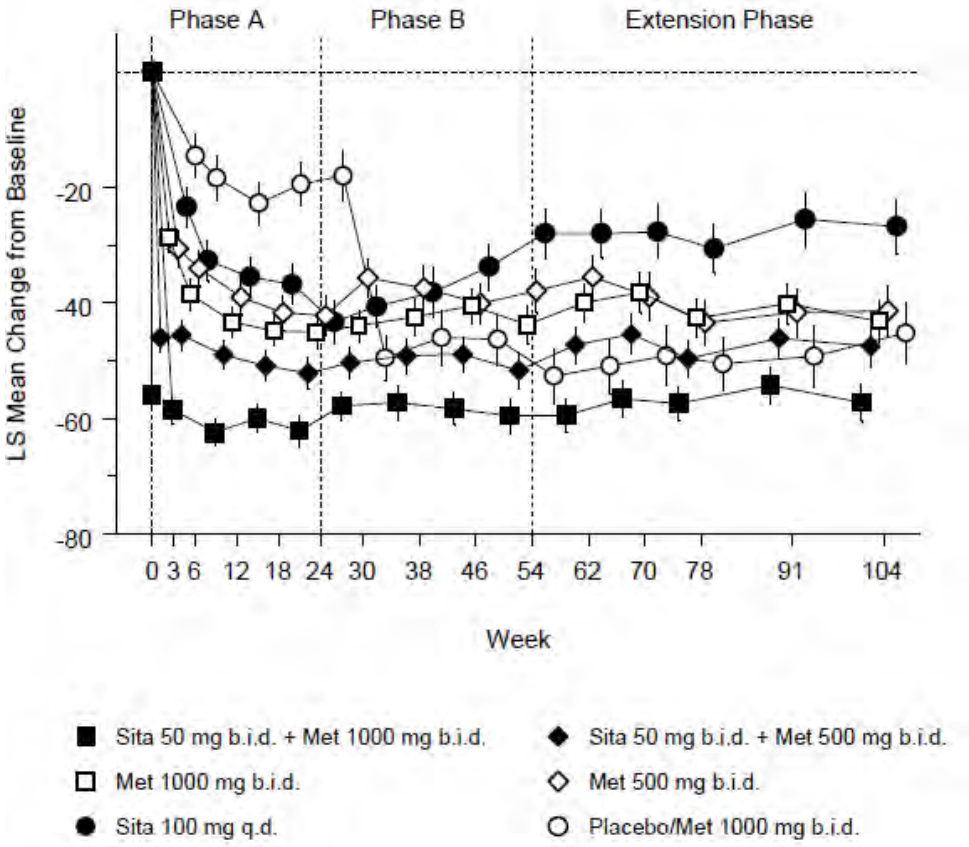
Figure 5. LS Mean Change from Baseline in HbA1c (%) Over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated in the Extension Phase.



Results for other efficacy outcomes

For FPG, the sitagliptin 100 mg group had a significant improvement from baseline: LS mean change (95% CI) -26.8 (-36.2 to -17.4) mg/dL (Table 13). However this improvement was the least for all the treatment groups and the greatest improvement was in the sitagliptin/metformin 1000 mg b.i.d. group (-57.3 [-63.7 to -50.8] mg/dL). The combination of sitagliptin and metformin had greater effect than either treatment alone (Table 13). For all the treatment groups the effect was maintained over the course of the study (Figure 6).

Figure 6. LS Mean Change from Baseline in Fasting Plasma Glucose (mg/dL) Over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated in the Extension Phase.



Similarly, in the sitagliptin group for 2 hr post-meal glucose there was a significant decrease from baseline to Week 104: LS mean change (95% CI) -71.1 (-90.3 to -57.9) mg/dL (Table 14). However, again the effect was the least in the sitagliptin 100 mg group, other than for metformin 500 mg b.i.d., and greatest in the sitagliptin/metformin 1000 mg b.i.d. (-110.0 [-120.9 to -99.1] mg/dL).

Table 13. Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) at Week 104 All-Patients-Treated in the Extension Phase.

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	50	178.0 (37.2)	156.0 (36.4)	-21.9 (5.9)	-26.8 (4.8)	(-36.2, -17.4)
Met 500 mg b.i.d.	63	178.1 (38.6)	141.3 (30.3)	-36.8 (5.1)	-41.4 (4.3)	(-49.8, -33.0)
Met 1000 mg b.i.d.	87	185.6 (45.4)	140.4 (40.0)	-45.2 (5.3)	-43.2 (3.6)	(-50.3, -36.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	96	187.7 (45.2)	137.0 (33.0)	-50.7 (5.5)	-47.5 (3.5)	(-54.3, -40.7)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	105	191.5 (51.9)	127.4 (32.7)	-64.1 (5.2)	-57.3 (3.3)	(-63.7, -50.8)
Placebo/Met 1000 mg b.i.d.	41	160.0 (31.0)	133.7 (34.1)	-26.3 (7.0)	-45.2 (5.3)	(-55.7, -34.8)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-6.1 (-16.9, 4.6)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-20.7 (-32.3, -9.2)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-14.0 (-23.6, -4.4)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-30.5 (-41.9, -19.0)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	-10.1 (-17.3, -2.9)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-4.3 (-14.1, 5.5)

Root Mean Square Error of Change = 33.6

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Table 14. Analysis of Change from Baseline in 2 Hour Post Meal Glucose (mg/dL) at Week 104 All-Patients-Treated in the Extension Phase.

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	40	247.9 (75.9)	189.6 (61.4)	-58.3 (11.6)	-74.1 (8.2)	(-90.3, -57.9)
Met 500 mg b.i.d.	49	270.2 (65.8)	195.4 (56.6)	-74.7 (11.0)	-72.7 (7.4)	(-87.4, -58.1)
Met 1000 mg b.i.d.	69	269.2 (83.1)	180.7 (51.1)	-88.6 (8.6)	-86.7 (6.2)	(-99.0, -74.5)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	78	277.6 (81.4)	173.4 (46.6)	-104.1 (10.0)	-96.2 (5.9)	(-107.8, -84.6)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	88	274.9 (81.3)	158.1 (56.3)	-116.7 (8.7)	-110.0 (5.5)	(-120.9, -99.1)
Placebo/Met 1000 mg b.i.d.	31	230.8 (55.1)	166.2 (57.2)	-64.6 (15.0)	-93.3 (9.4)	(-111.8, -74.9)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-23.4 (-42.0, -4.9)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-22.1 (-42.0, -2.2)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-23.3 (-39.7, -6.9)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-35.9 (-55.6, -16.3)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	-23.4 (-35.7, -11.0)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-9.5 (-26.3, 7.4)

Root Mean Square Error of Change = 51.7

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

In the sitagliptin 100 mg group there was no significant change from baseline in fasting serum insulin: LS mean change (95% CI) 1.6 (-0.8 to 4.0) µIU/mL (Table 15). In the

sitagliptin 100 mg group there was a significant decrease from baseline in fasting serum proinsulin: LS mean change (95% CI) -12.6 (-19.7 to -5.6) pmol/L (Table 16).

Table 15. Analysis of Change from Baseline in Fasting Serum Insulin (µIU/mL) at Week 104 All-Patients-Treated in the Extension Phase.

		Mean (SD)		Change from Baseline		
Treatment Group	N	Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	43	11.9 (9.7)	14.0 (10.9)	2.0 (1.4)	1.6 (1.2)	(-0.8, 4.0)
Met 500 mg b.i.d.	55	13.1 (10.7)	13.1 (9.6)	0.1 (0.8)	-0.1 (1.1)	(-2.2, 2.0)
Met 1000 mg b.i.d.	78	14.2 (9.1)	12.5 (7.4)	-1.7 (0.8)	-1.6 (0.9)	(-3.3, 0.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	85	13.7 (12.6)	14.9 (10.2)	1.1 (0.9)	1.2 (0.9)	(-0.5, 2.9)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	98	14.3 (12.0)	15.1 (14.0)	0.9 (1.0)	1.0 (0.8)	(-0.6, 2.6)
Placebo/Met 1000 mg b.i.d.	35	14.8 (7.2)	14.2 (11.5)	-0.6 (1.8)	-0.2 (1.3)	(-2.9, 2.4)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	1.2 (-1.5, 4.0)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.4 (-3.4, 2.5)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	2.6 (0.2, 4.9)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-0.6 (-3.5, 2.3)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	1.9 (0.1, 3.7)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	2.8 (0.3, 5.2)

Root Mean Square Error of Change = 7.9

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Table 16. Analysis of Change from Baseline in Fasting Serum Proinsulin (pmol/L) at Week 104 All-Patients-Treated in the Extension Phase.

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	24	23.9 (14.5)	17.2 (10.7)	-6.8 (2.1)	-12.6 (3.6)	(-19.7, -5.6)
Met 500 mg b.i.d.	29	31.3 (32.2)	23.0 (23.5)	-8.2 (3.3)	-10.6 (3.3)	(-17.1, -4.2)
Met 1000 mg b.i.d.	61	41.0 (38.7)	21.8 (25.6)	-19.3 (3.7)	-16.5 (2.2)	(-20.9, -12.1)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	65	35.3 (40.5)	22.8 (26.4)	-12.5 (3.0)	-12.7 (2.2)	(-16.9, -8.4)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	79	37.0 (32.2)	22.2 (26.1)	-14.9 (2.8)	-13.9 (2.0)	(-17.8, -10.0)
Placebo/Met 1000 mg b.i.d.	30	32.3 (21.9)	21.6 (23.2)	-10.7 (3.9)	-12.5 (3.2)	(-18.8, -6.2)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-2.0 (-9.7, 5.6)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.0 (-8.3, 8.2)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	2.6 (-3.2, 8.5)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-1.2 (-9.3, 6.8)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences[†]: Sita + Met vs. Met	0.3 (-4.5, 5.1)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	3.9 (-2.3, 10.0)
Root Mean Square Error of Change = 17.4	

[†]LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

There was no significant change from baseline, or difference between treatment groups, in fasting serum C-peptide. HOMA-β improved from baseline in all the treatment groups, with apparent additive effect for sitagliptin and metformin (Table 17). There was an improvement in HOMA-IR in the metformin treatment groups with no apparent additive effect for sitagliptin (Table 18). There was an apparent improvement in QUICKI with metformin with no additive effect for sitagliptin (Table 19).

Table 17. Analysis of Change from Baseline in HOMA-β at Week 104 All-Patients-Treated in the Extension Phase.

		Mean (SD)		Change from Baseline		
Treatment Group	N	Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	43	43.6 (38.5)	67.5 (72.6)	23.8 (7.6)	27.8 (9.2)	(9.8, 45.9)
Met 500 mg b.i.d.	55	44.4 (38.8)	72.4 (72.9)	27.9 (7.1)	30.7 (8.1)	(14.8, 46.6)
Met 1000 mg b.i.d.	78	47.5 (34.6)	71.6 (53.1)	24.1 (4.9)	23.5 (6.8)	(10.2, 36.8)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	85	45.1 (40.4)	86.9 (75.3)	41.7 (6.0)	43.6 (6.5)	(30.8, 56.4)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	98	46.0 (38.3)	98.3 (89.0)	52.3 (7.7)	51.3 (6.1)	(39.4, 63.1)
Placebo/Met 1000 mg b.i.d.	35	58.9 (32.5)	83.6 (72.3)	24.7 (13.2)	24.3 (10.2)	(4.3, 44.3)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	12.9 (-7.5, 33.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	15.7 (-6.3, 37.7)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	27.8 (9.9, 45.6)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	23.4 (1.7, 45.1)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	20.3 (6.8, 33.9)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	20.1 (1.6, 38.6)
Root Mean Square Error of Change = 59.8	

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Table 18. Analysis of Change from Baseline in HOMA-IR at Week 104 All-Patients-Treated in the Extension Phase.

		Mean (SD)		Change from Baseline		
Treatment Group	N	Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	43	5.1 (4.3)	5.3 (4.5)	0.2 (0.7)	-0.4 (0.6)	(-1.5, 0.7)
Met 500 mg b.i.d.	55	5.8 (4.9)	4.6 (3.4)	-1.2 (0.4)	-1.5 (0.5)	(-2.4, -0.5)
Met 1000 mg b.i.d.	78	6.6 (4.9)	4.4 (3.0)	-2.2 (0.4)	-2.0 (0.4)	(-2.9, -1.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	85	6.3 (6.3)	5.1 (3.9)	-1.2 (0.5)	-1.2 (0.4)	(-1.9, -0.4)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	98	6.8 (6.4)	5.1 (5.3)	-1.7 (0.5)	-1.4 (0.4)	(-2.2, -0.7)
Placebo/Met 1000 mg b.i.d.	35	5.9 (3.0)	5.3 (6.6)	-0.6 (1.1)	-0.8 (0.6)	(-2.0, 0.4)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	0.3 (-0.9, 1.5)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.8 (-2.1, 0.6)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	0.6 (-0.5, 1.7)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-1.1 (-2.4, 0.3)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	0.4 (-0.4, 1.3)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	0.9 (-0.2, 2.0)
Root Mean Square Error of Change = 3.6	

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Table 19. Analysis of Change from Baseline in QUICKI at Week 104 All-Patients-Treated in the Extension Phase.

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	43	0.315 (0.029)	0.314 (0.033)	-0.001 (0.004)	0.003 (0.004)	(-0.005, 0.011)
Met 500 mg b.i.d.	55	0.311 (0.037)	0.321 (0.036)	0.009 (0.004)	0.011 (0.004)	(0.004, 0.018)
Met 1000 mg b.i.d.	78	0.303 (0.028)	0.320 (0.031)	0.017 (0.003)	0.015 (0.003)	(0.009, 0.021)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	85	0.312 (0.049)	0.314 (0.030)	0.003 (0.004)	0.004 (0.003)	(-0.001, 0.010)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	98	0.304 (0.031)	0.322 (0.037)	0.017 (0.003)	0.016 (0.003)	(0.011, 0.021)
Placebo/Met 1000 mg b.i.d.	35	0.303 (0.023)	0.319 (0.032)	0.015 (0.005)	0.014 (0.005)	(0.005, 0.023)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-0.007 (-0.016, 0.002)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	0.001 (-0.008, 0.011)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	0.001 (-0.007, 0.009)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	0.013 (0.003, 0.023)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences[T]: Sita + Met vs. Met	-0.003 (-0.009, 0.003)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-0.011 (-0.019, -0.002)
Root Mean Square Error of Change = 0.027	

[T]LS mean differences are averaged over the two metformin dose levels.
b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

There was no change in 2 hr post meal insulin in the sitaglitin 100 mg group: LS mean change (95% CI) -0.4 (-11.2 to 10.4) µIU/mL. There was no significant change in 2 hr post-meal C-peptide in any of the treatment groups. Glucose AUC decreased from baseline in the stagliptin 100 mg group: LS mean change (95% CI) -105.7 (-132.4 to -79.1) mg.hr/dL (Table 20). However the improvement was greater in the metformin groups and there was an additive effect for both sitagliptin and metformin. Insulin AUC did not change significantly in the sitagliptin 100 mg group: LS mean change (95% CI) 7.1 (-6.3 to 20.5) µIU.hr/mL (Table 21).

Table 20. Analysis of Change from Baseline in Glucose Total AUC (mg.hr/dL) at Week 104 All-Patients-Treated in the Extension Phase.

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	39	469.7 (104.9)	389.5 (102.5)	-80.3 (18.0)	-105.7 (13.6)	(-132.4, -79.1)
Met 500 mg b.i.d.	50	503.1 (94.6)	382.2 (88.5)	-120.9 (16.6)	-120.0 (12.0)	(-143.5, -96.5)
Met 1000 mg b.i.d.	67	509.4 (120.6)	362.9 (82.6)	-146.5 (13.9)	-138.8 (10.3)	(-159.0, -118.6)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	78	509.8 (130.4)	342.8 (79.5)	-167.0 (16.3)	-160.3 (9.6)	(-179.1, -141.4)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	86	512.1 (127.4)	310.7 (89.4)	-201.4 (13.6)	-190.5 (9.1)	(-208.4, -172.6)
Placebo/Met 1000 mg b.i.d.	30	447.9 (82.4)	343.8 (89.8)	-104.1 (22.5)	-146.0 (15.5)	(-176.4, -115.5)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-40.3 (-70.3, -10.3)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-54.5 (-87.1, -21.9)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-51.7 (-78.7, -24.7)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-84.8 (-117.0, -52.5)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	-46.0 (-66.2, -25.8)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-21.4 (-49.0, 6.1)
Root Mean Square Error of Change = 84.1	

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Table 21. Analysis of Change from Baseline in Insulin Total AUC (µIU.hr/mL) at Week 104 All-Patients-Treated in the Extension Phase.

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	35	78.3 (43.3)	84.8 (45.1)	6.5 (6.2)	7.1 (6.8)	(-6.3, 20.5)
Met 500 mg b.i.d.	44	86.4 (52.4)	104.3 (75.6)	17.9 (7.2)	19.4 (6.1)	(7.4, 31.4)
Met 1000 mg b.i.d.	66	81.8 (42.0)	89.4 (54.6)	7.6 (3.9)	7.5 (4.9)	(-2.2, 17.3)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	68	81.4 (47.5)	98.4 (58.5)	17.1 (4.7)	17.4 (4.9)	(7.8, 27.0)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	81	80.2 (50.1)	83.2 (53.0)	3.0 (4.8)	2.1 (4.5)	(-6.7, 10.9)
Placebo/Met 1000 mg b.i.d.	29	92.6 (38.7)	95.4 (56.2)	2.8 (8.7)	4.7 (7.5)	(-10.1, 19.4)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-1.9 (-17.2, 13.4)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	10.3 (-6.1, 26.8)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-5.4 (-18.6, 7.7)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-5.0 (-21.2, 11.1)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	-3.7 (-13.8, 6.4)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	9.9 (-3.8, 23.6)
Root Mean Square Error of Change = 40.1	

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

There were no significant changes in C-peptide AUC. HbA1c <7% at Week 104 was achieved by 16 (32%) subjects in the sitagliptin 100 mg group. HDL-C increased in all the treatment groups with no apparent difference between the treatments (Table 22). There were no other significant changes in plasma lipids. There was no significant change in body weight in the sitagliptin 100 mg group (Table 23). Waist circumference decreased from baseline only in the sitagliptin/metformin 1000 mg b.i.d. group: LS mean change (95% CI) -2.3 (0.9) (-4.1 to -0.6) cm.

Table 22. Analysis of Percent Change from Baseline in Plasma HDL-C (mg/dL) at Week 104 All-Patients-Treated in the Extension Phase.

		Mean (SD)		Percent Change from Baseline		
Treatment Group	N	Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	45	41.4 (7.6)	44.2 (9.8)	7.3 (2.6)	6.5 (2.7)	(1.1, 11.8)
Met 500 mg b.i.d.	59	42.6 (8.6)	46.0 (11.1)	8.1 (2.1)	7.8 (2.4)	(3.1, 12.4)
Met 1000 mg b.i.d.	83	44.8 (11.1)	48.3 (12.4)	8.7 (1.8)	9.4 (2.0)	(5.5, 13.3)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	86	44.2 (9.5)	46.0 (9.4)	5.9 (2.0)	6.4 (2.0)	(2.5, 10.2)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	102	43.6 (11.3)	46.7 (13.7)	8.2 (2.3)	8.3 (1.8)	(4.7, 11.8)
Placebo/Met 1000 mg b.i.d.	37	41.3 (8.7)	45.5 (10.2)	11.2 (2.6)	10.3 (3.0)	(4.4, 16.2)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-1.4 (-7.5, 4.6)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.1 (-6.7, 6.5)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-1.1 (-6.4, 4.2)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	1.8 (-4.6, 8.3)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences[T]: Sita + Met vs. Met	-1.3 (-5.3, 2.8)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-3.0 (-8.5, 2.5)
Root Mean Square Error of Change = 18.1	

[T]LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Table 23. Analysis of Change from Baseline in Body Weight (kg) at Week 104 All-Patients-Treated in the Extension Phase.

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	50	83.9 (19.6)	84.6 (18.8)	0.7 (0.5)	0.5 (0.6)	(-0.7, 1.7)
Met 500 mg b.i.d.	59	86.1 (21.3)	85.4 (21.1)	-0.7 (0.6)	-0.8 (0.6)	(-1.9, 0.3)
Met 1000 mg b.i.d.	81	89.6 (24.0)	87.1 (23.2)	-2.5 (0.5)	-2.4 (0.5)	(-3.3, -1.5)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	94	85.8 (21.9)	85.9 (21.7)	0.1 (0.4)	0.0 (0.4)	(-0.8, 0.9)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	100	85.3 (19.2)	84.1 (19.3)	-1.2 (0.5)	-1.2 (0.4)	(-2.0, -0.3)
Placebo/Met 1000 mg b.i.d.	42	88.4 (20.4)	87.3 (19.9)	-1.1 (0.7)	-1.1 (0.7)	(-2.3, 0.2)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	0.8 (-0.5, 2.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.4 (-1.9, 1.0)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	1.2 (0.0, 2.5)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-1.6 (-3.1, -0.2)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	1.0 (0.1, 2.0)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	2.4 (1.2, 3.7)
Root Mean Square Error of Change = 4.2	

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Study P049

Study design, objectives, locations and dates

Study P049 was a multicentre, double blind randomised, comparator (metformin) controlled, parallel group, non-inferiority study in subjects with Type 2 diabetes mellitus with inadequate glycaemic control. The study was conducted from 4 April 2007 to 25 July 2008 at 121 sites, including 22 in the US and Puerto Rico.

Inclusion and exclusion criteria

The inclusion criteria included:

- Type 2 diabetes mellitus and glycaemic control has not responded to diet and exercise
- HbA1c ≥6.5% and ≤9.0%.
- ≥18 and ≤78 years of age
- Not treated with anti hyperglycemic medication for at least 4 months (16 weeks)
- ≥85% compliance (as measured by site performed tablet count) with placebo treatment during run-in.

The exclusion criteria included:

- History of Type 1 diabetes mellitus or of ketoacidosis.
- Subject assessed by the investigator as possibly having Type 1 diabetes confirmed with a C-peptide ≤0.26 nmol/L
- Exclusionary laboratory values (serum creatinine ≥123.8 µmol/L for males or 114.9 µmol/L for females; creatinine clearance (Cockroft-Gault) <60 mL/min; alanine aminotransferase (ALT), aspartate aminotransferase (AST) or creatine phosphokinase (CPK) >2x upper limit of normal (ULN); thyroid stimulating hormone (TSH) outside

the normal range; triglycerides (TG) >6.8 mmol/L, haemoglobin (Hb) below the normal range)

- FPG <6.66 mmol/L or >13.88 mmol/L

Study treatments

The study treatments were:

1. Sitagliptin 100 mg once daily
2. Metformin 500 mg tablets, two orally twice daily (increased from 500 mg daily to 2000 mg daily over a maximum of 5 weeks[5])

Subjects were randomised 1:1 by computer generated schedule. No anti hyperglycemic medication (sulfonylureas, meglitinides, biguanides, glucosidase inhibitors, TZDs, exenatide, insulin, fixed-dose combination therapy, DPP-4 inhibitors) were permitted during the study except for medication indicated as part of the study protocol.

Efficacy variables and outcomes

The primary efficacy outcome measure was the change from baseline in HbA1c. The secondary efficacy outcome measures were:

- Change from baseline in FPG
- Change from baseline in 1.5-anhydroglucitol
- Change from baseline in proinsulin
- Change from baseline in proinsulin to insulin ratio
- Change from baseline in HOMA-β
- Change from baseline in HOMA-IR
- Proportion of subjects achieving primary treatment goal: HbA1c <6.5%
- Proportion of subjects achieving secondary treatment goal: HbA1c <7%
- Change from baseline in serum lipid parameters: triglycerides (TG), LDL-C, HDL-C, non-HDL-C, TG/HDL-C ratio, and total cholesterol

Sample size

A sample size of 400 subjects per group was estimated to deliver 97% power to determine a non-inferiority margin of 0.4% assuming the true mean difference between treatments is <0.1%, using a SD of 1.1% for the change in HbA1c from baseline to Week 24. Assuming a dropout rate of 20%, the final sample size determination was 500 subjects per treatment group. The sample size calculation used data from Study PN021.

Statistical methods

Hypothesis tests were performed using ANCOVA.The criterion for non-inferiority was an upper boundary of the 95% confidence interval of the treatment effect (sitagliptin minus metformin) less than 0.4%. Primary efficacy outcome measure was tested for the per-protocol population and the full analysis set; and the secondary efficacy outcome measures were tested only for the per-protocol population.

Participant flow

A total of 2092 subjects were screened, and 1058 were randomised: 532 to sitagliptin and 526 to metformin. A total of 917 subjects completed: 468 (88.0%) in the sitagliptin group and 449 (85.4%) in the metformin. The per-protocol data set included 455 (86.2%)

[5] Sponsor corrected the period of treatment to 5 rather than 3 weeks as stated in original CER.

subjects in the sitagliptin group and 439 (84.1%) in the metformin. The full analysis set included 512 (97.0%) subjects in the sitagliptin group and 498 (95.4%) in the metformin.

Baseline data

There were 574 (54.3%) females, 484 (45.7%) males, and the age range was 20 to 78 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline disease characteristics. Concomitant medications were taken by 404 (76.5%) subjects in the sitagliptin group and 389 (74.5%) in the metformin. The most common concomitant medication was agents acting on the renin-angiotensin system: 232 (43.9%) subjects in the sitagliptin group and 214 (41.0%) in the metformin. Lipid modifying agents were taken by 185 (35.0%) subjects in the sitagliptin group and 183 (35.1%) in the metformin.

Results for the primary efficacy outcome

The pre specified criteria for non-inferiority were met. The LS mean difference (95% CI) for the change in HbA1c from baseline to Week 24 (sitagliptin – metformin) was 0.14 (0.06 to 0.21) % (Table 24). However, by this analysis metformin was actually superior to sitagliptin because the lower 95% CI was greater than 0. The FAS also demonstrated superiority for metformin: LS mean difference (95% CI) for the change in HbA1c from baseline to Week 24 (sitagliptin – metformin) 0.18 (0.10 to 0.25) % (Table 25). The subgroup analysis did not indicate any subgroup with potential benefit for sitagliptin in comparison with metformin.

Table 24. Analysis of Change from Baseline in HbA1c (%) at Week 24 (Per-Protocol Population)

		Baseline	Week 24	Change from Baseline at Week 24	
Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	LS Mean (95% CI) [†]
Sitagliptin	455	7.22 (0.73)	6.80 (0.71)	-0.42 (0.03)	-0.43 (-0.48, -0.38)
Metformin	439	7.25 (0.69)	6.68 (0.62)	-0.57 (0.03)	-0.57 (-0.62, -0.51)
Estimated Difference				Difference in LS Means (95% CI)	
Sitagliptin vs. Metformin				0.14 (0.06, 0.21) [‡]	
Root Mean Square Error of Change =0.57					
[†] Based on analysis of covariance with terms for treatment and baseline HbA_{1c} as a covariate. [‡] Non-inferior based upon pre-specified non-inferiority upper bound of 0.4.					

Table 25. Analysis of Change from Baseline in HbA1c (%) at Week 24 (Full Analysis Set)

		Baseline	Week 24	Change from Baseline at Week 24	
Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	LS Mean (95% CI) [†]
Sitagliptin	512	7.25 (0.75)	6.87 (0.84)	-0.37 (0.03)	-0.38 (-0.43, -0.32)
Metformin	498	7.25 (0.69)	6.70 (0.65)	-0.55 (0.03)	-0.55 (-0.61, -0.50)
Estimated Difference				Difference in LS Means (95% CI)	
Sitagliptin vs. Metformin				0.18 (0.10, 0.25) [‡]	
Root Mean Square Error of Change =0.62					
[†] Based on analysis of covariance with terms for treatment and baseline HbA_{1c} as a covariate. [‡] Non-inferior based upon pre-specified non-inferiority upper bound of 0.4.					

Results for other efficacy outcomes

A greater proportion of subjects in the metformin group achieved HbA1c <6.5% at Week 24: 172 (39.2%) subjects compared with 153 (33.6%) in the sitagliptin. A significantly greater proportion of subjects in the metformin group achieved HbA1c <7% at Week 24: difference in proportions (95% CI) (sitagliptin - metformin) -7.1 (-12.9 to -1.2) %. FPG was lower in the metformin group at Week 24: LS mean difference (95% CI) 8.0 (4.5 to 11.4)

mg/dL. Mean 1,5-anhydroglucitol was higher in the metformin group: LS mean difference (95% CI) -0.9 (-1.5 to -0.3) µg/mL.

There was no significant difference in the change in fasting serum insulin to Week 24: LS mean difference (95% CI) 1.1 (-0.8 to 3.1) µIU/mL. Fasting serum proinsulin decreased to a greater extent in the metformin group: LS mean difference (95% CI) 6.0 (3.2 to 8.7).The fasting serum proinsulin to insulin ratio decreased to a greater extent in the metformin group: LS mean difference (95% CI) 0.050 (0.027 to 0.074). There was no significant difference between treatment groups in the change in HOMA-β: LS mean difference (95% CI) -4.5 (-14.6 to 5.7).There was no significant difference between treatment groups in the change in HOMA-IR: LS mean difference (95% CI) 0.3 (-0.9 to 1.4).

Total cholesterol increased in the sitagliptin group relative to metformin: LS mean difference (95% CI) 3.3 (0.9 to 5.8) mg/dL. LDL-C increased from baseline in the sitagliptin group: LS mean change (95% CI) 11.2 (8.0 to 14.5) mg/dL; and to a significantly greater extent than in the metformin group: LS mean difference (95% CI) 8.7 (4.1 to 13.3) mg/dL. There was no significant difference in triglycerides or HDL-C.

Other efficacy studies

Study 010-C2

Study 010-C2 was a 52 week second extension study of two Phase II dose ranging studies (Protocol 010-20 and Protocol 014-20). Both of the initial studies had been comprised of a 12 week base study followed by a 40 week first extension. The study included subjects who had completed the first extension studies for Protocol 010-20 or Protocol 014-20. Both studies originally included subjects with Type 2 diabetes mellitus with inadequate glycaemic control. To be eligible for inclusion in the second extension there had to be ≥75% compliance with study medication during the first extension period. Subjects from Protocol 014-20 were excluded if in subjects ≤65 years of age, serum creatinine was ≥132.7 µmol/L in men and ≥123.9 µmol/L in; and in subjects >65 years of age, serum creatinine ≥1.2 mg/dL in men or ≥1.1 mg/dL in women.

The study treatments were:

1. Sitagliptin 100 mg once daily, with placebo for glipizide or metformin
2. Glipizide 5 mg[6]
3. Metformin 850 mg twice daily

Metformin or pioglitazone /rosiglitazone were used as rescue therapy.

The primary efficacy outcome measure was change in HbA1c from baseline. Secondary efficacy outcome measures were: FPG, HOMA-β, HOMA-IR, QUICKI, fasting insulin and lipid panel. Safety outcome measures were: AEs, hypoglycaemic episodes, laboratory safety parameters, vital signs, ECG and body weight.

A total of 587 subjects were entered into the second extension: 488 treated with sitagliptin and 99 with comparator. A total of 435 (74.1%) subjects completed; 126 (25.8%) in the sitagliptin group and 26 (26.3%) in the comparator group discontinued (Figure 7). There were 253 subjects included in the efficacy analysis at Week 106; 141 (55.7%) male, 112 (44.3%) female and the age range was 21 to 73 years (Table 26). It is not clear why so many subjects were excluded from the efficacy analysis because there was no text explanation and no tabular summary of the reasons for exclusion.[7]

[6] Sponsor correction: "The dose was up-titrated to a maximum of 20 mg based on glycaemic control."

[7] Sponsor comment: "The sponsor responded to this in the Section 31 Response to Questions (see page 45) and the Reply to Completed Evaluation Reports (see page 59)."

Figure 7. Overall Disposition of Patients Pooled Phase IIb Second Extension Data, Including Data After Initiation of Glycemic Rescue Therapy.

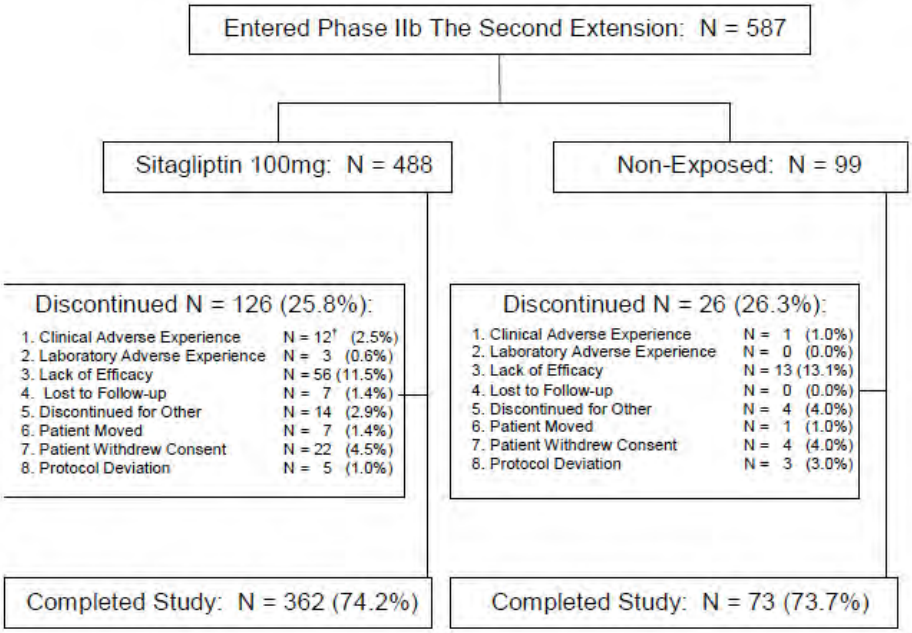


Table 26. Patient Accounting for the Analysis of HbA1c (%) at Week 106 (Pooled P010-20 and P014-20).

	Number (%)			
	Sitagliptin 100 mg TDD†	Placebo /Metformin	Glipizide	Total
TOTAL RANDOMIZED	345	111	123	579
ENTERED THE SECOND EXTENSION	154	43	56	253
Prior to Initiation of Rescue Therapy	120	37	45	202
Included in APT‡ Analysis	112 (93.3)	33 (89.2)	43 (95.6)	188 (93.1)
Included in WEEK 106 COMPLETERS Analysis§	73 (60.8)	22 (59.5)	22 (48.9)	117 (57.9)
EXCLUDED FROM APT‡ ANALYSIS	8 (6.7)	4 (10.8)	2 (4.4)	14 (6.9)
No Baseline Data	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No Data up to Week 106 in The Second Extension	8 (6.7)	4 (10.8)	2 (4.4)	14 (6.9)
EXCLUDED FROM WEEK 106 COMPLETERS ANALYSIS§	39 (32.5)	11 (29.7)	21 (46.7)	71 (35.1)
Rescued in The Second Extension Prior to Week 106‖	24 (20.0)	8 (21.6)	13 (28.9)	45 (22.3)
No Data at Week 106 ¶	15 (12.5)	3 (8.1)	8 (17.8)	26 (12.9)

Percentages are calculated using the number of patients entering the second extension without being rescued in the first extension as the denominator (i.e., number of patients prior to initiation of rescue therapy in the second extension).

† Includes sitagliptin 50 mg b.i.d./100 mg q.d. (from P010), sitagliptin 50 mg b.i.d./100 mg q.d. (from P014) and sitagliptin 100 mg q.d./100 mg q.d. (from P014).

‡ APT: All-Patients-Treated.

§ The Week 106 completers analysis, without missing data imputed, is a subset of the second extension APT population including all patients with Week 106 data.

‖ Efficacy data obtained on a patient after initiation of rescue therapy are treated as missing.

¶ For patients not on rescue medication.

TDD=Total Daily Dose.

The LS mean change from baseline to Week 106 in HbA1c was -0.39 (-0.54 to -0.24) % (Table 27). In the second year of the 2 year follow up period there was little difference in mean HbA1c between sitagliptin, glipizide and metformin (Figure 8). The coefficient of durability (95% CI) was 0.002 (0.001 to 0.005) % per week for sitagliptin and 0.006 (0.002 to 0.009) % per week for glipizide. For sitagliptin, there was no significant change in FPG from baseline to Week 106: LS mean (95% CI) -3.9 (-11.0 to 3.1) mg/dL. However there was a statistically significant improvement in FPG with metformin: LS mean (95%

CI) -23.7 (-38.2 to -9.3) mg/dL. Whilst effect for sitagliptin and glipizide decreased over time the effect for metformin was maintained (Figure 9).[8]

Table 27. Analysis of Change From Baseline in HbA1c (%) at Week 106 All-Patients-Treated Population (Pooled PN010-20 and PN014-20).

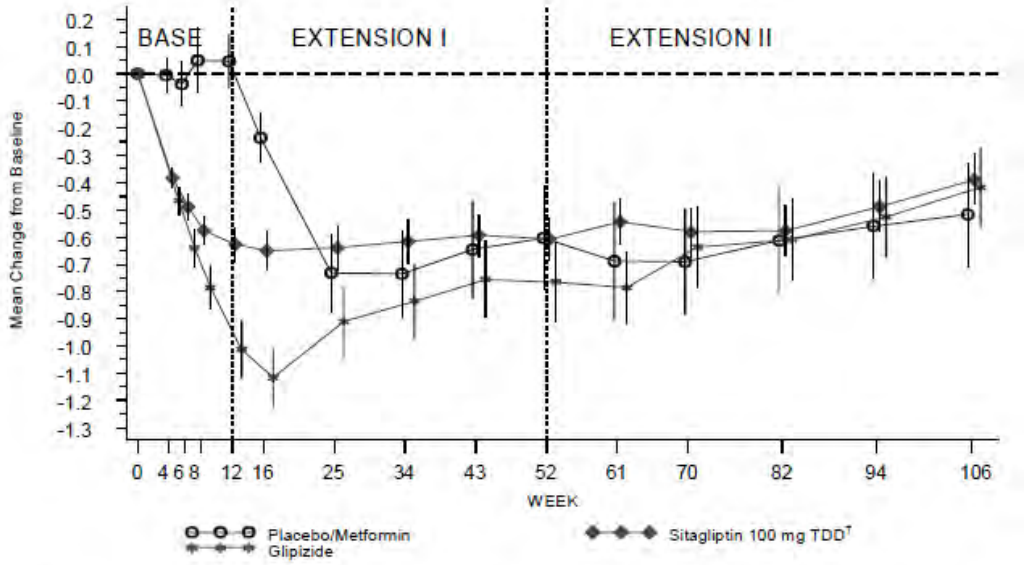
Treatment	N	Mean (SD)		Change From Baseline		
		Baseline	Week 106	Mean (SD)	LS Mean	95% CI for LS Mean
Placebo/Metformin	33	7.35 (0.86)	6.96 (0.83)	-0.38 (1.09)	-0.52	(-0.83, -0.20)
Sitagliptin 100 mg TDD†	112	7.50 (0.82)	7.13 (0.82)	-0.37 (0.97)	-0.39	(-0.54, -0.24)
Glipizide	43	7.66 (0.90)	7.14 (0.85)	-0.52 (0.93)	-0.42	(-0.70, -0.13)
p-Value for Effect						
Protocol					0.873	
Baseline					<0.001	
Treatment					0.739	
Prior Anti-hyperglycemic Medication					0.598	
Root Mean Square Error of Change = 0.79						

† Includes sitagliptin 50 mg b.i.d./100 mg q.d. (from PN010), sitagliptin 50 mg b.i.d./100 mg q.d. (from PN014), and sitagliptin 100 mg q.d./100 mg q.d. (from PN014).
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; TDD=Total Daily Dose.

There was no significant change in fasting serum insulin for any of the treatment groups. There was no significant change in HOMA- β, HOMA-IR or QUICKI for any of the treatment groups. There were no significant changes over time in cholesterol, triglycerides, LDL-C or HDL-C for sitagliptin (change from baseline (95% CI) were respectively 5.7 (-45.4 to 67.3) mg/dL, 5.1 (-66.6 to 238.7) mg/dL, 8.3 (-63.7 to 108.5) mg/dL and 0.0 (-33.9 to 74.4) mg/dL). The number (%) subjects with HbA1c <7% at Week 106 was 50 (44.6%) subjects for sitagliptin, 21 (63.6%) for metformin and 22 (51.2%) for glipizide.

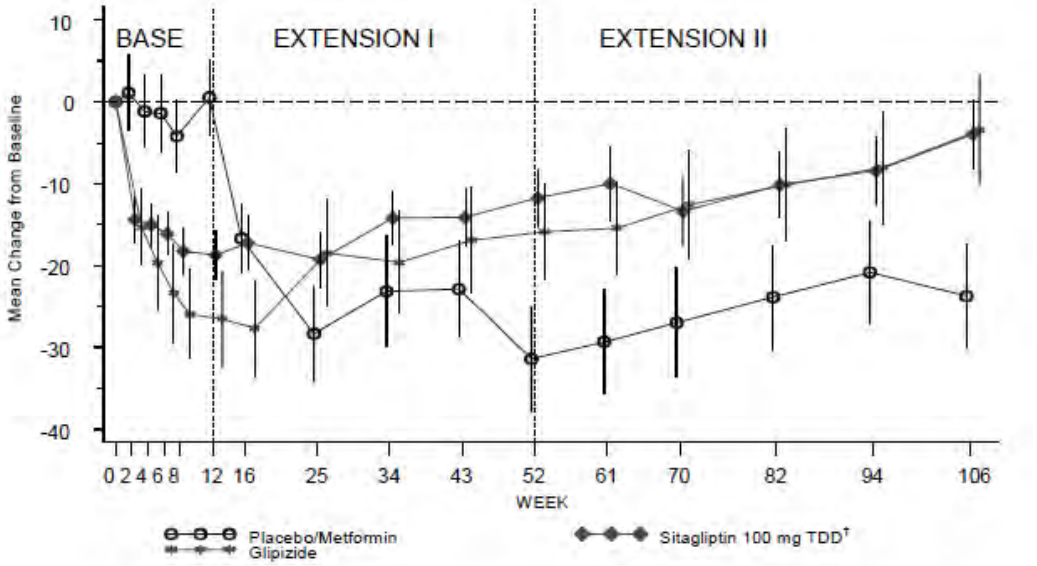
[8] Sponsor comment: "There was a difference in the timing of the initiation of the treatments and inherent differences in the populations due to early discontinuation in some placebo patients prior to metformin initiation. Therefore, it is difficult to make comparisons between the sitagliptin and metformin groups at Week 106."

Figure 8. Mean Change From Baseline in HbA1c (%) Over Time (LS Mean ± SE) All-Patients-Treated Population (Pooled PN010-20 and PN014-20).



† Includes sitagliptin 50 mg b.i.d./100 mg q.d. (from PN010), sitagliptin 50 mg b.i.d./100 mg q.d. (from PN014), and sitagliptin 100 mg q.d./100 mg q.d. (from PN014).

Figure 9. Mean Change From Baseline in Fasting Plasma Glucose (mg/dL) Over Time (LS Mean ± SE) All-Patients-Treated Population (Pooled PN010-20 and PN014-20)



† Includes sitagliptin 50 mg b.i.d./100 mg q.d. (from PN010), sitagliptin 50 mg b.i.d./100 mg q.d. (from PN014), and sitagliptin 100 mg q.d./100 mg q.d. (from PN014).

Analyses performed across trials (pooled analyses and meta-analyses)

There were no pooled analyses included in the dossier.

Evaluator's conclusions on clinical efficacy

The efficacy data indicate a sustained effect for sitagliptin over a 2 year period. However, sitagliptin had lesser efficacy than either pioglitazone or metformin[9]. Sitagliptin appears to be best used in combination with metformin.

Study P021 demonstrated a sustained improvement in HbA1c over a 2 year period. The improvement was greater in the 200 mg dose group than the 100 mg: mean decrease in HbA1c 0.4% compared with 0.27%. However the magnitude of this improvement in HbA1c was small and the same as that used as the criterion for non-inferiority in Study P049 (0.4%). The effect also decreased over the two year treatment period. There was no improvement in FPG. There was an increase in fasting serum cholesterol in both treatment groups and an increase in HDL-C and LDL-C in the 100 mg dose group.

In Study P023, over a 54 week period the time profile of HbA1c appeared to be more favourable for pioglitazone than for either sitagliptin 100 mg or 200 mg.[10] At Week 54, using confidence interval testing, there was a significantly greater decrease in HbA1c in the pioglitazone group than in either sitagliptin group: LS mean (95% CI) change from baseline in HbA1c -0.28 (-0.42, to -0.14) % for sitagliptin 100 mg, -0.19 (-0.33 to -0.05) % for sitagliptin 200 mg and -0.87 (-1.08 to -0.66) % for placebo/pioglitazone. The time profile for FPG also appeared to be more favourable for pioglitazone than for either sitagliptin group. In the sitagliptin 100 mg group there was an increase from baseline in LDL-C: mean (95% CI) 6.8 (2.3 to 11.3) mg/dL.

In Study P036X1 relatively few of the subjects included in the extension phase were included in the analysis. Hence, limited conclusions can be drawn from the data. However, in the 50 (48.5%) subjects in the sitagliptin group included in the analysis there was a significant decrease in HbA1c from baseline to end of study: LS mean (95% CI) -1.15 (-1.37 to -0.92) %. Although the study indicated that sitagliptin was less effective than metformin, sitagliptin in combination with metformin had additive efficacy.

The sponsor concluded from Study P049 non-inferiority for sitagliptin 100 mg daily in comparison with metformin 2000 mg daily. However an alternative interpretation from the data is that metformin was superior to sitagliptin. The LS mean difference (95% CI) for the change in HbA1c from baseline to Week 24 (sitagliptin – metformin) was 0.14 (0.06 to 0.21) %. This difference between treatments would be of marginal clinical significance. Total cholesterol and LDL-C increased in the sitagliptin group.

Study 010-C2 had relatively few subjects included in the efficacy analysis. However, the results were supportive of a statistically significant decrease in HbA1c after 2 years treatment with sitagliptin: LS mean change from baseline (95% CI) -0.39 (-0.54 to -0.24) %. However, this effect is of marginal clinical significance and the effect diminished over time. In addition there was no significant effect on FPG.

Hence for the majority of patients with Type 2 diabetes, sitagliptin would not be the first choice of antidiabetic agent. Its place in the management of Type 2 diabetes appears to be in combination with metformin. However in subjects where metformin, pioglitazone or sulfonylurea drugs were contraindicated, sitagliptin might be considered as an initial monotherapy treatment.

[9] Sponsor comment: "However, direct head-to-head comparisons between sitagliptin and pioglitazone were not part of this application"

[10] Sponsor comment: "Although there was a difference in the timing of the initiation of the treatments and inherent differences in the populations due to discontinuation/rescue initiation in some placebo patients prior to pioglitazone initiation. Therefore, it is difficult to make comparisons between the sitagliptin groups and pioglitazone group at Week 54."

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

- Three pivotal extension studies in support of efficacy and safety: Study P021, Study P023, and Study P036X1
- One randomised controlled study in comparison with metformin: Study P049
- One supportive extension study in support of efficacy and safety: Study 010-C2

There were no additional studies evaluable for safety.

Patient exposure

In Study P021, a total of 238 subjects were exposed to sitagliptin 100 mg, 153 for ≥360 days and 56 for ≥720 days. A total of 250 subjects were exposed to sitagliptin 200 mg, 137 for ≥360 days and 62 for ≥720 days.

In Study P023, a total of 205 subjects were exposed to sitagliptin 100 mg once daily, 101 for more than 51 weeks; and 206 subjects were exposed to sitagliptin 200 mg, 90 for more than 51 weeks.

In Study P036X1, 52 subjects were exposed to sitagliptin 100 mg once daily as monotherapy, with 28 subjects exposed for ≥270 days (in addition to the 54 weeks exposure during the preceding study). A total of 100 subjects were exposed to sitagliptin 50 mg twice daily in combination with metformin 500 mg twice daily, with 67 exposed for ≥270 days. A total of 107 subjects were exposed to sitagliptin 50 mg twice daily in combination with metformin 1000 mg twice daily, with 81 exposed for ≥270 days.

In Study P049, a total of 528 subjects were exposed to 100 mg sitagliptin once daily, with 250 exposed for ≥24 weeks.

In Study 010-, 488 subjects who had already been exposed to sitagliptin for one year were exposed to sitagliptin 100 mg once daily; 346 for between 48 and 56 weeks and 14 for more than 56 weeks.

Adverse events

All adverse events (irrespective of relationship to study treatment)

Pivotal studies

In Study P021 AEs were reported in 192 (80.7%) subjects in the 100 mg group and 199 (79.6%) in the 200 mg. The most commonly reported AEs were nasopharyngitis, diarrhoea and constipation.

In Study P023, treatment-emergent AEs (TEAEs) were reported in 132 (64.4%) subjects in the sitagliptin 100 mg group, 128 (62.1%) in the sitagliptin 200 mg and 70 (63.6%) in the placebo/pioglitazone. The pattern of TEAEs was similar for the three treatment groups.

In Study P036X1, TEAEs were reported in 19 (36.5%) subjects in the sitagliptin group, 53 (53.0%) in the sitagliptin/metformin 500 mg b.i.d., 59 (55.1%) in the sitagliptin/metformin 1000 mg b.i.d., 22 (33.8%) in the metformin 500 mg b.i.d., 48 (54.5%) in the metformin 1000 mg b.i.d. and 23 (54.8%) in the placebo/metformin group. Infections were more common in the subjects treated with metformin, with or without sitagliptin.

In Study P049, TEAEs were reported in 198 (37.5%) subjects in the sitagliptin group and 215 (41.2%) in the metformin. There was a lower rate of gastrointestinal AEs in the sitagliptin group: 61 (11.6%) subjects compared with 108 (20.7%) in the metformin group: difference in proportions (95% CI) -9.1 (-13.6 to -4.7). The rate of diarrhoea was significantly greater in the metformin group: 57 (10.9%) subjects compared with 19 (3.6%) in the sitagliptin. Nausea was reported in 16 (3.1%) subjects in the metformin group and six (1.1%) in the sitagliptin. At Week 24 the mean (SE) decrease in body weight was 0.6 (0.1) kg in the sitagliptin group and 1.9 (0.1) kg in the metformin group.

Other studies

In Study 010-C2 adverse events were reported by 321 (65.8%) subjects in the sitagliptin group and 64 (64.6%) in the control (glipizide or metformin). Back pain, extremity pain and rash were more common in the sitagliptin group but hypoglycaemia was more common in the control.

Treatment-related adverse events (adverse drug reactions)

Pivotal studies

In Study P021 treatment related AEs were reported in 37 (15.5%) subjects in the 100 mg group and 37 (14.8%) in the 200 mg. There was no apparent pattern to drug related AEs, the most frequent being headache (occurring in five [2.1%) subjects in the 100 mg group).

In Study P023, drug related AEs were reported in 31 (15.1%) subjects in the sitagliptin 100 mg group, 32 (15.5%) in the sitagliptin 200 mg and 21 (19.1%) in the placebo/pioglitazone.

In Study P036X1, drug related AEs were reported in two (3.8%) subjects in the sitagliptin group, seven (7.0%) in the sitagliptin/metformin 500 mg b.i.d., eight (7.5%) in the sitagliptin/metformin 1000 mg b.i.d., five (7.7%) in the metformin 500 mg b.i.d., three (3.4%) in the metformin 1000 mg b.i.d. and two (4.8%) in the placebo/metformin group.

In Study P049 drug related AEs were reported in 31 (5.9%) subjects in the sitagliptin group and 87 (16.7%) in the metformin group.

Other studies

In Study 010-C2 treatment related AEs were reported in 20 (4.1%) subjects in the sitagliptin group and nine (9.1%) in the control (glipizide or metformin) group. There was no discernable pattern to the treatment related AEs.

Deaths and other serious adverse events (SAEs)

Pivotal studies

In Study P021 SAEs were reported in 22 (9.2%) subjects in the 100 mg group and 25 (10.0%) in the 200 mg group. There was no apparent pattern to the SAEs. There were two deaths: one in the 100 mg group (lung adenocarcinoma) and one in the 200 mg (mesothelioma).

In Study P023, SAEs were reported in twelve (5.9%) subjects in the sitagliptin 100 mg group, nine (4.4%) in the sitagliptin 200 mg and ten (8.2%) in the placebo/pioglitazone group. There was no apparent pattern to the SAEs. There were no deaths reported during the study.

In Study P036X1, SAEs were reported in one (1.9%) subjects in the sitagliptin group, four (4.0%) in the sitagliptin/metformin 500 mg b.i.d., four (3.7%) in the sitagliptin/metformin 1000 mg b.i.d., one (1.5%) in the metformin 500 mg b.i.d., six (6.8%) in the metformin 1000 mg b.i.d. group and two (4.8%) in the placebo/metformin group. There was no apparent pattern to the SAEs. There was one death in the sitagliptin/metformin 500 mg b.i.d. group (coronary artery disease) and one in the placebo/metformin (unknown cause).

In Study P049, SAEs were reported in ten (1.9%) subjects in the sitagliptin group and eight (1.5%) in the metformin group. There was no apparent pattern to the non-fatal SAEs. One subject in the sitagliptin group died from metastatic lung cancer and bone metastases.

Other studies

In Study 010-C2 SAEs were reported in 27 (5.5%) subjects in the sitagliptin group and six (6.1%) in the control (glipizide or metformin) group. There was no discernable pattern to the SAEs. In Study 010-C2 death occurred for two subjects in the sitagliptin group and none in the control (glipizide or metformin). Both deaths were due to acute myocardial infarction.

Discontinuation due to adverse events (DAE)

Pivotal studies

In Study P021 DAEs were reported in nine (3.8%) subjects in the 100 mg group and nine (3.6%) in the 200 mg group. The commonest SOC involved in DAE was neoplasms: five (2.1%) subjects in the 100 mg group and four (1.6%) in the 200 mg group.

In Study P023, discontinuation due to AE occurred for seven (3.4%) subjects in the sitagliptin 100 mg group, five (2.4%) in the sitagliptin 200 mg group and five (4.5%) in the placebo/pioglitazone group. There was no apparent pattern to the DAEs. In addition, two subjects, one in each sitagliptin group, discontinued because of elevated ALT.

In Study P036X1, discontinuation due to AE was not reported in the sitagliptin group, the sitagliptin/metformin 500 mg b.i.d. group, the sitagliptin/metformin 1000 mg b.i.d. group or the metformin 1000 mg b.i.d. group. There were two (3.1%) subjects in the metformin 500 mg b.i.d. group (palpitations and lung neoplasm) and one (2.4%) in the placebo/metformin group (cholelithiasis) that discontinued due to AE. Two subjects in the sitagliptin group discontinued after initiation of glycaemic rescue.

In Study P049, DAE was reported for nine (1.7%) subjects in the sitagliptin group and 19 (3.6%) in the metformin group. The excess of DAE in the metformin group was primarily due to diarrhoea: six (1.1%) subjects compared with none in the sitagliptin group.

Other studies

In Study 010-C2, DAE occurred for seven (1.4%) subjects in the sitagliptin group and one (1.0%) in the control (glipizide or metformin). In the sitagliptin group DAE was due to diarrhoea (1), cerebrovascular accident (1), myocardial infarction (1), renal cell carcinoma (1), adrenal adenoma (1), depression (1) and hypersensitivity reaction (1). In addition, three subjects in the sitagliptin group discontinued because of laboratory test abnormalities: increased serum creatinine; elevated ALT; and elevated ALT and AST. In the comparator group the DAE was due to complete atrioventricular block.

Adverse events of special interest

In Study P023, hypoglycaemia was reported in five (2.4%) subjects in the sitagliptin 100 mg group, three (1.5%) in the sitagliptin 200 mg group and one (0.9%) in the placebo/pioglitazone group. Gastrointestinal AEs were reported in 15 (7.3%) subjects in the sitagliptin 100 mg group, 18 (8.7%) in the sitagliptin 200 mg and eight (7.3%) in the placebo/pioglitazone group. Body weight was stable in the sitagliptin groups but increased in the placebo/pioglitazone group: LS mean change from baseline (95% CI) 0.1 (-0.7 to 0.9) kg for sitagliptin 100 mg, -0.1 (-0.9 to 0.8) kg for sitagliptin 200 mg and 2.7 (1.5 to 3.9) kg for placebo/pioglitazone. There were no significant changes in ECG parameters.

In Study P036X1, hypoglycaemic episodes were reported in no subjects in the sitagliptin group, two (2.0%) in the sitagliptin/metformin 500 mg b.i.d., five (4.7%) in the

sitagliptin/metformin 1000 mg b.i.d., one (1.5%) in the metformin 500 mg b.i.d., two (2.3%) in the metformin 1000 mg b.i.d. and one (2.4%) in the placebo/metformin.

In Study P049 hypoglycaemia was more common in the metformin group: 17 (3.3%) subjects compared with nine (1.7%) in the sitagliptin.

In Study 010-C2 hypoglycaemia was reported in 16 (3.3%) subjects in the sitagliptin group and ten (10.1%) in the comparator group. Nausea was reported in eight (1.6%) subjects in the sitagliptin group and none in the comparator group; vomiting in six (1.2%) in the sitagliptin group but none in the comparator group; abdominal pain in 14 (2.9%) in the sitagliptin group compared with three (3.0%) subjects in the comparator group and diarrhoea in 15 (3.1%) in the sitagliptin group and two (2.0%) in the comparator group.

Laboratory tests

In Study P021 abnormalities in laboratory tests were infrequent. Two (0.9%) subjects in the 100 mg group and four (1.6%) in the 200 mg group had elevations in ALT.

In Study P023, laboratory AEs were reported in 41 (20.2%) subjects in the sitagliptin 100 mg group, 25 (12.3%) in the sitagliptin 200 mg group and 18 (16.8%) in the placebo/pioglitazone group. The excess of reports in the sitagliptin group appears to be due to an excess in reports of hyperglycaemia and hyperkalaemia.

In Study P036X1, abnormal laboratory tests were reported as AEs in one (1.9%) subject in the sitagliptin group, three (3.0%) in the sitagliptin/metformin 500 mg group b.i.d., one (0.9%) in the sitagliptin/metformin 1000 mg b.i.d. group, 4 (6.2%) in the metformin 500 mg b.i.d. group, two (2.3%) in the metformin 1000 mg b.i.d. group and none in the placebo/metformin group. There was no apparent pattern in the laboratory AEs.

In Study P049, a higher proportion of subjects in the sitagliptin group had increases in ALT >200% and >ULN: eight (1.6%) compared with one (0.2%) in the metformin group.

In Study 010-C2 laboratory adverse events occurred at similar rates in the sitagliptin and control groups.

Post marketing experience

No post marketing data were included in the submission.

Evaluator's overall conclusions on clinical safety

Sitagliptin appears to have a favourable safety profile as indicated by:

- Study P021 indicated that the rate of AEs did not increase with an increasing dose of sitagliptin from 100 mg daily to 200 mg daily.
- Study P036X1 indicated the rate of AEs with sitagliptin 100 mg daily was less than that with metformin.
- Study P023 indicated a similar rate of AEs with sitagliptin 100 mg once daily and pioglitazone.
- The rate of SAEs with sitagliptin was similar to that of the comparators and there was no apparent pattern of the SAEs in the sitagliptin group. There were few deaths reported.
- Discontinuation due to AE was uncommon and there was no apparent pattern in the sitagliptin groups.
- Hypoglycaemia was less common with sitagliptin than metformin.

- Weight gain occurred with pioglitazone in comparison with sitagliptin.
- Mild elevations in ALT were reported at a rate of 1.6% with sitagliptin in some studies. This may represent a weak signal.

List of questions

General

In what way does the submission differ to the data submitted in other countries to support monotherapy and initial combination therapy with metformin? [11]

Efficacy

Can the sponsor provide a tabulated summary of the reasons for exclusion from analysis for subjects in Study 010-C2?[12]

Clinical summary and conclusions

First round benefit-risk assessment

Benefits

The efficacy data indicate a sustained effect for sitagliptin over a 2 year period. However, sitagliptin had lesser efficacy than either pioglitazone or metformin. Sitagliptin appears to be best used in combination with metformin.

Study P021 demonstrated a sustained improvement in HbA1c over a 2 year period. The improvement was greater in the 200 mg dose group than the 100 mg group: mean decrease in HbA1c 0.4% compared with 0.27%. However the magnitude of this improvement in HbA1c was small and the same as that used as the criterion for non-inferiority in Study P049 (0.4%). The effect also decreased over the two year treatment period. There was no improvement in FPG. There was an increase in fasting serum cholesterol in both treatment groups and an increase in HDL-C and LDL-C in the 100 mg dose group.

In Study P023, over a 54 week period the time profile of HbA1c appeared to be more favourable for pioglitazone than for either sitagliptin 100 mg or 200 mg. At Week 54, using confidence interval testing, there was a significantly greater decrease in HbA1c in the pioglitazone group than in either sitagliptin group: LS mean (95% CI) change from baseline in HbA1c -0.28 (-0.42, to -0.14) % for sitagliptin 100 mg, -0.19 (-0.33 to -0.05) % for sitagliptin 200 mg and -0.87 (-1.08 to -0.66) % for placebo/pioglitazone. The time profile for FPG also appeared to be more favourable for pioglitazone than for either sitagliptin group. In the sitagliptin 100 mg group there was an increase from baseline in LDL-C: mean (95% CI) 6.8 (2.3 to 11.3) mg/dL.

In Study P036X1 relatively few of the subjects included in the extension phase were included in the analysis. Hence limited conclusions can be drawn from the data. However, in the 50 (48.5%) subjects in the sitagliptin group included in the analysis there was a significant decrease in HbA1c from baseline to end of study: LS mean (95% CI) -1.15 (-1.37

[11] Sponsor comment: "The sponsor responded to this in the Section 31 *Response to Questions* (see page 45)."

[12] Sponsor comment: "The sponsor responded to this in the Section 31 *Response to Questions* (see page 45) and the *Reply to Completed Evaluation Reports* (see page 59)."

to -0.92) %. Although the study indicated that sitagliptin was less effective than metformin, sitagliptin in combination with metformin had additive efficacy.

The sponsor concluded from Study P049 non-inferiority for sitagliptin 100 mg daily in comparison with metformin 2000 mg daily. However an alternative interpretation from the data is that metformin was superior to sitagliptin. The LS mean difference (95% CI) for the change in HbA1c from baseline to Week 24 (sitagliptin – metformin) was 0.14 (0.06 to 0.21) %. This difference between treatments would be of marginal clinical significance. Total cholesterol and LDL-C increased in the sitagliptin group.

Study 010-C2 had relatively few subjects included in the efficacy analysis. However, the results were supportive of a statistically significant decrease in HbA1c after 2 years treatment with sitagliptin: LS mean change from baseline (95% CI) -0.39 (-0.54 to -0.24)%. However, this effect is of marginal clinical significance and the effect diminished over time. In addition there was no significant effect on FPG.

Hence for the majority of patients with Type 2 diabetes, sitagliptin would not be the first choice of antidiabetic agent. Its place in the management of Type 2 diabetes appears to be in combination with metformin. However in subjects where metformin, pioglitazone or sulfonylurea drugs were contraindicated, sitagliptin might be considered as an initial monotherapy treatment.

Risks

Sitagliptin appears to have a favourable safety profile as indicated by:

- Study P021 indicated that the rate of AEs did not increase with an increasing dose of sitagliptin from 100 mg daily to 200 mg daily.
- Study P036X1 indicated the rate of AEs with sitagliptin 100 mg daily was less than that with metformin.
- Study P023 indicated a similar rate of AEs with sitagliptin 100 mg once daily and pioglitazone.
- The rate of SAEs with sitagliptin was similar to that of the comparators and there was no apparent pattern of the SAEs in the sitagliptin group. There were few deaths reported.
- Discontinuation due to AE was uncommon and there was no apparent pattern in the sitagliptin groups.
- Hypoglycaemia was less common with sitagliptin than metformin. Weight gain occurred with pioglitazone in comparison with sitagliptin.
- Mild elevations in ALT were reported at a rate of 1.6% with sitagliptin in some studies. This may represent a weak signal.

Benefit-risk balance

The benefit-risk balance of sitagliptin (Januvia) is favourable given the proposed usage. This is primarily because of the favourable safety profile and demonstrable long term efficacy. However, sitagliptin (Januvia) appears to have lesser efficacy than metformin and pioglitazone and would appear to be best used in combination with metformin.

First round recommendation regarding authorisation

Approval is recommended for the proposed replacement indication:

Monotherapy

> *Januvia is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus.*

Individual Combination Therapy with metformin

Januvia is indicated in patients with Type 2 diabetes mellitus to improve glycaemic control in combination with metformin as initial therapy.

Add-on combination Therapy with Antihyperglycemic agents

For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

First round comments on clinical aspects of the safety specification in the draft RMP

The Safety Specification in the draft Risk Management Plan is not entirely satisfactory and should be revised, having regard to the comments below:

Changes in plasma lipids were observed in the long-term extension studies. These were:

- In Study P021 there was an increase in fasting serum cholesterol in bothsitagliptin 100 mg and 200 mg once daily treatment groups, and an increase in HDL-C and LDL-C in the 100 mg dose group.
- In Study P023, in the sitagliptin 100 mg once daily group there was an increase from baseline in LDL-C: mean (95% CI) 6.8 (2.3 to 11.3) mg/dL.
- In Study P049 total cholesterol and LDL-C increased in the sitagliptin 100 mg once daily group.

These observed changes in plasma lipids raise concerns regarding long-term cardiovascular safety and this should be addressed to a greater extent in the RMP. [13]

Second round evaluation of clinical data submitted in response to questions

General

In answer to the clinical evaluator's question, the sponsor referred to information presented in tabular format in the submission (in Module 1.10.3). In the original dossier for this submission, Module 1.10.3 stated:

1.10.3-Data Set Similarities

This application to support the use of Januvia as monotherapy and as initial combination therapy with metformin for the treatment of patients with T2DM, is supported by clinical data from P010, P014, P021, P023, P036, P049 and P036, respectively. These same studies have been used to support applications for the use of Januvia as monotherapy and initial combination therapy with metformin in other countries as well.

A tabular comparison was presented in the sponsor's response to the TGA. The studies included in the original dossier for registration of sitagliptin in Australia were similar to those submitted in the European Union (EU), USA, Canada and New Zealand that supported the use of sitagliptin as a monotherapy. These studies were two Phase II monotherapy studies (P010 and P014) with 52 week treatment periods (including the 12 week base and 40 week first extension periods) and two Phase III monotherapy studies (P021 and P023) with 24 and 18 week treatment periods, respectively. The dossiers also included results through Week 12 from a monotherapy study in patients with renal

[13]Sponsor comment: "The sponsor responded to this in the *Reply to Completed Evaluation Reports* (see page 59)."

insufficiency (P028) and results from a 12 week monotherapy study conducted in Japan (PA201).

In the submission described in this AusPAR, use as monotherapy is supported by longer-term results from Phase II and Phase III studies. These include the combined results from the second 54 week extensions to P010 and P014, results to Week 104 from P021 and to Week 54 from P023, the overall 2 year data from extension P036X1 of the factorial study (P036) of sitagliptin and metformin as initial combination therapy and a 24 week, active controlled monotherapy study of sitagliptin versus metformin (P049).

The latter study was previously submitted to the EU and Canada in supplemental marketing applications that supported the approval of sitagliptin for use as monotherapy in patients for whom metformin is inappropriate due to contraindications or intolerance.

> *Comment*: The response shows the additional study data that were presented with this submission.
>
> The initial statement indicated that Study P036 was included to support overseas applications for monotherapy and initial therapy in combination with metformin. The tabular comparison provided in the sponsor's response states that P036 was 'not in application' for EU, US, NZ and Canada to support sitagliptin monotherapy registration. The response indicates that P036 and the extension P036X1 as well as P049 are additional data for this Australian submission. The first round clinical evaluator appears to have described the results from baseline to Week 104 for the numbers entering the extension phase P036X1 (Figures 5 and 6).
>
> Based on Study P049, in the EU the Indication for sitagliptin as monotherapy was restricted to those who "are not satisfactorily controlled on diet and exercise and in whom metformin is not suitable".

Efficacy

The sponsor answered this question by referring to a table (Table 10-2 in Section 10-4) in the CSR for Study 010-C2.

The sponsor explained that the table refers only to reasons why patients were excluded from HbA1c analyses.

> *Comment*: This table is included under *Clinical Findings* (Table 26 of this AusPAR).
>
> The reasons for exclusion from primary efficacy analysis are understandable. However there appears to be an unexplained inconsistency. The number entering the second extension for placebo/metformin matches that given in the overall disposition of patients, (n = 99, see Table 26 and Figure 7 of this AusPAR) but the numbers stated as entering the second extension and receiving sitagliptin 100 mg TDD do not match (n = 488 in the Disposition of Patients Figure 7 but n = 154 in Table 26). These numbers appear in Figure 10-1 and Table 10-2 on successive pages, 101 and 102, of the company study report (CSR) for Study 010-C2 (not in this AusPAR).
>
> This evaluator is unable to understand the discrepancy. Initially it appeared that 488 may refer to subjects receiving all doses of sitagliptin, but the submission clearly states the number exposed to sitagliptin 100 mg daily to be 488. This seems to indicate a much lower rate of HbA1c data availability for sitagliptin 100 mg exposed compared to non-exposed subjects in the extension study and thus a high number of sitagliptin subjects excluded from the efficacy analysis, as noted in the Round 1 evaluation and referred to in at *Other Efficacy Studies* above and *List of Question* above. Conversely, there would be a significant effect on adverse event rates if the numbers exposed to sitagliptin 100 mg daily in the extension were 154 rather than 488.

> This study was not considered a pivotal study, and as noted by the Round 1 evaluator, the decrease in HbA1c after 2 years, obtained from relatively few subjects included in the efficacy analysis, was of marginal clinical significance.
>
> *However this aspect remains unresolved; the numbers entering the extension study and accounted for in the efficacy and safety analysis should be adequately explained.*[14]

Second round benefit-risk assessment

Benefits

No new clinical information was submitted in response to questions. Accordingly, the benefits are unchanged from those identified in the primary assessment above.

As stated by the first round clinical evaluator:

> 'The efficacy data indicate a sustained effect for sitagliptin over a 2 year period. However, sitagliptin had lesser efficacy than either pioglitazone or metformin. Sitagliptin appears to be best used in combination with metformin.'

The conclusion on benefit was:

> "Hence for the majority of patients with Type 2 diabetes, sitagliptin would not be the first choice of antidiabetic agent. Its place in the management of Type 2 diabetes appears to be in combination with metformin. However in subjects where metformin, pioglitazone or sulfonylurea drugs were contraindicated, sitagliptin might be considered as an initial monotherapy treatment."

Benefits demonstrated by sitagliptin over two years as known initial monotherapy versus active comparator metformin rely on n = 50 subjects in Study P036X1; in this study the effect sizes are larger for metformin alone or sitagliptin in combination with metformin. Study P049 has 24 week data versus metformin in which criteria for non-inferiority were satisfied.

The results indicate that, in practice, initial monotherapy with sitagliptin would not be the first choice if metformin could be used.

Risks

No new clinical information was submitted in response to questions. Accordingly, the risks of sitagliptin (Januvia) are unchanged from those identified by the first round clinical evaluator; sitagliptin was assessed as having a favourable safety profile.

Review of the 7 deaths mentioned by the evaluator shows that six were in the sitagliptin exposed group; three were due to neoplasm and three to coronary artery disease (CAD). The other, in a placebo/metformin group was of unknown cause. A possible signal for elevated ALT was noted.

Benefit-risk balance

The first Round evaluator noted that the benefit-risk balance was favourable because of the favourable safety profile and demonstrable long-term efficacy but that sitagliptin appears to have lesser efficacy than metformin and pioglitazone and would appear to be best used in combination with metformin.

[14] Sponsor comment: "The sponsor responded to this in *the Reply to Completed Evaluation Reports* (see page 59)."

Second round recommendation regarding authorisation

Based on the first round evaluation and answers to questions, monotherapy with sitagliptin could be considered for patients when metformin is contraindicated or unsuitable. The current indication as 'dual combination therapy with metformin' does not appear to either specify or preclude use as initial combination therapy. Approval is recommended for the following amended replacement Indications:

Monotherapy

> *Januvia is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus, when metformin cannot be used.*

Individual Combination Therapy with metformin

> *Januvia is indicated in patients with Type 2 diabetes mellitus to improve glycaemic control in combination with metformin as initial therapy when dual sitagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects for response to monotherapy).*

Add-on combination Therapy with Antihyperglycemic agents

> *For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing safety Concerns which are shown at Table 28.

OPR reviewer comment

Pursuant to the evaluation of the clinical aspects of the Safety Specifications (SS), the above summary of the Ongoing Safety Concerns was considered acceptable.

The clinical evaluator has indentified a mechanism by which cardiovascular risk may be increased with respect to elevated serum lipids seen in patients in clinical trials. The sponsor has identified cardiovascular events as Important missing information. It is recommended that:

1. Increased serum lipids be identified as an Important potential risk
2. Routine pharmacovigilance activities should be undertaken for this Potential risk and a specific consideration of elevated serum lipids from the studies in the pharmacovigilance plan, Annex 3 (where they differ), literature and spontaneous adverse event reports be provided in the PSURs.

3. Routine risk minimisation should be undertaken for the Important potential risk in the form of language in the PI, this could be in the *Adverse events* section or in the *Precautions* section. [15]

The sponsor has provided an explanation for the addition of the Important Potential Risk 'Suicidal ideation, suicide and depression' in the current version of the RMP, including the reasons for its omission from the previous version. The sponsor has provided a justification for the modification to the safety specifications which is acceptable.

Table 28. Summary of the Ongoing Safety Concerns as specified by the sponsor.

Identified Risks	Hypersensitivity reactions, including anaphylactic reaction, angio-oedema, rash, urticaria, Cutaneous vasculitis, skin exfoliation and Stevens-Johnson syndrome
	Hypoglycaemia with concomitant sulphonylurea
	Hypoglycaemia with insulin
	Musculoskeletal disorders: Osteoarthritis, pain in extremity, and related terms (e.g. arthralgia, myalgia, myopathy)
	Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, abdominal pain upper and related terms (dyspepsia and gastritis)
Potential risks	Infections: URTI, nasopharyngitis and related terms(bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis)
	Neurotoxicity: tremor, ataxia, and balance disorders
	Suicidal ideation, suicide and depression
	Skin reactions: pruritis and contact dermatitis
	Drug-drug interactions in renal insufficiency patients
	Pancreatitis
	Impaired renal function, including renal failure (sometimes requiring dialysis)
Missing Information	Patients below 18 years of age
	Exposure during pregnancy and lactation
	Adverse events in renal insufficiency patients
	Cardiovascular events in patients on sitagliptin or on a combination of sitagliptin and a PPARγ agonist
	Theoretic carcinogenic potential

Pharmacovigilance plan

The sponsor recommended mainly routine pharmacovigilance with the following additions;

- **Potential risks**
  - *Pancreatitis*: Monitoring of pancreatitis events in P082 (ongoing) provided the following detailed account of the pharmacovigilance plan.

[15]Sponsor comment: "The sponsor responded to these in the *Reply to Completed Evaluation Reports* (see page 59)."

- **Missing information**
  - *Patients below 18 years of age*: Clinical research trials in paediatric patients. Planned trials: P083, P170 and P289
  - *Cardiovascular events in patients on sitagliptin or on a combination of sitagliptin and a PPARγ agonist:* Monitoring of cardiovascular events in P082 (ongoing).
  - *Theoretic carcinogenic potential*: Monitoring of malignancies in P082 (ongoing)

The sponsor has provided the following milestones for the study protocols in the pharmacovigilance plan:

The sponsor has provided the study protocols for studies P082, P083 and P170.

In the previous RMP (Version3.0) the following studies with dates for the submission of final data after first quarter of 2012 were included in the pharmacovigilance program; P229, P082, P083, P121, P130, P170, P180, P251, P253, P254.

The sponsor has advised that the Drug Utilisation Study identified in RMP Version 3.0 does not qualify as an additional pharmacovigilance activity and is not mentioned in Version 4.0.

In Annex 3 of RMP Version 4.0 the sponsor provides a table of synopses of completed and ongoing clinical trials. In this table P082, P121, P130, P229, P251 are listed as ongoing, however the pharmacovigilance plan only identifies P082, P083 and P170 as the additional pharmacovigilance activities. The sponsor has provided justification for the difference between the two pharmacovigilance plans. Some studies did not include specific safety objectives designed to address the Important identified/potential risks or Important missing information from the RMP and are therefore removed. The sponsor indicates that additional safety information obtained from these studies will be conveyed to the TGA via PSURs.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The sponsor has provided a satisfactory explanation of the proposed pharmacovigilance plan in Version 4.0 of the RMP.

The study protocols for P170 and P083 have been provided in Annex 5. It is acceptable for the sponsor to include these as additional pharmacovigilance activities. The sponsor states that Study P289 is yet to have a finalised study protocol. The sponsor is requested to provide a synopsis of this study to the TGA upon finalisation, for review.[16]

Furthermore, it is acceptable for the sponsor to include additional safety information derived from studies outside the pharmacovigilance plan with the PSURs.

There are expected pharmacovigilance activities for the additional safety concern of elevated serum lipids (as identified by the CER).

Risk minimisation activities

The sponsor indicated that routine risk minimisation activities in the form of the information provided in the Product Information is sufficient. The sponsor also identifies that there is sufficient patient information in the Consumer Medicines Information leaflet. The sponsor also clearly identifies in Annex 8 that no educational program is proposed for this change of indication.

[16]Sponsor comment: "The sponsor provided the TGA with the synopsis for Study P289 post approval."

OPR reviewer comment

The sponsor has not provided an updated proposed Australian PI and CMI to accompany the RMP Version 4.0. Therefore the documents provided with the original submission documents are considered the risk minimisation activities referred to in RMP Version 4.0.

The above table is a copy of Table 3.1 The outlined risk minimisation activities in the table "Summary table for Important Safety Concerns" differ from the table "Summary of the Risk Management Plan".

The language in the labelling is mentioned by the sponsor as risk minimisation in both tables but the safety concerns addressed by the labelling differ between the two tables. It is assumed by the evaluator that the more detailed should be referred to when identifying the sponsor's planned risk minimisation activities.

The sponsor states in the Australian Specific risk Minimisation Plan to the RMP Version 3.0 that the risk minimisation activities identified as having been addressed in the product labelling are dealt with in a comparable way in the Australian PI with the exception of the wording for pancreatitis. The wording of the section on pancreatitis was considered acceptable.

No Australian specific annex is provided to RMP Version 4.0 but there is no indication in the Australian specific annex to Version 3.0 that this same provision would not apply to future iterations of the RMP.

With respect to the other safety concerns the language in the proposed PI ((MK043-T-092010S-D11022(first line) v1 Tracer No: 0431-AUS-2011-02729 (110321) is not consistent with the claims in the RMP in that there is:

- No mention of suicidal ideation, suicide or depression as reported events
- No mention of neurotoxicity
- Although dosing in renal failure is mentioned drug-drug interaction in patients with renal insufficiency is not.
- No direct mention of hypoglycaemia with concomitant insulin use (this is mentioned in the provided SPC)

Therefore, the language in the proposed Australian PI does not address the safety specifications as specified by the sponsor and does not provide routine risk minimisation activities for all Identified and Potential risks. No justification was provided for the omission of the above information from the Australian PI upon provision of RMP Version 4.0, nor for the inconsistency between two tables. It was recommended these deficiencies be addressed before the RMP is deemed acceptable.

As noted with respect to the Identified potential risk 'Elevated serum lipids' derived from the CER, routine risk minimisation should be undertaken for the Important potential risk in the form of language in the PI, this could be in the *Adverse events* section or in the *Precautions* section.

In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the *draft PI be revised* as follows:

- The sponsor should include the dosing schedule for monotherapy in the proposed PI.
- The overdose section does not include the Poisons Information Centre generic number and it is recommended that this be included.[17]

[17]Sponsor comment: "These were included in the PI submitted by the sponsor pre-ACPM."

- The PI should be amended to include mention of all Important and Potential risks as indicated in the risk minimisation plan.
- A mention of elevated serum lipids in clinical trials should be included to provide risk minimisation for this potential risk identified by in the CER.[18]

In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft consumer medicine information document be revised as follows: The CMI should be amended to reflect the changes in the proposed PI.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of RMP Version 4.0 is imposed as a condition of registration when so qualified:

Safety specifications

The safety concerns should be amended to include elevated serum lipids and table amended to include elevated serum lipids as an Important Potential Risk.

Pharmacovigilance plan

The sponsor stated that Study P289 is yet to have a finalised study protocol. The sponsor was requested to provide a synopsis of this study to the TGA upon finalisation, for review.[19]

The sponsor was requested to amend the pharmacovigilance plan to incorporate routine pharmacovigilance for the above additional Important Potential Risk and to give specific consideration to elevated serum lipids in the PSURs.

Risk minimisation

The PI should be amended to include mention of all Important and potential risks as indicated in the risk minimisation plan as the language in the labelling is the only proposed risk minimisation activity. There should also be mention of elevated serum lipids in clinical trials.

PI and CMI

The sponsor should include the dosing schedule for monotherapy in the proposed PI.

The overdose section does not include the Poisons Information Centre generic number, and it is recommended that this be included.

The CMI should be amended to reflect the changes in the proposed PI.[20]

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

[18]Sponsor comment: "The sponsor responded to these in the *Reply to Completed Evaluation Reports* (see page 59)."

[19]Sponsor comment: "The sponsor provided the TGA with the synopsis for Study P289 post approval."

[20]Sponsor comment: "These were included in the PI submitted by the Sponsor pre-ACPM."

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

No new pharmacokinetic or pharmacodynamic studies were submitted. Long term morbidity or mortality studies have not been submitted.

No postmarketing data were included in the submission.

Efficacy

Monotherapy Studies

(As add–on to diet and exercise).

Study P021V1 was in the initial submission and it originally enrolled 741 patients for randomisation to placebo or sitagliptin 100 mg mane or sitagliptin 200 mg mane. The patients need not have been treatment naïve. As originally noted, over 25 weeks both doses were superior to placebo but not significantly different from each other for the primary outcome, Hb A1c. Metformin was offered as rescue therapy.

The extension phase, evaluated with this submission, had two treatment groups (sitagliptin 100 mg and 200 mg) and was double blind with randomisation of the placebo group to either active treatment at the commencement of the extension study. They had not been previously "rescued". Patients who had been treated with placebo during the initial 24 week phase of the study were re-randomised to sitagliptin 100 mg or 200 mg in a 1:1 ratio; as before the primary efficacy outcome measure was change from baseline in HbA1c. A total of 555 (74.9% of the original 741) patients entered the extension phase but under half of these, 229 (30.9% of the original 741) subjects, completed the study. Lack of efficacy was a common reason for discontinuation (230 patients or 31% of the original 741).

See the clinical evaluation report for more detail.

Efficacy was reported as, "For the 100 mg group the mean (95% CI) change from baseline was -0.27 (-0.41 to -0.13)% and for 200 mg -0.40 (-0.53 to -0.26)%" which is a modest result.

The evaluator observed that efficacy declined over time (see Figure 1).

Study P023

This was similar to the above but initially it ran for 18 weeks, randomised 523 patients and found both doses of sitagliptin 100 mg and 200 mg /day to be superior to placebo. Subjects were initially randomised 2:2:1 for 100 mg: 200 mg: placebo. The study included adult patients with Type 2 diabetes mellitus (HbA1c ≥7% and ≤10%) and either: (1) not on anti hyperglycemic agent (off for ≥8 weeks); or (2) on a single anti hyperglycemic agent; or (3) on low doses of dual oral combination agent therapy (at ≤50% of maximal dose of both components). Patients rescued (with metformin) during this phase were allowed to enter the extension phase.

The extension phase ran for 36 weeks (following on from the initial 18 week treatment phase). The placebo group was switched to pioglitazone 30mg once daily. Metformin was used as recue therapy in this study. At entry into the extension phase there were 162

subjects in the 100 mg group, 162 in the 200 mg group and 74 in the placebo/pioglitazone. There were 152 subjects in the 100 mg, 144 in the 200 mg and 80 in the placebo/pioglitazone group that completed the study. A sample size calculation was not performed for the extension study. Within group comparisons were performed using ANCOVA models. Formal hypothesis tests between treatment groups were not performed for the extension study.

Table 29. Patient Accounting in the Analysis of HbA1c at Week 18

Table 10-3

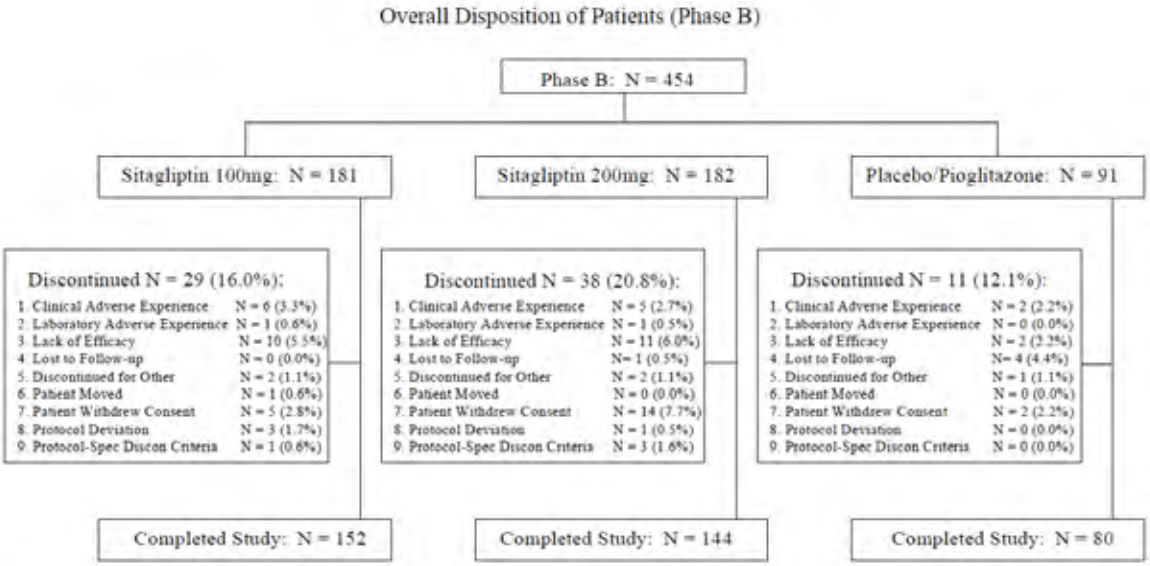
Patient Accounting in the Analysis of HbA_{1c} at Week 18

	Number (%)			
	MK-0431 100 mg	MK-0431 200 mg	Placebo	Total
Total Randomized	205	206	110	521
Included in the APT† Analysis	193 (94.1)	199 (96.6)	103 (93.6)	495 (95.0)
Included in the Completers Analysis	168 (82.0)	161 (78.2)	74 (67.3)	403 (77.4)
Excluded from the APT†Analysis	12 (5.9)	7 (3.4)	7 (6.4)	26 (5.0)
No Baseline Data	3 (1.5)	1 (0.5)	1 (0.9)	5 (1.0)
No On-treatment Data	9 (4.4)	6 (2.9)	6 (5.5)	21 (4.0)
Excluded from the Completers Analysis‡	25 (12.2)	38 (18.4)	29 (26.4)	92 (17.7)
Rescued Prior to Week 18§	13 (6.3)	17 (8.3)	15 (13.6)	45 (8.6)
No Data at Week 18‖	12 (5.9)	21 (10.2)	14 (12.7)	47 (9.0)

† APT: All-Patients-Treated.
‡ The completers population is a subset of the APT population including all patients with Week 18 data.
§ Efficacy data obtained on a patient after initiation of rescue therapy are treated as missing.
‖ For patients not on rescue medication.

In the extension phase, the disposition of patients was as described in Figure 10.

Figure 10. Overall disposition of patients (Phase B).



The primary efficacy outcome measures were the time profile plot of mean change from baseline in HbA1c. Fasting plasma glucose (FPG) was a secondary endpoint. The evaluator considered that efficacy was perhaps better with pioglitazone and that efficacy with sitagliptin waned over time (see Figures 3 and 4).

See the clinical evaluation report for more detail.

> *Comment*: The results of this study are perhaps confounded by rescue therapy. To avoid this, the applicant reported that, "The primary approach to handling missing data for the ANCOVA was the last observation carried forward (LOCF) method. To avoid the confounding influence of rescue therapy on efficacy comparisons in Phase A, efficacy analyses (both the primary approach and the secondary approach described below) treated data as missing after the initiation of rescue therapy". According to the applicant's summary, "Discontinuations due to clinical adverse experiences were uncommon during the 54-week treatment period, occurring with a generally similar incidence across treatment groups: 4.9% (10 patients including 3 rescued patients), 2.4% (5 patients), and 5.5% (6 patients, including 1 rescued patient) in the sitagliptin 100 mg, sitagliptin 200 mg, and placebo/pioglitazone groups, respectively."

Study P036:

This study was submitted as part of the supporting data in connection with the original application to register Janumet. It began as a Phase III, multicentre, randomised double blind study of sitagliptin in patients with Type 2 diabetes mellitus who had inadequate glycaemic control on diet and exercise (HbA1c ≥7.5% and ≤11%; either not on antidiabetic drugs at study entry or after a run-in/wash-off period). The primary objective was to ascertain the safety and efficacy of the combination therapy versus the individual components. The initial phase was of 24 weeks duration. The treatments in the initial phase allocated amongst the following groups: sitagliptin 50mg b.i.d.with metformin 500 mg b.i.d.; sitagliptin 50mg b.i.d.with metformin 1000 mg b.i.d.; metformin 500mg b.i.d., metformin 1000 mg b.i.d., sitagliptin 100mg daily or placebo.

It was initially reported at **24** weeks (end of Phase A) with these results for HbA1c as shown in Table 30 below.

Table 30. Change from baseline at Week 24

Treatment group	N	Mean (SD)		Change from Baseline			
		Baseline	24 weeks	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	LS mean diff (95%CI) from placebo
STG 100 mg daily	175	8.87 (0.99)	8.18 (1.45)	-0.69 (0.10)	-0.66 (0.08)	(-0.83,-0.50)	-0.83 (-1.06,-0.60)
MET 500 mg b.i.d.	178	8.90 (1.00)	8.04 (1.36)	-0.85 (0.09)	-0.82 (0.08)	(-0.98, 0.66)	-0.99 (-1.22, 0.75)
MET 1000 mg b.i.d.	177	8.68 (0.91)	7.58 (1.27)	-1.09 (0.08)	-1.13 (0.08)	(-1.29, 0.97)	-1.30 (-1.53,-1.06)
SGL 50 mg b.i.d.+ MET 500 mg b.i.d.	183	8.79 (1.00)	7.37 (1.20)	-1.42 (0.09)	-1.40 (0.08)	(-1.56,1.24)	-1.57 (-1.80,-1.34)
SGL 50 mg b.i.d.+ MET 1000 mg b.i.d.	178	8.76 (0.95)	6.87 (1.09)	-1.89 (0.08)	-1.90 (0.08)	(-2.06,-1.74)	-2.07 (2.30,-1.84)
Placebo	165	8.68 (1.00)	8.21 (1.81)	0.20 (0.09)	0.17 (0.09)	(-0.00, 0.33)	-

The study was extended thereafter to 54 weeks. In this first extension phase, those on placebo were switched to metformin.

Study P036X1, submitted in this data set, was a 50 week extension phase to the 54 week time point of the above. Compliant patients from Phase A were enrolled in the first extension phase (Phase B), including those given rescue treatment (glibenclamide). Patients who were given placebo were then switched to metformin after Week 24 of 54. A total of 685 subjects entered the study: 103 sitagliptin 100 mg, 134 sitagliptin 50 mg/metformin 500 mg b.i.d., 122 sitagliptin 50 mg/metformin 1000 mg b.i.d.; 107 metformin 500 mg b.i.d., 121 metformin 1000 mg b.i.d. and 98 placebo/metformin. Sample size calculations were not done. There was no randomisation or re-randomisation into the study extension. There were no formal hypothesis tests defined in the study protocol.

As noted in the clinical evaluation report, efficacy was better for sitagliptin/metformin 1000 mg and for metformin 1000 mg alone than sitagliptin alone. Efficacy in general waned over time (see Figure 5).

The evaluator concluded, "In Study P036X1 relatively few of the subjects included in the extension phase were included in the analysis. Hence limited conclusions can be drawn from the data. However, sitagliptin in combination with metformin had additive efficacy. The effect was apparent over a 104 week follow-up period."

Study (P049)

This is a newly submitted non-inferiority (against metformin) Phase III study that is intended to support first line monotherapy. It is described as was a multicentre, double blind randomised, comparator (metformin) controlled, parallel group, non-inferiority study in subjects with Type 2 diabetes mellitus with inadequate glycaemic control. The study included adult patients with Type 2 diabetes mellitus (HbA1c ≥6.5% and ≤9.0%) not responding to diet and exercise not on antihyperglycemic agent (for ≥16 weeks). The patients had to show compliance with treatment during a placebo run-in phase.

The interventions were sitagliptin 100 mg once daily or *metformin* 500 mg tablets, two orally twice daily (increased from 500 mg daily to 2000 mg daily over 5 weeks). Some 1,058 patients were randomised: 532 to sitagliptin and 526 to metformin. The primary efficacy outcome measure was the change from baseline in HbA1c. Numerous secondary outcomes were reported. A sample size of 400 subjects per group was estimated to deliver 97% power to determine a non-inferiority margin of *0.4%* assuming the true mean difference between treatments is <0.1%, using a SD of 1.1% for the change in HbA1c from baseline to Week 24. The study recruited above these numbers.

As noted by the evaluator, "The pre-specified criteria for non-inferiority were met. The LS mean difference (95% CI) for the change in HbA1c from baseline to Week 24 (sitagliptin – metformin) was 0.14 (0.06 to 0.21) % (Table 24). However, by this analysis metformin was actually superior to sitagliptin because the lower 95% CI was greater than 0." That is, the sponsor might have switched to superiority *for metformin* if this had been specified.

Secondary endpoints did not in general favour sitagliptin.

Study 010-C2

This is a composite of two earlier Phase II studies, Study P014 and Protocol 010. Both of the initial studies involved a 12 week base study and a 40 week extension. Both studies originally included subjects with Type 2 diabetes mellitus with inadequate glycaemic control.

As originally submitted, Study P014 was a large Phase II study. As evaluated in the initial application to register sitagliptin, the 12 week initial part of the study did not show an advantage for sitagliptin 100mg dose versus sitagliptin 50mg dose. Both were better than sitagliptin 25 mg dose in terms of HbA1c. The original clinical evaluator believed that the minimal effective dose has not been defined. There followed two extensions.

In the second extension phase, treatments were sitagliptin 100 mg once daily, glipizide 5 mg twice daily or metformin 850 mg twice daily. To enter the second extension (this study), ≥75% compliance with study medication during the first extension period was a selection criterion. A total of 587 subjects were entered into the second extension: 488 treated with sitagliptin and 99 with comparator.

There were 253 subjects included in the efficacy analysis at Week 106.

[see Figure 8 and Table 27 above].

The evaluator was of the view that the effects of sitagliptin and glipizide decreased over time but the effect for metformin was maintained. In regard to secondary endpoints, the results were variable but the number (%) subjects with HbA1c <7% at week 106 was 50 (44.6%) subjects for sitagliptin, 21 (63.6%) for metformin and 22 (51.2%) for glipizide.

Efficacy conclusions

Put concisely, "The efficacy data indicate a sustained effect for sitagliptin over a 2 year period. However, sitagliptin had lesser efficacy than either pioglitazone or metformin. Sitagliptin appears to be best used in combination with metformin." Study by study comments are made in the report. "…for the majority of patients with Type 2 diabetes,

sitagliptin would not be the first choice of antidiabetic agent. Its place in the management of Type 2 diabetes appears to be in combination with metformin. However in subjects where metformin, pioglitazone or sulfonylurea drugs were contraindicated, sitagliptin might be considered as an initial monotherapy treatment."

Adverse effects

No new safety signals emerged excepting a possible weak signal with respect to elevated ALT. See the clinical evaluation report for the evaluator's conclusions. Adverse changes in plasma lipids were observed in the long term extension studies. See the report for the evaluator's suggestions. See the sponsor's reply to the clinical evaluation report for the sponsor's tabulations of lipid changes in Study P10-C2.

First round risk: benefit conclusion

Some efficacy was shown. The conclusions are the same as those made concerning efficacy. Sitagliptin appears to have lesser efficacy than metformin and pioglitazone and would appear to be best used in combination with metformin. Some improvements were suggested for the text of the product information document (PI).

Second round evaluation

A few questions were asked of the applicant (data set differences in foreign submissions; a request for a tabulated summary of the reasons for exclusion from analysis for subjects in Study 010-C2), resulting in a secondary evaluation of these replies.

In regard to the first answer, the evaluator suggested, "Based on Study P049, in the EU the Indication for sitagliptin as monotherapy was restricted to those who 'are not satisfactorily controlled on diet and exercise and in whom metformin is not suitable' ..."

The evaluator was unable to reconcile the numbers of patients excluded from the efficacy analysis in Study 010-C2. See the clinical evaluation report.

The suggested indication is:

Monotherapy

> *Januvia is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus, when metformin cannot be used.*

Individual Combination Therapy with metformin

> *Januvia is indicated in patients with Type 2 diabetes mellitus to improve glycaemic control in combination with metformin as initial therapy when dual sitagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects for response to monotherapy).*

Add-on combination Therapy with Antihyperglycemic agents

> *For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.*

Various significant and relevant changes to the text of the product information document (PI) were suggested.

Risk management plan

The evaluator of the risk management plan notes that the applicant intends to pursue routine pharmacovigilance activities and proposes international clinical trials for all Identified and Potential risks and Missing information. The sponsor proposed routine risk

minimisation in the form of the text of the Product Information document (PI), and patient education via the Consumer Medicine Information document (CMI).

Unresolved issues relate to the text of the PI, the CMI and the implementation of RMP Version 4.0 to be imposed as a condition of registration.

Sponsor's reply to completed evaluation reports

1. Clinical evaluation report

The applicant has provided a detailed explanation and headcount of patients involved in the different phases of Studies P010 & P014 [combined with P010 as Study 010-C2]. The Delegate was satisfied with this explanation.

The evaluator's reference to small elevations of LDL-cholesterol levels are said not to be a cause for concern because it has not been consistently found in comparison with placebo and the applicant is unaware of a biological basis for elevation of LDL-cholesterol. Moreover, [a point that also applies to efficacy] "... the comparator group during Phase B [extension phase] of these studies does not represent a randomized population, but reflects the differential rates of dropout/rescue that occurred during the conduct of the study. Thus, comparisons between treatment groups during the longer-term extensions of these studies must be viewed with caution." Some studies have also shown small increases in HDL-cholesterol. No cardiovascular risk signal has emerged from analyses of pooled studies (limited to 2 years).

On the matter of observations about relative efficacy, "The studies presented in this application were not designed to compare sitagliptin with pioglitazone or sulfonylurea agents." The populations in the extension phases are more likely to represent a responder population, confounding these comparisons.

A number of relatively minor errors of fact have also been corrected.

2. Risk management plan evaluation report

Potential risks need not be included in the PI, the applicant responds.

Risk-benefit analysis

Delegate considerations

The original conclusions drawn in the submission to register sitagliptin included these remarks:

> "*Sitagliptin appears to offer some effects in early diabetes mellitus Type 2. The placebo controlled studies in monotherapy show that sitagliptin is better than nothing over 24 weeks. The phase 3 efficacy studies appear to have been well designed, with appropriate run-in periods and primary efficacy endpoints. It is their applicability to Australia that is the problem with this data set. Failure to conduct a direct monotherapy comparison with metformin is a serious problem at least as far as assessing the place of sitagliptin in the Australian context. ... There are no grounds for displacing metformin in patients with insulin resistance. An appropriate active comparator trial is needed for sitagliptin to have any empirically tested role.*"

This submission remedies the last mentioned omission by providing Study P049 in which metformin might have been more efficacious but this is not testable. Sitagliptin was within the margin on non-inferiority, a margin which was large in relation to the absolute efficacy of sitagliptin in the initial phases of some other studies presented in this package.

> *"In principle, sitagliptin might offer most benefit to patients with obesity and insulin resistance, making it likely to be used with metformin and in earlier stages of the disease when weight loss is still a possibility."*

Weight gain was not a feature of sitagliptin in these studies in comparison with sulfonylureas or pioglitazone.

> *"The current data set supports some role of sitagliptin in monotherapy but the durability of its effect is not known – this should be canvassed I the product information document."*

In the extension phase of the studies, sitagliptin showed signs of less durability of effect than metformin. It is expected that thiazolidinediones and metformin would show a durable effect for two years.

> *"Sitagliptin appears to be an acceptably safe add-on agent to metformin."*

The study that was later submitted to support the registration of Janumet, Study P036, confirms this observation. However, it does not directly support first line combination therapy apart from suggestion that sitagliptin 50 mg bd + metformin 1000 mg b.i.d.showed a greater therapeutic response than metformin 1000 mg b.i.d..Study P036 did not appear to be stratified by baseline HbA1c levels. This stratification would have enabled a sub-analysis to support an advantage for initial combination therapy in those with higher baseline HbA1c levels. Given that the registered indication is,

> "Januvia is indicated, as dual combination therapy, with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate", no change would seem to be warranted.

No data were submitted to support the use of add on metformin to sitagliptin in that sequence.

The extension studies support continued efficacy and safety in responders but with a tendency to loss of efficacy over time, that is, durability remains of concern and the evaluators' recommendations for a clear representation of this in the PI is supported. The studies have limited use for making inferences about comparative efficacy for reasons stated by the sponsor in reply to the evaluation reports. However, it is an inescapable conclusion that metformin appears to have a more durable treatment effect and that the limited durability of sitagliptin is out of step with other registered members of the class of DDP-4 inhibitors. It will be necessary for the applicant to annotate the version that is attached to the pre-ACPM response with the rational basis for declining these changes.

The clinical evaluator's suggested indication is:

Monotherapy

> *Januvia is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus, when metformin cannot be used.*

Individual Combination Therapy with metformin

> *Januvia is indicated in patients with Type 2 diabetes mellitus to improve glycaemic control in combination with metformin as initial therapy when dual sitagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects for response to monotherapy).*

Add-on combination Therapy with Antihyperglycemic agents

> *For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate*

In regard to monotherapy, the second line indication is not supported by a specific study but it is in principle reasonable.

The second indication is theoretically reasonable but the studies submitted do not seem to have been stratified by baseline HbA1c and the Study P049 allowed *pretreated* patients to be enrolled after a washout period. It therefore seems hard to justify it by necessity when combination therapy is already included in the register and the evidence to support the indication is weak. Moreover, it is the Delegate's view that the currently registered indication does not preclude initial combination therapy.

The third indication represents a distortion of the registered indication,

> *"For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise: as dual combination therapy with metformin or with a sulfonylurea or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate"*

because the initial part before the colon comprises the heading under which all indications should follow. By fusing this into one sentence, the meaning has been altered.

The existing indication should refer to "*Combination Therapy*" and not "*Add-on combination Therapy with Anti hyperglycemic agents*" and be integrated into the text to avoid "future-proofing".

Proposed actions

The application by Merck Sharp & Dohme (Australia) Pty Ltd to register an extended indication for Januvia 25, Januvia 50 and Januvia 100 tablets containing 25, 50 or 100 mg sitagliptin base equivalent in film coated, unscored tablets should be approved. The registered indication should be:

Januvia is indicated for the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise:

- *as monotherapy, as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus, when metformin cannot be used.*
- *as dual combination therapy, with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.*

The application was submitted to the Advisory Committee on Prescription Medicines for advice.

Response from sponsor

Monotherapy

Merck Sharp & Dohme (MSD) concurred with the Delegate's proposed action to recommend the approval of Januvia (Sitagliptin phosphate) for the monotherapy indication. MSD accepts the Delegate's proposal for restricted first line indication but proposes to modify the wording in order to clearly define the circumstances where sitagliptin can be used as monotherapy. Note that MSD's proposed wording is also consistent with the EU Summary of Product Characteristics (SmPC) text. The proposed text is as follows with the Delegate's text proposed in italics:

> *"Januvia is indicated for the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise:*
>
> *-as monotherapy, as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus, when metformin is inappropriate due to contraindications or intolerance.*

-as dual combination therapy, with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate."

In this way, the prescriber is drawn to consider not only intolerance, to any agent, but other contraindications to those agents. As an example, metformin is contraindicated in patients with renal impairment.

In addition, the Delegate commented on the durability of effect and requested other Product Information (PI) changes. MSD responded to the Delegate's comments on durability of effect of sitagliptin and amendments to the PI.

Durability of effect

MSD acknowledges the Delegate's comments regarding the continued efficacy and safety of sitagliptin monotherapy in patients but with a tendency to loss of efficacy over time. However, loss of efficacy over time is common to all antihyperglycemic agents requiring either increase in dose or the addition of a second or third agent to achieve adequate glycemic control. Progressive deterioration of beta-cell function is observed with increasing duration of disease in patients with Type 2 diabetes mellitus; this continued worsening of beta-cell function is believed to underlie the waning of clinical responses observed with most of the current treatment options for Type 2 diabetes mellitus, including metformin, sulfonylureas, thiazolidinediones and DPP-IV inhibitors as demonstrated in randomised, controlled clinical trials. It also explains why many patients eventually require insulin therapy for glucose control.

All studies submitted in the sitagliptin application included an assessment of the durability of effect which was evaluated by computing a 'coefficient of durability' (COD). The COD was calculated as follows: The A1C at Week 24 or 25 was considered as the lowest point reached (nadir) A1C; the LS means for A1C at each subsequent time point were then treated as individual values in a simple linear regression. The COD is the slope of the regression line fit to the LS means. A COD of 0.005 for example, implies that the A1C increases (on average) 0.005% per week after reaching its nadir at Week 24 or 25. Higher (more positive) values for the COD suggest a less durable response. The table below shows the COD for the studies with ≥104 weeks of duration submitted in this filing. The COD was similar for all treatment groups, suggesting that the A1C-lowering observed with sitagliptin monotherapy is likely to be at least as durable as that observed with either glipizide or metformin monotherapy over the same period of time.

Table 31.

Coefficient of Durability (COD)
Determined Using HbA_{1c} LS Means from Week 24/25 to Week 104/106
All-Patients-Treated

Protocol Number	Duration of Study (Weeks)	COD (% per Week)	SE	95% CI
Sitagliptin as Monotherapy (100 mg/day)				
P021	104	0.007	0.001	(0.005, 0.008)
P036	104	0.007	0.001	(0.004, 0.010)
P010C2[†]	106	0.002	0.001	(0.001, 0.005)
Metformin as Monotherapy (1000 mg b.i.d.)				
P036	104	0.005	0.001	(0.003, 0.006)
Sulfonylurea as Monotherapy				
P010C2	106	0.006	0.002	(0.002, 0.009)

LS=Least Squares; SE=Standard Error; CI=Confidence Interval
[†] Results are from the sitagliptin total daily dose (TDD) group, which includes sitagliptin 50 mg b.i.d./100 mg q.d. (from P010), sitagliptin 50 mg b.i.d./100 mg q.d. (from P014), and sitagliptin 100 mg q.d./100 mg q.d. (from P014).

In addition, the proportion of patients who achieved (at Week 24/25) and maintained (at Week 104/106) a desired A1C goal (for example <7.0%) was also evaluated (see Table 32 below). Across the three studies of ≥104 weeks duration, substantial proportions (43.7% to 56.1%) of patients in the sitagliptin monotherapy groups who achieved the A1C goal of <7.0% at Week 24/25 maintained this goal at Week 104/106.

Taken together, these data (on the COD and the proportion of patients who achieved and maintained A1C at goal) indicate a relatively high and similar durability of effect for the monotherapies of sitagliptin, metformin, and glipizide used for initial therapy of patients with Type 2 diabetes mellitus.

Finally, the basis for the statement that "sitagliptin is out of step with other registered members of the class of DPP-IV inhibitors" in regards to durability is unclear. No results from randomised controlled head-to-head studies between DPP-IV inhibitors of sufficient duration are available to compare durability of different DPP-IV inhibitors.

Furthermore, given the known mechanisms of DPP-IV inhibitors to affect glucose control, it is unlikely that a difference in durability exists between drugs of this class.

Table 32.

Proportion of Patients with HbA_{1c} Value < 7.0% at Week 24/25 and Week 104/106 All-Patients-Treated

Protocol Number	Duration of Study (Weeks)	N	n (%)
Sitagliptin as Monotherapy (100 mg/day)			
P021	104	87	38 (43.7)
P036	104	30	15 (50.0)
P010C2[†]	106	66	37 (56.1)
Metformin as Monotherapy (1000 mg b.i.d.)			
P036	104	55	35 (63.6)
Sulfonylurea as Monotherapy			
P010C2	106	30	19 (63.3)

N = Number of patients who met goal of HbA_{1c} Value < 7.0% at Week 24 (P021 and P036) or Week 25 (P010C2).

n = Number of patients who also met the goal of HbA_{1c} Value < 7.0% at Week 104 (P021 and P036) or Week 106 (P010C2).

[†]Results are from the sitagliptin total daily dose (TDD) group, which includes sitagliptin 50 mg b.i.d./100 mg q.d. (from P010), sitagliptin 50 mg b.i.d./100 mg q.d. (from P014), and sitagliptin 100 mg q.d./100 mg q.d. (from P014).

Combination therapy

MSD accepted the Delegate's revisions to the dual combination therapy section of the indication and acknowledged that the indication allows for the use of sitagliptin as add-on and initial combination therapy with metformin.

Conclusion

In conclusion, whilst the sponsor agreed with the Delegate's proposed action to recommend the approval of Januvia (sitagliptin phosphate) for the indications of restricted first line monotherapy and initial combination therapy with metformin, the sponsor considered the following indications, with the modifications below in bold text, to be appropriate:

> *"Januvia is indicated for the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise:*
>
> *-as monotherapy, as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus,* ***when metformin is inappropriate due to contraindications or intolerance****.*
>
> *-as dual combination therapy, with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate."*

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered these products to have an overall positive benefit–risk profile for the indication:

> *Januvia is indicated for the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise:*

as monotherapy, as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus, when metformin cannot be used.

as dual combination therapy, with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate

In making this recommendation, the ACPM noted and expressed disappointment in the study design due to the inadequacy in the design and selection of patients for the post 24 week duration of therapy.

The ACPM agreed with the Delegate to the proposed amendments to the PI and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the Clinical Trials section of the PI to accurately reflect the limitations in the study design in terms of demonstrating the durability of the initial efficacy.
- a statement in the Dosage and Administration section of the PI and CMI to include reference to GFR and monitoring of the renal function and adverse effects.

The ACPM advised that the Risk Management Plan be reviewed to ensure effective pharmacovigilance of the identified safety signals.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Januvia (sitagliptin (as phosphate monohydrate)) for oral administration at 100 mg once daily, indicated for:

Januvia is indicated for the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise;

- as monotherapy, as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus, when metformin cannot be used.
- as dual combination therapy, with metformin, or with a sulfonylurea, or with a or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

Specific conditions applying to these therapeutic goods:

1. The implementation in Australia of the Januvia sitagliptin (as phosphate monophosphate) RMP version 4.0 dated 12 January 2012 and any subsequent revisions with any accompanying caveats and requests for pharmacovigilance activities as agreed with the TGA and its Office of Product Review. The sponsor must undertake to give specific consideration of all reported occurrences of hypoglycaemia in the Periodic Safety Update Reports.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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Reference/Publication #