European Medicines Agency

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ASSESSMENT REPORT
FOR
TESAVEL

International Nonproprietary Name:
Sitagliptin

Procedure No. EMEA/H/C/910/II/0009

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

Sitagliptin phosphate (Tesavel) is an orally active selective inhibitor of the enzyme dipeptidyl peptidase 4 (DPP-4). DPP-4 inhibitors act by enhancing the levels of active incretin hormones. These hormones, including glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, are released from the intestine in response to a meal and are part of an endogenous system involved in glucose homeostasis.

Tesavel was approved in the EU in March 2007 and currently has the following indications: *"For patients with type 2 diabetes mellitus, Tesavel is indicated:*

- to improve glycaemic control when diet and exercise alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- to improve glycaemic control in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- to improve glycaemic control in combination with 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.
- to improve glycaemic control in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

For patients with type 2 diabetes mellitus in whom use of a PPARγ agonist (i.e. a thiazolidinedione) is appropriate, Tesavel is indicated:

- in combination with the PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.
- in combination with the PPARγ agonist and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control."

The MAH submitted this type II variation application to extend the indication as follows:
"To improve glycaemic control as an adjunct to diet and exercise in combination with insulin and metformin."

To support this extension of indication, the MAH presented the results of study P051. This is a 24-week-during phase III, multicenter, randomized, double-blind clinical trial to study the safety and efficacy of sitagliptin in patients with type 2 Diabetes Mellitus who have inadequate glycaemic control on insulin therapy (alone or in combination with metformin).

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the MAH included an EMEA Decision {EMEA-000470-PIP01-08} on the agreement of a Paediatric Investigation Plan and on the granting of a deferral and on the granting of a waiver for sitagliptin phosphate monohydrate (Tesavel).
The waiver applies to "Children of less than 10 years, for sitagliptin film-coated tablets, oral use, on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset."
The deferral was granted for the subset(s) of the paediatric population concerned by the paediatric development from 10 to less than 18 years for sitagliptin film-coated tablets (25 mg, 50 mg and 100 mg), oral use.

2. Non- clinical aspects

Environmental Risk Assessment
The ERA for sitagliptin phosphate submitted in the application for the current type II variation is an updated version of the ERA submitted by the MAH at the time of the initial application.
Data from a new algae growth inhibition test pursuant to the latest OECD 201were missing in the previous version, thus preventing a conclusion of the ERA for sitagliptin.

The MAH has submitted in July 2009 the requested new algal study pursuant to the latest OECD 201.
The CHMP concluded that the test was valid and that the risk to the surface water of sitagliptin can be assumed to be negligible.

3. Clinical aspects

3.1. Clinical efficacy

The MAH stated that "clinical trials carried out outside of the European Union meet the ethical requirements of Directive 2001/20/EC." The MAH also stated that "all trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed."

3.1.1.Main study

3.1.1.1. Methods

Study P051 was a 24-week, multicenter, randomized, double-blind, parallel-group Phase III study comparing the efficacy of sitagliptin 100 mg with placebo in patients with T2DM who had inadequate glycaemic control on insulin therapy (alone or in combination with metformin). Patients, age ≥21 years, with inadequate glycaemic control (A1C ≥7.5% and ≤11.0%) on either pre-mixed (NPH and regular or short-acting mixture), intermediate- (NPH or Lente), or long-acting (Glargine, Detemir, or Ultralente) insulin therapy (and not on routine pre-meal short- or rapid-acting insulin, except as pre-mixed insulin or if short-acting insulin was used <3 times a week), alone or in combination with metformin (at a dose of ≥1500 mg/day), were randomized in a 1:1 ratio to receive either sitagliptin 100 mg or matching placebo (see Figure 1). Randomization was stratified by 1) use of metformin at Visit 1 (i.e., on insulin alone, or on insulin in combination with metformin), 2) the patient's use of pre-mixed insulin at Visit 1 (i.e., on pre-mixed insulin, or not on pre-mixed insulin), and 3) participation in a 10-point, frequently sampled, meal tolerance test (MTT), for a total of 8 strata. The proportion of patients on insulin in combination with metformin was capped at approximately 75%; the proportion of patients on pre-mixed insulin was capped at approximately 25%.

Dosing regimens for open-label metformin and insulin therapy were to remain stable throughout the study period, except if the insulin dose needed to be reduced due to the occurrence, or prevention, of hypoglycaemia. Patients not meeting specific glycaemic goals were to receive rescue therapy that consisted of an adjustment of insulin dose(s), based on the investigator's clinical judgment. Rescue therapy was initiated after Visit 3/Day 1 for those patients with FPG level >280 mg/dL (15.6 mmol/L), repeated and confirmed within 7 days of the initial elevated value, or at/after Visit 5 for those patients with FPG >240 mg/dL (13.3 mmol/L), repeated and confirmed within 7 days of the initial elevated value.

Study Design

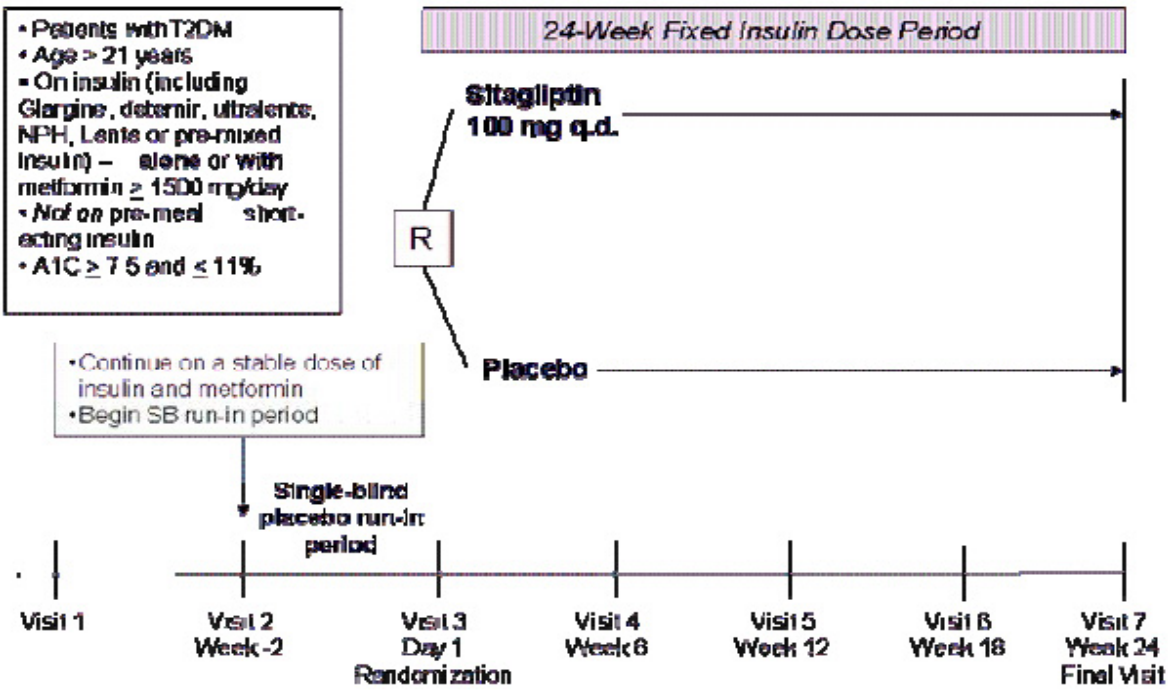


Figure 1: Study Design

3.1.1.2. Objectives Study P051

In patients with T2DM and who have inadequate glycaemic control (A1C ≥7.5% and ≤11%) on insulin (alone or in combination with metformin): Primary: 1) After 24 weeks to assess the effect of sitagliptin addition compared with placebo on HbA1c level. 2) To assess the safety and tolerability of sitagliptin. Secondary: After 24 weeks to assess the effect of sitagliptin addition compared with placebo on 1) HbA1c level in the sub-population of patients on a long-acting or intermediate-acting insulin alone or in combination with metformin. 2) Glycaemic response after a meal. 3) Fasting Plasma Glucose (FPG). 4) Proportion patients achieving HbA1c goal <7%. 5) Proportion patients achieving HbA1c goal <6.5%. 6) Glycaemic efficacy in patients on insulin alone, or on insulin in combination with metformin. 7) Body weight. 8) In the subset of patients who have a frequently sampled meal tolerance test, parameters describing pancreatic beta-cell function.

3.1.1.3. Evaluation Criteria

Primary efficacy endpoint: change from baseline in HbA1c.
Secondary efficacy endpoints: HbA1c change from baseline in the sub-population of patients on long-acting or intermediate-acting insulin; 2-hour post-meal glucose (PMG) after a standard meal challenge; fasting plasma glucose (FPG); glucose, insulin, proinsulin, and C-peptide levels measured immediately prior to a standard meal, and at 60 and 120 minutes from the start of the meal; in subsets of patients willing to undergo more extensive blood sampling: glucose, insulin and C-peptide levels measured at the following time points relative to the start of the meal: -10, 0, 10, 20, 30, 60, 90, 120, 180, and 240 minutes, and proinsulin levels measured at 0, 60, and 10 minutes relative to the start of the meal; insulin dose; 1,5-anhydroglucitol; and lipid panel.
Safety endpoints: Collection of adverse events, physical examinations, body weight and vital signs. Laboratory assessments including blood chemistry (including sodium, potassium, chloride, bicarbonate, albumin, uric acid, ALT, AST, alkaline phosphatase, creatinine, total bilirubin), lipid panel, haematology (including CBC, differential, absolute neutrophil count), urinalysis and ECG (read locally).

3.1.1.4. Statistical Methods

The Full Analysis Set (FAS) was the primary analysis population and consisted of all patients randomized who received at least one study dose, had a baseline measurement, and had at least one post-treatment measurement.
A completers population served as a secondary analysis population and included all patients who had a baseline and a Week 24 measurement prior to the initiation of rescue therapy.

For comparison of continuous efficacy parameters, an analysis of covariance (ANCOVA) model was used, including treatment, metformin stratum (i.e., on insulin alone, or on insulin and metformin), pre-mixed insulin stratum, and baseline values. An ordered testing procedure was applied for the primary and secondary efficacy hypotheses.
Data after the initiation of rescue therapy were treated as missing in order to avoid the confounding influence of rescue therapy on efficacy comparisons. The primary approach to handling missing data was the last observation carried forward (LOCF). No missing data were imputed for the completers analysis.
For the proportion of patients achieving HbA1c goals (<7.0% and <6.5%, respectively) at Week 24, a logistic regression model was used adjusting for baseline HbA1c values, metformin stratum, and pre-mixed insulin stratum.
A time-to-rescue analysis was performed using the Kaplan-Meier estimate and the logrank test. Similar analyses were performed to compare time to either rescue therapy or sustained increase in insulin dose of more than 10%, whichever came first.

3.1.1.5. Study population

Twelve hundred and eighty patients were screened, and 641 patients participated in the study at 100 sites worldwide. Of these 641 randomized patients, five hundred and sixty-four (564) patients completed 24 weeks of treatment (281 in sitagliptin group versus 283 in placebo group).

The number of drop outs was relatively low and similar among treatment groups. More than 90% of patients could be included in the primary analysis and more than 80% in the secondary analysis.

Demographic and anthropometric traits and baseline disease characteristics were generally similar across treatment groups. The study population ranged from 25 to 82 years of age.
The MAH clarified that N=81 (25.2%) and N=68 (21.3%) in the sitagliptin and placebo groups, respectively, were older than 65 years; only a very small number of patients, i.e. N=12 (3.7%) and N=7 (2.2%), respectively, were older than 75 years.

The CHMP requested the MAH to provide further clarifications on the patient population in study P051 and characteristics of the intended target population. The MAH clarified that study P051 was designed to assess the safety and efficacy of the addition of sitagliptin to a stable insulin regimen in a broad population of patients representative of those who had been maintained by their physicians on a stable dose of insulin but who had not achieved A1C treatment targets. Therefore, eligibility required that a patient be on a stable insulin regimen for at least 10 weeks prior to screening and have a screening A1C of 7.5%-11.0%. The vast majority (~75%) of patients had been on a stable insulin regimen for at least six months. Study P051 was not designed to evaluate patients with T2DM who had undergone aggressive titration of insulin, but instead to evaluate the efficacy and tolerability of the addition of sitagliptin to patients inadequately controlled on a stable regimen of insulin as administered in clinical practice. Information regarding whether or not the patients could have been titrated to a higher dose of insulin prior to enrollment into the study was not collected. Thus, a separate analysis cannot be performed for such patients.
The MAH acknowledged that further intensification of insulin regimen may be a clinically appropriate option for improving glycaemic control in some patients, but it generally involves a more complicated regimen consisting of a combination of basal (or intermediate) and pre-prandial short-acting insulin, leading to multiple (i.e., 3-4) daily injections and more intensified capillary blood glucose monitoring. Moreover, further intensification of insulin regimens can be associated with weight gain and increased hypoglycemia. Another treatment approach, commonly used in clinical practice, is the addition of an oral antihyperglycaemic agent to a regimen of stable insulin. This was evaluated in study P051.

The CHMP noted that due to this design an active-comparator group in whom insulin dosage was increased was lacking, but patients were on stable dose for at least 10 weeks and most for at least 6 months, suggesting that further increase of the insulin dose was not considered appropriate by the treating physician. It is also recognized that maximizing insulin therapy may not always be appropriate due to side effects and the complicated dosage regimen. Thus, CHMP considered it not necessary to require another study comparing the addition of sitagliptin with that of an increase in insulin dosage(s). It should also be noted that design of the study is in line with the current guideline on the evaluation of medicinal products in the treatment of diabetes mellitus where it is stated that efficacy of an oral antidiabetic agent in combination with insulin should be documented vs. placebo in patients already treated with insulin for a time sufficient to ensure stable HbA1c levels (i.e. at least 2 to 3 months).
The CHMP, however, requested the MAH to restrict the indication to the situation when diet and exercise plus "*stable*" dosage of insulin (i.e. a stable insulin regimen for at least ten weeks) with or without metformin do not provide adequate glycaemic control. See further in section 3.6 "Changes to the Product Information" for the exact indication.

3.1.1.6. Medical history in study population

Patients participating in this study had the expected high prevalence of medical disorders commonly associated with T2DM, such as hypertension, dyslipidaemia, and obesity. Although patients with unstable medical conditions, such as active liver disease or congestive heart failure (NYHA class II, III or IV), were excluded from participation, patients with a wide range of concurrent medical conditions and concomitant medications were included. Five hundred and ninety-nine (93.4%) of the 641 randomized patients had at least one medical history condition other than T2DM. Vascular disorders (70.2% and 66.8% of patients in the sitagliptin and placebo groups, respectively), metabolism and nutrition disorders (67.1% and 61.4% of patients in the sitagliptin and placebo groups, respectively), surgical and medical procedures (35.1% and 34.2% of patients in the sitagliptin and

placebo groups, respectively), musculoskeletal and connective tissue disorders (31.7% and 32.9% of patients in the sitagliptin and placebo groups, respectively), nervous system disorders (30.4% and 37.6% of patients in the sitagliptin and placebo groups, respectively), eye disorders (31.1% and 27.3% of patients in the sitagliptin and placebo groups, respectively) and gastrointestinal disorders (26.7% and 21.0% of patients in the sitagliptin and placebo groups, respectively) were the most common categories by system organ class (SOC) of medical history. The most common specific medical history conditions were hypertension, hyperlipidaemia, and dyslipidaemia. There were no clinically important differences among treatment groups in the frequency or type of medical history conditions.

Elderly patients were allowed to participate in this study, but no separate study was performed. The age of included patients varied between 25 and 82 years old. Children were excluded. Patients with kidney problems were excluded: Patients not on metformin therapy with serum creatinine concentrations consistently ≥1.7 mg/dL (151 μmol/L) in men and ≥1.5 mg/dL (133 μmol/L) in women, or estimated creatinine clearance <50 mL/min (using the Cockcroft-Gault formula) were excluded. Patients on metformin therapy with serum creatinine concentrations ≥1.5 mg/dL (133 μmol/L) in men or ≥1.4 mg/dL (124 μmol/L) in women, or estimated creatinine clearance <60 mL/min were excluded.

3.2. Efficacy results

3.2.1. Haemoglobin A_{1c} (A1C)

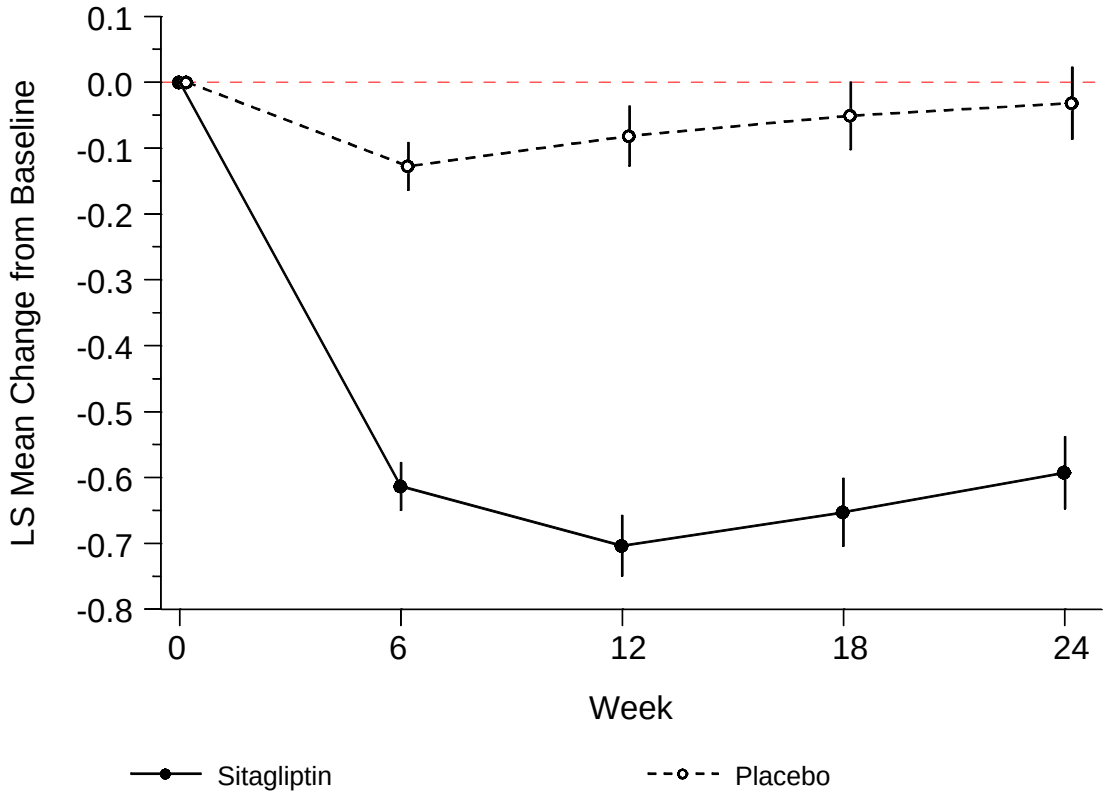
As shown in Table 1 and Figure 2, in both sitagliptin and placebo group there was a modest reduction in HbA1c level compared to baseline [LS mean (95%)] -0.59% (-0.70,-0.48) versus -0.03% (-0.14,-0/08) respectively. The reduction observed with the addition of sitagliptin was statistically significantly greater than that observed with placebo ($p<0.001$). The profile of change from baseline in A1C over time shows a greater reduction in A1C level in the sitagliptin group compared with the placebo group at all time points measured; the between-group difference was maintained through Week 24.

Table 1: Analysis of Change from Baseline in HbA1c (%) at Week 24 Excluding Data After Initiation of Rescue Therapy (Full Analysis Set)

Treatment	N	Baseline Mean (SD)	Week 24 Mean (SD)	Change from Baseline at Week 24	
				Mean (SE)	LS Mean (95% CI) †
Sitagliptin	305	8.72 (0.88)	8.07 (1.04)	-0.65 (0.05)	-0.59 (-0.70, -0.48)
Placebo	312	8.64 (0.95)	8.58 (1.17)	-0.07 (0.05)	-0.03 (-0.14, 0.08)
Pairwise Comparison				Difference in LS Means (95% CI)	p-Value
Sitagliptin vs. Placebo				-0.56 (-0.70, -0.42)	<0.001
Root Mean Square Error of Change =0.86					

† Based on ANCOVA model with a term for treatment, metformin stratum, pre-mixed insulin stratum and baseline A1C as a covariate.

Figure 2: Change from Baseline in A1C (%) Over Time (LS Mean ± SE) by Treatment Group Excluding Data After Initiation of Rescue Therapy (Full Analysis Set)



Subgroup Analysis by the Use of Pre-mixed Insulin Stratum

There were no differences found in changes of HbA1c from baseline in the subgroup analysis for type of insulin. For both patient groups, long-acting or intermediate-acting insulin users, the LS Mean decrease from baseline in A1C was significantly greater in the sitagliptin group compared with the placebo group ($p<0.001$). The between-group differences in both insulin strata were almost identical (nominal $p=0.949$ for treatment-by-stratum interaction).

Subgroup Analysis by the Use of Metformin Stratum

As shown in Table 2, no differences in changes of HbA1c from baseline were seen between patient on metformin or not on metformin (nominal $p=0.437$ for treatment-by-stratum interaction). For both patient groups on metformin or without metformin treatment, LS mean decreases from baseline in

A1C were significantly greater in the sitagliptin group compared with the placebo group (nominal p<0.001).

Table 2: Subgroup analysis of change from baseline in HbA1c (%) at week 24 by metformin statum Excluding data after initiation of rescue therapy (Full Analysis Set)

Treatment Group	N	Baseline Mean (SD)	Change from Baseline at Week 24			
			Mean (SE)	LS Mean (95% CI)	Difference in LS Mean vs. Placebo (95% CI)	p-Value† for Comparison with Placebo
Metformin: Patients not on Metformin						
Sitagliptin	82	8.68 (0.89)	-0.56 (0.08)	-0.55 (-0.74, -0.37)	-0.65 (-0.91, -0.39)	<0.001
Placebo	83	8.76 (1.08)	0.08 (0.11)	0.10 (-0.09, 0.28)		
Metformin: Patients on Metformin						
Sitagliptin	223	8.73 (0.88)	-0.68 (0.06)	-0.66 (-0.78, -0.54)	-0.53 (-0.69, -0.37)	<0.001
Placebo	229	8.60 (0.90)	-0.12 (0.06)	-0.13 (-0.25, -0.01)		
p-Value for Treatment by Subgroup Interaction =0.437						

† Based on ANCOVA model with terms for treatment, metformin stratum, pre-mixed insulin stratum, treatment by Metformin Stratum interaction, and baseline A1C as a covariate.

Patients with higher baseline HbA1c had a greater decrease from baseline in HbA1c than patients with lower baseline HbA1c in both sitagliptin and placebo groups, which was consistent with the significant covariate effect of baseline HbA1c in the primary ANCOVA analysis. The between-group differences were consistent across the range of baseline HbA1c.

Study P051 shows a modest, although statistically significant, reduction in HbA1c level during the sitagliptin therapy. The best results in HbA1c were seen after 12 weeks. The HbA1c level increased slightly after three months in the sitagliptin group. This phenomenon was seen in the placebo group as well. These results are similar as was seen in studies previously submitted for other indications.
Results from completers analyses were consistent with the FAS analyses except for a somewhat smaller mean effect in the non-metformin group (-0.55%) compared to the FAS analysis (-0.65%). Overall, the results suggest that the treatment effects (in terms of HbA1c) are modest but clinically relevant and consistent across subgroups.

Older patients
The placebo-adjusted mean treatment effects in the elderly (-0.72% and -0.79% in patients >65 y and > 75 y, respectively) were similar to or even larger than the overall response (-0.56%), although, patient numbers were small, precluding firm conclusions. Nevertheless, the data do not indicate a lack of efficacy in the elderly.

Table 3: Analysis of Change from Baseline in A1C (%) at Week 24 Subgroup of Patient with age>=65 Years Excluding Data After Initiation of Rescue Therapy (Overall Cohort, Full Analysis Set)

Treatment	N	Baseline Mean (SD)	Week 24 Mean (SD)	Change from Baseline at Week 24 Mean (SE)	LS Mean (95% CI) †
Sitagliptin	77	8.51 (0.79)	7.85 (0.84)	-0.66 (0.07)	-0.64 (-0.80, -0.48)
Placebo	66	8.45 (0.83)	8.49 (1.00)	0.05 (0.10)	0.08 (-0.10, 0.25)
Pairwise Comparison				Difference in LS Means (95% CI)	p-Value
Sitagliptin vs. Placebo				-0.72 (-0.94, -0.49)	<0.001
Root Mean Square Error of Change =0.67					
† Based on ANCOVA model with a term for treatment, pre-mixed insulin stratum, metformin stratum, and baseline A1C as a covariate.					

Table 4: Analysis of Change from Baseline in A1C (%) at Week 24 Subgroup of Patient with age>=75 Years Excluding Data After Initiation of Rescue Therapy (Overall Cohort, Full Analysis Set)

Treatment	N	Baseline Mean (SD)	Week 24 Mean (SD)	Change from Baseline at Week 24 Mean (SE)	LS Mean (95% CI) †
Sitagliptin	11	8.42 (1.01)	7.98 (1.06)	-0.44 (0.14)	-0.36 (-0.72, -0.00)
Placebo	6	8.32 (0.90)	8.87 (0.99)	0.55 (0.23)	0.43 (-0.07, 0.93)
Pairwise Comparison				Difference in LS Means (95% CI)	p-Value
Sitagliptin vs. Placebo				-0.79 (-1.40, -0.18)	0.015
Root Mean Square Error of Change =0.50					
† Based on ANCOVA model with a term for treatment, pre-mixed insulin stratum, metformin stratum, and baseline A1C as a covariate.					

HbA1c Goals

Table 5 displays Week 24 HbA1c results for the proportions of patients with Week 24 HbA1c values below 7.0% (12.8% of patients in the sitagliptin group compared with 5.1% of patients in the placebo group). The odds of achieving a Week 24 A1C level <7.0% were significantly higher in the sitagliptin group than in the placebo group (p<0.001).

The odds of achieving a HbA1c level <6.5% at Week 24 were similar in both groups in the FAS population (p=0.584). There were very small numbers of patients who achieved the secondary HbA1c goal of <6.5% in both treatment groups: 7/305 (2.3%) in the sitagliptin group versus 6/312 (1.9%) in the placebo group, p<0.001.

Table 5: Proportion of Patients with HbA1c Value <7.0% at Week 24 Excluding Data After Initiation of Rescue Therapy (Full Analysis Set)

Treatment	N	n (%)		
Sitagliptin	305	39 (12.8)		
Placebo	312	16 (5.1)		
Between Treatment Comparison	Difference in Proportion (%) (95% CI[†])	Relative Risk (95% CI[‡])	Odds-Ratio (95% CI[§])	p-Value [§]
Sitagliptin vs. Placebo	7.7 (3.2, 12.3)	2.50 (1.43, 4.37)	3.60 (1.89, 6.85)	<0.001

† Computed using the Wilson's Score method.
‡ Computed using the Cochran-Mantel-Haenszel (CMH) test with the interaction between the metformin stratum and the pre-mixed insulin stratum (i.e., 4 categories) as a CMH stratification factor
§ From the logistic regression model, adjusting for baseline A1C, the metformin stratum, and the pre-mixed insulin stratum.

The results of the entire cohort are comparable with the results in the subgroup of patients on metformin as shown in Table 6.

Table 6: Proportion of patients with HbA1c value <7.0% at week 24; patients on metformin Excluding data after initiation of rescue therapy (Full Analysis Set)

Treatment	N	n (%)		
Sitagliptin	223	32 (14.3)		
Placebo	229	12 (5.2)		
Between Treatment Comparison	Difference in Proportion (%) (95% CI[†])	Relative Risk (95% CI[‡])	Odds-Ratio (95% CI[§])	p-Value [§]
Sitagliptin vs. Placebo	9.1 (3.7, 14.8)	2.73 (1.45, 5.16)	4.02 (1.93, 8.34)	<0.001

[†] Computed using the Wilson's Score method.

[‡] Computed using the Cochran-Mantel-Haenszel (CMH) test with the pre-mixed insulin stratum as a CMH stratification factor

[§] From the logistic regression model, adjusting for baseline A1C and the pre-mixed insulin stratum.

3.2.2. 2-Hour Post-Meal Glucose (PMG)

Table 7 displays 2-hour PMG results for the FAS population at Week 24. The between-group difference in LS mean change from baseline in 2-hour PMG was statistically significant (p<0.001). Consistent with these results, analysis of the 2-hour incremental PMG showed a significantly greater decrease with sitagliptin compared with placebo (p<0.001) see Table 8.

Table 7: Analysis of Change from Baseline in 2-Hour Post-Meal Glucose (mg/dL) at Week 24 Excluding Data After Initiation of Rescue Therapy (Full Analysis Set)

Treatment	N	Baseline Mean (SD)	Week 24 Mean (SD)	Change from Baseline at Week 24	
				Mean (SE)	LS Mean (95% CI) [†]
Sitagliptin	240	290.9 (68.0)	252.0 (74.0)	-39.0 (4.5)	-30.9 (-40.0, -21.8)
Placebo	257	292.1 (66.4)	289.0 (78.5)	-3.1 (4.1)	5.2 (-3.6, 13.9)
Pairwise Comparison				Difference in LS Means (95% CI)	p-Value
Sitagliptin vs. Placebo				-36.1 (-47.1, -25.1)	<0.001
Root Mean Square Error of Change =62.2					
[†] Based on ANCOVA model with a term for treatment, metformin stratum, pre-mixed insulin stratum and baseline 2-Hour Post-Meal Glucose as a covariate.					

Table 8: Analysis of Change from Baseline in 2-Hour Post-Meal Incremental Glucose (mg/dL) at Week 24 Excluding Data After Initiation of Rescue Therapy (Full Analysis Set)

Treatment	N	Baseline Mean (SD)	Week 24 Mean (SD)	Change from Baseline at Week 24	
				Mean (SE)	LS Mean (95% CI) [†]
Sitagliptin	239	117.0 (49.4)	98.5 (48.3)	-18.6 (3.0)	-11.8 (-18.0, -5.7)
Placebo	257	117.7 (62.7)	122.7 (52.1)	5.1 (3.7)	11.8 (5.9, 17.8)
Pairwise Comparison				Difference in LS Means (95% CI)	p-Value
Sitagliptin vs. Placebo				-23.7 (-31.2, -16.2)	<0.001
Root Mean Square Error of Change =42.6					
[†] Based on ANCOVA model with a term for treatment, metformin stratum, pre-mixed insulin stratum and baseline 2-Hour Post-Meal Incremental Glucose as a covariate.					

The change from baseline in 2-hour post-meal glucose is clinically relevant (minus 39 mg/dl; minus 2.1 mmol/l) and statistically significant with sitagliptin in comparison with adding placebo. However, the 2-hour post-meal glucose level after 24 weeks of treatment with sitagliptin is still 252.0 mg/dl (14 mmol/l), which is far from the goal of <10 mmol/l. (180 mg/dl maximum).

The results of the entire cohort are comparable with the results in the subgroup of patients on metformin as shown in Table 9.

Table 9: Subgroup analysis of change from baseline in 2-hour post-meal glucose (mg/dl) at week 24 by metformin strata; excluding data after initiation of rescue therapy (Full Analysis Set)

Treatment Group	N	Baseline Mean (SD)	Change from Baseline at Week 24			
			Mean (SE)	LS Mean (95% CI)	Difference in LS Mean vs. Placebo (95% CI)	p-Value† for Comparison with Placebo
Metformin: Patients not on Metformin						
Sitagliptin	58	322.9 (72.2)	-34.0 (9.7)	-18.0 (-34.5, -1.6)	-23.3 (-45.1, -1.4)	0.037
Placebo	68	323.9 (66.4)	-10.3 (9.4)	5.3 (-9.9, 20.5)		
Metformin: Patients on Metformin						
Sitagliptin	182	280.7 (63.5)	-40.5 (5.0)	-39.0 (-48.7, -29.2)	-40.4 (-53.1, -27.7)	<0.001
Placebo	189	280.6 (62.7)	-0.5 (4.4)	1.5 (-8.2, 11.2)		
p-Value for Treatment by Subgroup Interaction =0.183						

† Based on ANCOVA model with terms for treatment, metformin stratum, pre-mixed insulin stratum, treatment by Metformin Stratum interaction, and baseline 2-Hour Post-Meal Glucose as a covariate.

3.2.3. Fasting Plasma Glucose (FPG)

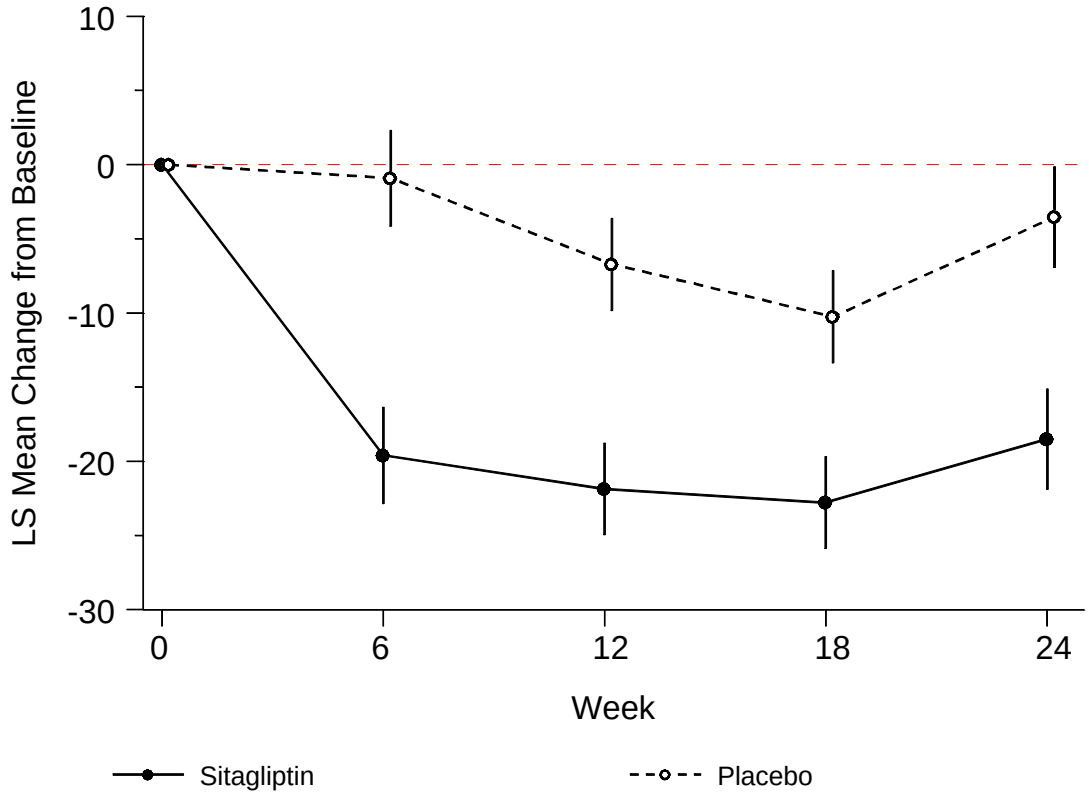
Table 10 displays FPG results for the FAS population at Week 24. The LS Mean decrease from baseline in FPG was significantly greater in the sitagliptin group compared with the placebo group (p<0.001). The profiles of mean change from baseline in FPG over time is shown in Figure 3.

Table 10: Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) at Week 24 Excluding Data After Initiation of Rescue Therapy (Full Analysis Set)

Treatment	N	Baseline Mean (SD)	Week 24 Mean (SD)	Change from Baseline at Week 24	
				Mean (SE)	LS Mean (95% CI) †
Sitagliptin	310	175.8 (51.6)	155.1 (54.2)	-20.7 (3.4)	-18.5 (-25.1, -11.9)
Placebo	313	179.1 (59.6)	171.0 (59.7)	-8.0 (3.9)	-3.5 (-10.2, 3.1)
Pairwise Comparison				Difference in LS Means (95% CI)	p-Value
Sitagliptin vs. Placebo				-15.0 (-23.4, -6.5)	<0.001
Root Mean Square Error of Change =53.5					

† Based on ANCOVA model with a term for treatment, metformin stratum, pre-mixed insulin stratum and baseline Fasting Plasma Glucose as a covariate.

Figure 3: Change from Baseline in Fasting Plasma Glucose (mg/dL) Over Time(LS Mean ± SE) by Treatment Group Excluding Data After Initiation of Rescue Therapy (Full Analysis Set)



The Fasting Plasma Glucose Level dropped in the sitagliptin group. However the amount of reduction is small, only about 20 mg/dl (1.1 mmol/l). The reduction in FPG was from 175.8 mg/dl (9.7 mmol/l) to 155.1 mg/d (8.6 mmol/l). From a clinical point of view, this (average) reduction in FPG is small and not enough for a proper treatment. In some patients this reduction might be sufficient, but for most people who are already on insulin this improvement is still not enough.

The results of the entire cohort are comparable with the results in the subgroup of patients on metformin as shown in Table 11.

Table 11: Subgroup Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) at Week 24 by Metformin Stratum Excluding Data After Initiation of Rescue Therapy (Full Analysis Set)

Treatment Group	N	Baseline Mean (SD)	Change from Baseline at Week 24			
			Mean (SE)	LS Mean (95% CI)	Difference in LS Mean vs. Placebo (95% CI)	p-Value† for Comparison with Placebo
Metformin: Patients not on Metformin						
Sitagliptin	85	182.1 (55.7)	-16.4 (7.0)	-12.0 (-23.5, -0.5)	-6.1 (-22.2, 10.1)	0.461
Placebo	84	188.5 (53.2)	-14.3 (6.5)	-5.9 (-17.5, 5.6)		
Metformin: Patients on Metformin						
Sitagliptin	225	173.5 (49.8)	-22.4 (3.9)	-22.2 (-29.7, -14.7)	-18.3 (-28.1, -8.4)	<0.001
Placebo	229	175.6 (61.5)	-5.7 (4.8)	-3.9 (-11.4, 3.6)		
p-Value for Treatment by Subgroup Interaction =0.207						

† Based on ANCOVA model with terms for treatment, metformin stratum, pre-mixed insulin stratum, treatment by Metformin Stratum interaction, and baseline Fasting Plasma Glucose as a covariate

3.2.4. Meal Tolerance Test (MTT)

A significant decrease in glucose total AUC was observed in the sitagliptin group compared with the placebo group (nominal p=0.005) in a subset of patients participating in 10-point MTT. Within the

sitagliptin group, a significant decrease from baseline in glucose total AUC was observed, and a numerical increase was observed in the placebo group.

3.2.5. Indices of Beta cell Function and Insulin Sensitivity

The index of basal beta-cell sensitivity to glucose and the index of overall beta-cell sensitivity to glucose were significantly improved in the sitagliptin group compared to the placebo group (nominal $p<0.05$). There was an increase from baseline in glucose at Week 24 in the sitagliptin group, and the 95% CI for the LS mean percent change from baseline excluded "0"; there was a decrease from baseline at Week 24 in the placebo group, and the 95% CI for the LS mean percent change from baseline excluded "0". There were no significant between-group differences in the rest of the indices of beta-cell function or insulin sensitivity including dynamic beta-cell sensitivity to glucose, delay between static phase secretion and glucose concentration, composite index of insulin sensitivity, static phase disposition index, dynamic phase disposition index, overall phase disposition index or insulinogenic index.

3.2.6. Other Efficacy Endpoints

There was an increase of fasting C-peptide at Week 24 in the sitagliptin group and a decrease in the placebo group; the between-group difference was significant (nominal $p<0.001$).
Furthermore, there was an increase of 2-hour post-meal C-peptide at Week 24 with sitagliptin and a decrease with placebo. The between-group difference was significant (nominal $p<0.001$).
No significant changes in fasting insulin, proinsulin, or proinsulin/insulin ratio were observed in either treatment group.
No significant changes in HOMA-β, index of fasting insulin secretion, or HOMA-IR, an index of insulin resistance, were observed in either treatment group.

3.2.7. Glycaemic Rescue

Patients not meeting specific glycaemic goals after randomization were to have rescue therapy initiated. There was a small, but no statistically significant difference in need for rescue therapy in the sitagliptin group and placebo group. As expected more patients of the placebo group (20/319; 6.3%) versus the sitagliptin group (15/322; 4.7%) needed rescue therapy during the 24 week Study.

3.2.8. Lipid Panel

None of the analyses of lipid panel endpoints demonstrated significant between-group differences.

3.2.9. Insulin Dosage

Patients on premixed insulin had a higher mean total daily dose of insulin at baseline (67.4 Units/day in sitagliptin group and 74.5 Units/day in the placebo group) compared with patients on long- or intermediate-acting insulin (44.2 Units/day in the sitagliptin group and 44.5 Units/day in the placebo group).
No clinically meaningful changes in the mean total daily dose of insulin for either treatment group or by stratum were noted at the end of the study in either treatment group in the entire cohort or in the stratum of patients on metformin.

3.2.10. Metformin Dosage

The mean dose of metformin was 2010.0 mg per day in the sitagliptin group and 1969.5 mg in the placebo group. The mean dose of metformin, as well as the distribution of the doses, was consistent between the treatment groups.
The inclusion of ≥1500 mg/day is consistent with that in previous studies with sitagliptin and other HbA1c lowering drugs.

3.3. Clinical safety

3.3.1. Patient exposure

Of the 641 randomized patients, 564 completed 24 weeks of treatment. A similar proportion of patients discontinued from the study in each treatment group. Reasons for discontinuation were generally similar between treatment groups.

Through Week 24, the mean duration of exposure was generally similar between the 2 treatment groups, see Table 12.

Table 12: Patients exposure by Treatment Group

Patient Exposure by Treatment Group
(All Patients Randomized)

Treatment Assigned (Any Dose)[†]	Number of Patients							Duration Range	Mean Duration
	<2 weeks	≥ 2 weeks to <6 weeks	≥ 6 weeks to <12 weeks	≥ 12 weeks to <16 weeks	≥ 16 weeks to <22 weeks	≥ 22 weeks	Total Patients		
Sitagliptin	8	8	15	3	12	276	322	1 to 212 days	155.2 days
Placebo	4	4	11	7	15	278	319	1 to 218 days	159.5 days

[†] Although some patients may have taken two or more different dosages, they have been counted only once with total durations.

Data Source: [16.4.5.2]

There were 16 patients in the sitagliptin group and 8 patients in the placebo group who had less than 6 weeks of exposure to the study medication due to early discontinuations for number of reasons without a discernable pattern. The most common reasons for early discontinuations (i.e., within the first 6 weeks) for patients in the sitagliptin group were: deviation from protocol (4 patients), lost to follow-up (3 patients), and withdrawal of consent (3 patients). The most common reason for early discontinuations (i.e., within the first 6 weeks) for patients in the placebo group was withdrawal of consent (4 patients).

Table 13 shows the exposure of sitagliptin in the subgroup "patients on metformin". The mean duration of treatment was 161.2 days, this was comparable with the entire study population.

Table 13: Patients exposure to sitagliptin in the subgroup "patients on metformin"

Sitagliptin	<2 weeks	≥ 2 weeks to <6 weeks	≥ 6 weeks to <12 weeks	≥ 12 weeks to <16 weeks	≥ 16 weeks to <22 weeks	≥ 22 weeks	Total Patients	Duration Range	Mean Duration
Any Dose	3	3	8	1	5	209	229	1 to 212 days	161.2 days
Sitagliptin 100 mg	3	3	8	1	5	209	229	1 to 212 days	161.1 days
Sitagliptin 200 mg	6	0	0	0	0	0	6	1 to 2 days	1.3 days

Each patient is counted once on each applicable dosage category row.

3.3.2. Adverse events

Table 14 gives an overview of the analysis of adverse events during the study.

Table 14: Analysis of Adverse Events

Analysis of Adverse Events
Including Data After Initiation of Rescue Therapy or Other Sustained Greater than 10% Insulin Dose Increase
(All Patients as Treated)

Type of Adverse Event	Treatment Group	n/N (%)	Difference in % vs. Placebo (95% CI)
with one or more adverse events	Sitagliptin Placebo	168/322 (52.2) 137/319 (42.9)	9.2 (1.5, 16.8)
with drug-related adverse events	Sitagliptin Placebo	50/322 (15.5) 27/319 (8.5)	7.1 (2.0, 12.1)
with serious adverse events	Sitagliptin Placebo	20/322 (6.2) 11/319 (3.4)	2.8 (-0.6, 6.3)
with serious drug-related adverse events	Sitagliptin Placebo	3/322 (0.9) 0/319 (0.0)	0.9 (-0.4, 2.7)
discontinued due to an adverse event	Sitagliptin Placebo	11/322 (3.4) 4/319 (1.3)	2.2 (-0.3, 4.9)
discontinued due to a drug-related adverse event	Sitagliptin Placebo	3/322 (0.9) 0/319 (0.0)	0.9 (-0.4, 2.7)

Data Source: [16.4.3.1]

Adverse events by SOC were reported most frequently for Infections and Infestations, Metabolism and Nutrition Disorders, Musculoskeletal and Connective Tissue Disorders, Gastrointestinal Disorders, Nervous System Disorders, and Investigations, see Table 15.

Table 15: Analysis of specific adverse events

Analysis of Specific Adverse Events
(Incidence ≥2% in One or More Treatment Groups)
Including Data After Initiation of Rescue Therapy or Other Sustained
Greater than 10% Insulin Dose Increase
(All Patients as Treated)

Specific Adverse Event	Treatment Group	n/N (%)	Difference in % vs. Placebo (95% CI)
Cardiac disorders	Sitagliptin Placebo	7/322 (2.2) 10/319 (3.1)	-1.0 (-3.7, 1.7)
Eye disorders	Sitagliptin Placebo	5/322 (1.6) 9/319 (2.8)	-1.3 (-3.9, 1.2)
Gastrointestinal disorders	Sitagliptin Placebo	30/322 (9.3) 22/319 (6.9)	2.4 (-1.9, 6.8)
General disorders and administration site conditions	Sitagliptin Placebo	12/322 (3.7) 10/319 (3.1)	0.6 (-2.4, 3.6)
Infections and infestations	Sitagliptin Placebo	67/322 (20.8) 57/319 (17.9)	2.9 (-3.2, 9.0)
Influenza	Sitagliptin Placebo	13/322 (4.0) 12/319 (3.8)	0.3 (-2.9, 3.5)
Nasopharyngitis	Sitagliptin Placebo	10/322 (3.1) 8/319 (2.5)	0.6 (-2.2, 3.4)
Upper respiratory tract infection	Sitagliptin Placebo	10/322 (3.1) 11/319 (3.4)	-0.3 (-3.3, 2.6)
Urinary tract infection	Sitagliptin Placebo	9/322 (2.8) 6/319 (1.9)	0.9 (-1.6, 3.5)
Injury, poisoning and procedural complications	Sitagliptin Placebo	13/322 (4.0) 12/319 (3.8)	0.3 (-2.9, 3.5)
Investigations	Sitagliptin Placebo	20/322 (6.2) 8/319 (2.5)	3.7 (0.5, 7.1)
Metabolism and nutrition disorders	Sitagliptin Placebo	60/322 (18.6) 30/319 (9.4)	9.2 (3.9, 14.6)
Hypoglycaemia	Sitagliptin Placebo	50/322 (15.5) 25/319 (7.8)	7.7 (2.7, 12.7)
Musculoskeletal **and connective tissue disorders**	Sitagliptin Placebo	33/322 (10.2) 30/319 (9.4)	0.8 (-3.8, 5.5)
Nervous **system disorders**	Sitagliptin Placebo	22/322 (6.8) 16/319 (5.0)	1.8 (-1.9, 5.6)
Headache	Sitagliptin Placebo	9/322 (2.8) 3/319 (0.9)	1.9 (-0.4, 4.4)
Psychiatric **disorders**	Sitagliptin Placebo	10/322 (3.1) 3/319 (0.9)	2.2 (-0.1, 4.8)
Respiratory, **thoracic and mediastinal disorders**	Sitagliptin Placebo	13/322 (4.0) 5/319 (1.6)	2.5 (-0.2, 5.4)
Skin **and subcutaneous tissue disorders**	Sitagliptin Placebo	13/322 (4.0) 14/319 (4.4)	-0.4 (-3.6, 2.9)

Data Source: [16.4.3.1]

The incidence of adverse events grouped by SOC was generally comparable between two treatment groups. However, in Metabolism and Nutrition Disorders SOC and the Investigations SOC, the incidences of adverse events were significantly higher in the sitagliptin group compared with the placebo group (the 95% CIs for the between-group differences excluded "0"). In the Metabolism and Nutrition Disorders SOC, the higher incidence in the sitagliptin relative to the placebo group was related to a notably higher incidence of the adverse event of hypoglycemia.

Differences between treatment groups in the incidence of specific adverse events were generally small (i.e., <2%). With the exception of hypoglycemia, there was no specific adverse event that occurred at a higher rate in the sitagliptin group and for which the 95% CI excluded "0". The following specific adverse events occurred with absolute incidence of >1% and with a numerically higher incidence (difference of >3 patients) in the sitagliptin group relative to placebo group: hypoglycemia (see section 3.4.4 of this report), headache, constipation, creatinine clearance decreased and back pain.

All of the AEs of headache reported in the sitagliptin group were considered mild (8 of 9) to moderate (1 of 9) in intensity and none resulted in the interruption or discontinuation of study medication. Four out of these 9 events were considered related to study medication. The slightly higher incidence of headache in patients treated with sitagliptin is consistent with the results from other randomized controlled studies of sitagliptin.
All of the reported AEs of constipation in the sitagliptin group were mild in intensity and none resulted in discontinuation of the study drug. Two out of these 6 events were considered by the investigators to be drug-related.
All of the 5 AEs of decreased creatinine clearance in the sitagliptin group were considered mild (4) or moderate (1) in intensity. Two of the 5 events were considered to be drug-related. Three out of these 5 AEs led to discontinuation; all 3 of these patients met the protocol-specified criterion for discontinuation due to decreased creatinine clearance.
Five of the 6 adverse events of back pain reported in the sitagliptin group were considered mild, and 1 of the 6 was considered moderate in intensity, none were considered drug-related and none resulted in the interruption or discontinuation of study medication.

The observed AE profile is generally in line with what is known about sitagliptin from previous studies and is adequately addressed in the SPC. However the CHMP considered the finding of 5 AEs of decreased creatinine clearance in the sitagliptin group compared to none in the placebo group disturbing, although an association of decreased creatinine clearance with sitagliptin has not previously been observed. In response to CHMP's concern, the MAH has provided a comprehensive pooled analysis including data from 12 previous controlled clinical trials. The AE of "creatinine clearance estimation decreased" was reported for 31 of the 3243 patients (1.0%) in the sitagliptin group and 14 of the 2551 patients (0.5%) in the non-exposed group who had the test performed, the difference not being statistically significant. Three studies completed after the pooled analysis did not indicate an increased frequency of this AE in association with sitagliptin. Although the difference in the pooled analysis was not statistically significant and although the somewhat higher frequency of the AE "creatinine clearance estimation decreased" may have been due to chance, the CHMP is of the opinion that the possible association should be further monitored. Results from the sitagliptin study in patients with moderate renal insufficiency are expected in 2011 and may provide further insight into this issue. According to the RMP version 2 the MAH is conducting a second study in this regard (P073).

3.3.3. Serious adverse events and deaths

Deaths

Over the 24-week treatment period, no deaths were reported.

Serious Adverse Events

Over the 24-week treatment period, serious adverse events were reported for 20 patients (6.2%) in the sitagliptin group and 11 (3.4%) in the placebo group and the 95% CI for the between group difference included "0," see Table 14. Serious adverse events that occurred during the study were distributed among different body systems with no discernable pattern in both treatment groups.

Among the 20 patients in the sitagliptin group with serious adverse events, 3 patients (0.9%) in the sitagliptin group compared with none in the placebo group had serious adverse events that were considered by the investigator to be related to study therapy - two patients with drug-related adverse events of hypoglycaemia (see section 3.4.4 of this report), and one patient with drug-related adverse events of leukocytoclastic vasculitis, balanoposthitis, and genital abscess. Acute infectious balanoposthitis is known to occur more frequently in patients with diabetes. Leukocytoclastic vasculitis usually affects the skin and can be induced by many medications. However, the timely association of this event and the disappearance after discontinuation of sitagliptin makes a causal

relationship with sitagliptin likely. The MAH has included cutaneous vasculitis in the RMP version 2 and into section 4.8 of the SPC.
Two patients in the sitagliptin group versus non in the placebo group had SAEs of cancer. Due to the short treatment duration, the two cases of cancer are highly unlikely to be causally related to sitagliptin. However, there is concern about theoretical oncological risks of DPP-IV inhibitors.

3.3.4. Adverse Events Leading to Discontinuation
Discontinuations due to adverse events occurred in 11 (3.4%) patients in the sitagliptin group compared with 4 (1.3%) patients in the placebo group, see Table 14. Three patients (0.9%) in the sitagliptin group compared with none in the placebo group were discontinued due to an adverse event considered by the investigator to be related to study drug. In two cases, discontinuation was due to a serious drug-related adverse event. One patient quit the study due to a serious drug-related leukocytoclastic vasculitis; and one patient was discontinued due to a serious drug-related adverse event of hypoglycaemia. The third case was a non-serious drug-related adverse event of decreased creatinine clearance, having met protocol-specified discontinuation criteria.

3.3.5. Hypoglycaemia
In the study, a total of 75 patients had one or more episodes of hypoglycaemia. The incidence of patients with at least one hypoglycaemic episode was higher in the sitagliptin group than the placebo group. There were 50 (15.5%) patients in the sitagliptin group with at least one hypoglycaemic episode compared with 25 (7.8%) patients in the placebo group (p=0.003 for between-group difference). In the overall cohort, there were 155 episodes of hypoglycaemia reported for patients in the sitagliptin group and 76 episodes reported for patients in the placebo group. Most of the episodes were mild to moderate in intensity.

There were 2 episodes (in 2 patients) in the sitagliptin group and 1 episode in the placebo group that met the protocol-specified criteria of marked severity (defined as markedly depressed level of consciousness, loss of consciousness, or seizure) or required medical assistance. One patient in the sitagliptin group (and none in the placebo group) was discontinued due to the adverse event of severe hypoglycemia.
The mean number of episodes among patients with at least one episode of hypoglycemia was 3.1 (range 1 to 19) in the sitagliptin group and 3.0 (range 1 to 19) in the placebo group.

Hypoglycaemia was, as expected by the reduction in HbA1c, more common in the sitagliptin group. The number of all episodes of hypoglycaemia was statistically significant higher in the sitagliptin group (50/322; 15.5%) versus placebo (25/319, 7.8%) (p=0.003). There were only three patients who needed medical assistance for a hypoglycaemia during the 24 week study. Two of these patients were in the sitagliptin group. The numbers were too low to notice a difference between the groups.

Patients with and without hypoglycaemic events did not differ in a relevant manner in most baseline characteristics, in particular age or BMI, but did have more frequently better glycaemic control and a longer duration of diabetes (13.9 vs. 12.2 years) and insulin use (5.4 vs. 3.5 years). Tighter glycaemic control is known to be associated with an increased risk of hypoglycaemia. In addition, risk of hypoglycaemia is also known to increase with decreasing endogenous insulin reserve in patients with diabetes.
The incidence of hypoglycaemic events with sitagliptin in the stratum of patients on metformin was similar to that of the entire cohort.

3.3.6. Vital signs
No clinically meaningful differences between groups in mean changes from baseline in vital signs (pulse rate, temperature, respiration, blood pressure [diastolic, systolic, and mean arterial], waist circumference and body mass index [BMI]) were observed in the entire cohort.

3.3.7. Body Weight
There was no increase in Body Weight during the 24 week study in either the sitagliptin group (-0.1 kg) or the placebo group (-0.2 kg). The 95% CI for change in Body weight was small in both groups in the entire cohort.

3.3.8. Laboratory findings

Across the laboratory chemistry and haematology analytes, the frequency of results meeting PDLC criteria was generally similar between the sitagliptin and the placebo groups. However, for haemoglobin the incidence of last value decrease ≥1.5 gm/dL was higher in the sitagliptin group (6.0%) compared with the placebo group (2.1%) with a between-group difference of 4.0% around which the 95% confidence internal excluded "0," see Table 16. There were no adverse events of anaemia reported in the study, and the mean change from baseline in haemoglobin for sitagliptin compared with placebo was not clinically meaningful. Additionally, review of laboratory values, medical history, and concomitant conditions and medications for individual patients with laboratory values that met the PDLC criteria for haemoglobin decreased supported the conclusion that the low incidence of this generally small change in haemoglobin was unlikely to be clinically meaningful.

Table 16: Summary of Change from Baseline in Haemoglobin levels

Summary of Change from Baseline in Hemoglobin (gm/dL) by Time Point
Including Data After Initiation of Rescue Therapy
or Other Sustained Greater than 10% Insulin Dose Increase
(All Patients as Treated)

		Baseline	Time Point	Change from Baseline at Time Point		
Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Median	Range
Week 24						
Sitagliptin	270	13.9 (1.4)	13.7 (1.5)	-0.3 (0.0)	-0.2	-3.4 to 1.9
Placebo	278	14.0 (1.2)	13.9 (1.3)	-0.1 (0.0)	-0.1	-1.8 to 3.3

Data Source: [16.4.4.3]

No clinically meaningful changes in mean values for chemistry analytes were observed. Slight between-group differences in mean changes over time were observed for alkaline phosphatase and uric acid. As in other studies throughout the sitagliptin development program, a slight decrease from baseline in mean alkaline phosphatase level was observed in the sitagliptin group compared with the placebo group (maximum difference of 2.9 IU/L). This decrease was present at Week 6 and remained relatively stable through Week 24. The between-group differences in mean changes were small and unlikely to be clinically meaningful. No adverse event related to alkaline phosphatase was reported in either treatment group.

As in other studies throughout the sitagliptin development program, a slight increase from baseline in mean uric acid levels was observed in the sitagliptin group compared with the placebo group (maximum difference of 0.2 mg/dL). This increase was present at Week 6, peaked at Week 12 and decreased slightly through Week 24. The between group differences in mean changes were small and unlikely to be clinically meaningful.
Three adverse events of gout were reported for 1 patient in the sitagliptin treatment group and 2 patients in the placebo group; in addition, the adverse experience of gouty arthritis was reported for zero patients in the sitagliptin group and for one patient in the placebo group.

Seven patients in the sitagliptin group and 2 patients in the placebo group had laboratory values that met the pre-defined limits of change criterion for serum creatinine (last value >/= 0.3 mg/dL greater than baseline).

3.4 Risk Management Plan (RMP)

The MAH did submit an updated RMP (version 2) in May 2009, shortly after the submission of this type II variation. The RMP version 2 includes assessment of the data available from study P051. The assessment of the RMP version 2 has been completed in August 2009 and Annex II has been updated in this type II variation to reflect this version number. A further updated RMP version will be submitted by the MAH on the 1 of December 2009. As a consequence an updated RMP was not submitted as part of this type II variation to extend the indication.

3.5 Changes to the Product Information

The CHMP requested the MAH to restrict the indication to the situation when diet and exercise plus "*stable"* dosage of insulin (i.e. a stable insulin regimen for at least ten weeks) with or without metformin do not provide adequate glycaemic control.
The MAH proposed to change the indication in section 4.1 of the SPC as follows: *"Tesavel is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dosage of insulin do not provide adequate glycaemic control."* This was accepted by the CHMP.

In addition the CHMP requested the MAH to reflect in section 5.1 of the SPC the specific clinical situation described in study P051. The agreed wording in section 5.1 reads as follows: *"A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to insulin (at a stable dose for at least 10 weeks) with or without metformin (at least 1500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking non-pre-mixed (intermediate/long-acting) insulin, the mean daily dose was 44.3 U/day. The addition of sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group."*

As a result of the new indication and to reflect data from study P051 further changes were made to sections 4.1 (re-arrangement of text), 4.2, 4.4, 4.8, 5.1. The Package Leaflet has been updated accordingly.
Also minor corrections were made in sections 4.5 and 5.2 of the SPC.
In addition the MAH took the opportunity to update the version number of the RMP in annex II.

4. Overall conclusion and Benefit-Risk Assessment

In support of the extension of the indication, results of one clinical trial were submitted. Study P051 was a 24-week multicenter, double-blind, randomized, placebo-controlled parallel-group phase III study to compare the efficacy and safety of addition of sitagliptin 100 mg in T2DM patients who were already on stable insulin treatment, specified as either pre-mix or long-acting insulin with stable dosage for a minimum of 10 weeks prior randomization and with metformin (at least 1500 mg/day, in stable dosage) or without metformin therapy. Patients with HbA1c levels between 7.5% and 11.0% (inclusive) were included. The majority (75%) of the participating patients used open-label metformin (mean dose 2000 mg). The studied population is, based on the baseline characteristics, expected to be representative of patients with T2DM.
This trial was designed to evaluate the effect of sitagliptin addition on top of insulin treatment with or without metformin. Due to this design an active-comparator group in whom insulin dosage was increased was lacking, but patients were on a stable dose for at least 10 weeks and most for at least 6 months, suggesting that further increase of the insulin dose was not considered appropriate by the treating physician. This is in line with the current guideline on the evaluation of medicinal products in the treatment of diabetes mellitus It is also recognized that maximizing insulin therapy may not always be appropriate due to side effects and the complicated dosage regimen. Thus, CHMP considered it not necessary to require another study comparing the addition of sitagliptin with that of an increase in insulin dosage(s).

Benefits
In study P051, sitagliptin as add-on therapy in patients with inadequate control on stable dosage of insulin and with or without stable dosage of metformin provided a modest, but statistically significant improvement in glycaemic control compared with placebo. The HbA1c level decreased in the sitagliptin group [LS mean change in HbA1c (%) (95% CI)] -0.59 (-0.70,-0.48) versus -0.03 (-0.14, 0.08) in control group. The reduction observed with the addition of sitagliptin was statistically significantly greater than that observed with placebo ($p<0.001$). The size of effect in HbA1c reduction is in line with other trials with sitagliptin. The best results in HbA1c were seen after 12 weeks. The HbA1c level increased slightly after three months in the sitagliptin group. This phenomenon was seen in the placebo group as well. Analysis of secondary parameters confirmed these results. The efficacy was present both in patients with and without concomitant therapy with metformin. The data

did not indicate a lack of efficacy in the elderly, although only a very small number of patients was older than 75 years.

Risks

The safety profile observed in study P051 is generally in line with what is known about sitagliptin from previous studies. The observed ADRs are adequately addressed in the SPC. Hypoglycaemia was, as expected by the reduction in HbA1c, more common in the sitagliptin group. The number of all episodes of hypoglycaemia was statistically significant higher in the sitagliptin group (50/322; 15.5%) versus placebo (25/319, 7.8%) (p=0.003). There were only three patients (2 sitagliptin, 1 placebo) who needed medical assistance for a hypoglycaemia during the 24 week study. Most cases of hypoglycaemia were mild. Patients with hypoglycaemic events had more frequently better glycaemic control and a longer duration of diabetes (13.9 vs. 12.2 years) and insulin use (5.4 vs. 3.5 years), as is known to be associated with an increased risk of hypoglycaemia.

There were 5 cases of decreased creatinin clearance in the sitagliptin group. A comprehensive pooled analysis by the MAH of studies with sitagliptin did not indicate a statistically increased frequency of this AE in association with sitagliptin, but its incidence was slightly increased and the possible association should be further monitored. Results from the sitagliptin study in patients with moderate renal insufficiency are expected in 2011 and a second study is underway. The MAH should indicate in the next PSUR when the results of this study can be expected.

One case of leukocytoclastic vasculitis was reported, which appears likely related to sitagliptin. The MAH has already included cutaneous vasculitis in the RMP and into section 4.8 of the SPC through a recent type II variation.

Balance

The addition of sitagliptin to insulin (with or without metformin) resulted in a modest statistically significant improvement of glycaemic control with no unexpected adverse events.Therefore, the CHMP recommends to extend the indication for Tesavel as add-on to insulin (with or without metformin) when diet and exercise plus stable dosage of insulin do not provide adequate glycaemic control.