European Medicines Agency

London, 29 May 2009
Doc. Ref: EMEA/364144/2009

ASSESSMENT REPORT
FOR
XELEVIA

International Nonproprietary Name:
Sitagliptin

Procedure No. EMEA/H/C/762/II/0007

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu
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1. Introduction

Sitagliptin phosphate 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.

Sitagliptin was approved for marketing in the EU in 2007 and currently has therapeutic indications as a second line treatment for patients with type 2 diabetes mellitus (T2DM) to be used in combination with metformin, a PPAR-γ agonist, or a sulphonylurea (alone or in combination with metformin).

This variation was filed to extend the indication for patients with T2DM in whom the use of a PPARγ agonist (i.e. a thiazolidinedione) is appropriate, to be used in triple combination with the PPARγ agonist and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

In support of this extension of the indication, the Marketing Authorisation Holder (MAH) has presented the results of a 54-weeks efficacy and safety study (P052). This was a Phase III clinical study designed to assess the glycaemic efficacy and tolerability of sitagliptin added to the combination of metformin and rosiglitazone compared with placebo in patients with inadequate glycaemic control on dual combination therapy. 18-week results of this study were already presented in April 2008 as a Follow-up Measure.

Changes to sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the Summary of Product Characteristics (SPC) have been proposed to reflect the results of this study.

In addition, a minor revision to Section 5.1 of the SPC was proposed to include two sentences to describe the effects of sitagliptin and metformin on GLP-1 concentrations. These GLP-1 data have been reviewed by the CHMP in a previous submission. An update of section 4.9 (overdose) of the SPC was also proposed to include data from a Phase-I multiple dose study.

2. Non-Clinical aspects

Environmental risk assessment (ERA)

The ERA submitted for the active ingredient sitagliptin is an updated version of the ERA submitted by the MAH in the dossier for Xelevia (EMEA/H/C/0762).

In Phase I the MAH calculated a $PEC_{surface\ water}$ of 0.5 µg/L for sitagliptin under the assumption of a Fpen of 1%, which is above the trigger of 0.01 µg/L. As the $PEC_{surface\ water}$ is larger than 10 ng/l, the MAH has provided an environmental risk assessment according to Phase II of the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006).

Sitagliptin is not susceptible to photodegradation. The substance is hydrolytically stable. The MAH stated a K_{ow} of 0.6, and the respective study is missing. Provided that this K_{ow} is valid there is no indication of a bioaccumulation potential. The K_{oc} is less than 10,000 ($\log K_{oc}$ = 2.88). Therefore, an evaluation of the risk to the terrestrial compartment is not required.

Sitagliptin is not readily biodegradable. The MAH submitted the results of a test on the aerobic and anaerobic transformation in aquatic sediment systems according to OECD 308. In both aerobic and anaerobic conditions, there is a shifting of parent to sediment of >10% on day 14. Therefore, a prolonged sediment toxicity with Chironomus riparius has been performed. The results show that the PECsed/PNEC was below 1, thus, no risk for sediment dwelling organism is expected.

The MAH has submitted data on the ecotoxicity of sitagliptin. The comparison of the predicted concentration in surface water with the predicted no-effect concentration did not result in risk quotients above 1 (for algae, fish and water flea) or 0.1 (for micro-organisms). The $PEC_{ground\ water}$ to $PNEC_{daphnia}$ risk quotient is also below 1. The MAH did not provide data on the PECsediment but stated that the results suggested that the drug substance is not toxic to sediment organisms.

The results for toxicity to algae were obtained from a test performed in 2004 in accordance with the OECD guideline for the Algae Growth Inhibition Test (OECD 201, 1984 Version). The study was conducted in accordance and in full compliance with Good Laboratory Practices (GLP) regulations for tests of substances as promulgated by the OECD Guidelines for Testing of Chemicals (OECD, 1998). A new algae test has been completed in June 2009, according to the most recent version of OECD 201.

Environmental properties of sitagliptin phosphate are given in the table below.

Sitagliptin phosphate mono hydrate		CAS: 654671-77-9		
PBT assessment	P: Issue not resolved yet	B: no	T: no	
Physical-chemical properties				
	Log Kow	- 0.25	pH 7	Citation, study report is missing
	pKa	7.7		
	Water solubility	42.2 mg/ml	pH 7.1; 22 °C	
	Molecular mass	523.32 g/mol		
	Melting point	Decomposition at about 220 °C		
Environmental fate and behaviour				
Adsorption		Kd	Koc	
	HPLC method	-	759	
Degradation	Zahn-Wellens/EMPA Test	Not biodegradable		
	Hydrolysis	Dt_{50} = 895 d	pH 7, 25 °C, extrapolated	
	Photolysis	none	295 – 800 nm	
	Aerobic and anaerobic transformation in aquatic sediment systems	*Aerobic system*: dt50 = 6.5 d (water) dt50 = 138.6 d (whole system) Sediment extracts: 60.5-65.1% parent at d 103 Bound residues: 26.6-28.7% at d 103 Volatiles: 1.8% - 2.2% at d 103 *Anaerobic system:* dt50 = 20.9 d (water) dt50 = 266.5 d (whole system) Sediment extracts: 76.9-78.4% parent at d 103 Bound residues: 13.5-14.6% at d 103 Volatiles: <0.1% d 103		Citation, study report is missing

Ecotoxicological information		*Duration*	*Criterion*	Value [mg/l]
	Pseudokirchneriella subcapitata	72 h	NOEC	Test not valid, results not plausible
	Daphnia magna	21 d	NOEC	9.8
	Pimephales promelas	33 d	NOEC	9.2
	Chironomus riparius	28 d	NOEC	500 mg/kg; not validated yet. Citation, study report is missing
	Activated sludge respiration inhibition test	3 h	NOEC	≥ 150

The MAH has committed to perform and submit the results of an algae growth inhibition test (OECD 201) by July 2009.

3. Clinical aspects

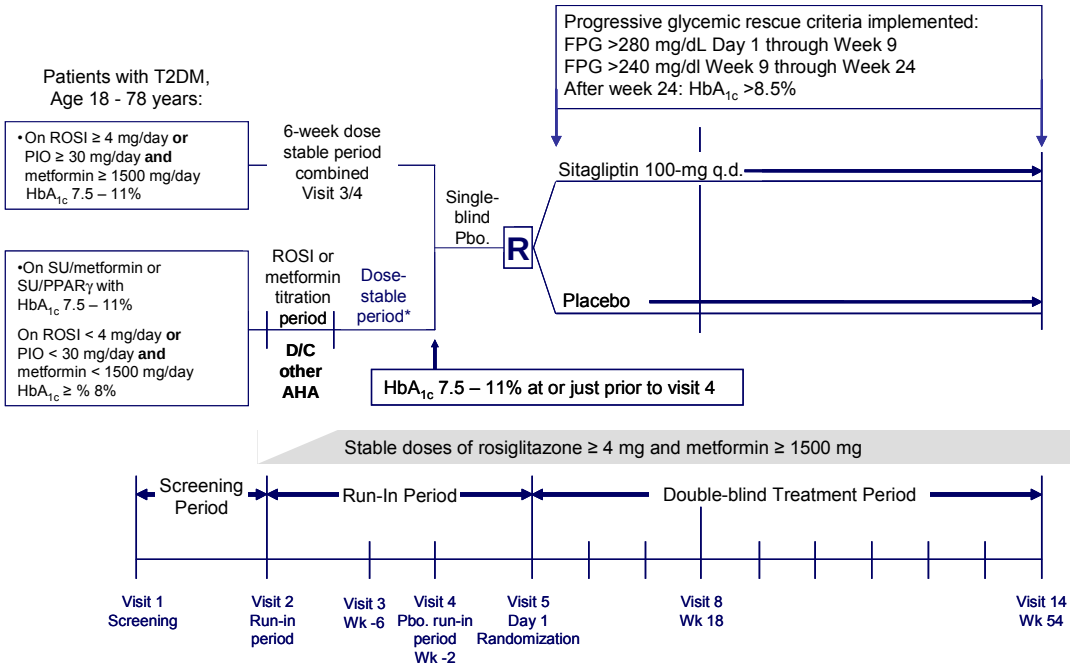
3.1 Clinical efficacy

A) Main study/Methods

Study P052 was a multicenter, multinational, double-blind, randomized, parallel-group, 54-week Phase III study to compare the efficacy and safety of sitagliptin 100 mg with placebo in patients with T2DM who had inadequate glycaemic control on combination therapy with metformin (at a dose of ≥1500 mg/day) and rosiglitazone (at a dose of ≥4 mg/day). Patients with T2DM on dual combination therapy with metformin and a PPARγ agonist, a PPARγ agonist and a sulfonylurea agent, or metformin and a sulfonylurea agent were eligible.

Male and female patients who were between 18 and 78 years old with inadequate glycaemic control (HbA1c ≥7.5% and ≤11%) when on dual combination therapy with metformin at a dose of ≥1500 mg/day and rosiglitazone at a dose of ≥4 mg/day (either at study entry or after a wash-off/dose-titration/dose-stable period -see study design below-) were randomized in a 2:1 ratio to either sitagliptin 100 mg or matching placebo. Patients were on a stable dose of metformin and rosiglitazone for at least 12 weeks prior to randomisation. Dosing regimen for open-label metformin and rosiglitazone was to remain stable for the duration of the study. Sites conducted a patient telephone contact midway between each clinic visit to reinforce diet/exercise and to review study therapy dosing instruction. Patients not meeting specific glycaemic goals were to receive rescue therapy with an open-label sulfonylurea (SU), primarily glipizide.

Figure 1: Design of study P052



* Visit 2 to Visit 4 dose-stable period of variable duration depending on if patient on PPARγ at Visit 1, and on Visit 1 HbA_{1c} (see Section E.2.).

AHA = antihyperglycemic agent; R=randomization; SU=sulfonylurea

The primary efficacy endpoint was the change from baseline in HbA1c; 2-hour post-meal glucose (PMG) after a standard meal challenge, and fasting plasma glucose (FPG) were key secondary endpoints. Other secondary endpoints/objectives included the proportion of patients meeting glycaemic goals and glucose, insulin, proinsulin, and C-peptide levels obtained during a 3-point meal tolerance test (MTT). This study has been completed and data from the 54 weeks (double blind) treatment period are reviewed.

The medical risk of inadequate glycaemic control was considered and efforts to limit this risk were implemented in this protocol. To ensure that patients were not exposed to poorer control for an undue period of time, strict glycaemic rescue and discontinuation criteria were included in the study design.

The population studied in P052 was the one using sitagliptin as add-on therapy to dual combination therapy with metformin and a PPARγ agonist (rosiglitazone) in the clinical setting. The entry criteria, as well as a worldwide enrolment of the study, supported the inclusion of a broad range of adult patients with T2DM, with a variety of racial backgrounds and across the usual age range of patients with this disease.

While patients with unstable medical conditions, such as active liver disease, and patients with medical conditions that limited the use of metformin (e.g., moderate to severe renal insufficiency) or rosiglitazone (e.g., NYHA Class II-IV heart failure) were excluded from participation, patients with a wide range of concurrent medical conditions and concomitant medications were included. The study allowed for the inclusion of older patients (≥65 years) with T2DM, while patients <18 years were excluded.

Patients could be switched and titrated from their own therapy to metformin and PPARγ agonist. For metformin, the washout/titration period of 12 weeks would be long enough to measure the therapeutic effect. However, the CHMP questioned whether the maximum therapeutic effect would be achieved in this titration period for the PPARγ agonist and considered that more time might be needed to measure the maximum therapeutic effect of the PPARγ agonist.

Furthermore, a higher proportion of patients in the placebo group had been on combination therapy with a PPARγ agonist and metformin (60.9%), relative to the sitagliptin group (48.8%), while in the sitagliptin group a higher proportion of patients had been on combination therapy with a sulfonylurea and metformin (48.2%), relative to the placebo group (37%). If the therapeutic effect of the PPARγ agonist lasts longer than the 12 week period, then this will favour the results in the Sitagliptin group. The CHMP requested during its January 2009 plenary meeting that the MAH should demonstrate that the maximum time period of the achieved therapeutic effect of a PPARγ agonist is 12 weeks.

In response to the CHMP concerns, the MAH showed data of the placebo group in which patients who were on a PPARγ agonist at screening had a slightly greater HbA1c response at Week 18. The change in baseline after Week 54 was also comparable between the patients who were on PPARγ agonist treatment and the patients who were not on PPARγ agonist therapy at screening. Furthermore, there was a non-significant (p=0.251) covariate effect of diabetes pharmacotherapy at screening on the HbA1c change from baseline. This data suggests that the HbA1c decrease in the sitagliptin group in the P052 Study is not caused by the higher proportion of patients in the sitagliptin group who were not on a PPARγ agonist at screening. The small change in HbA1c from baseline is more likely to be a direct effect of sitagliptin.

GCP

The clinical trial was performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that the clinical trial, which included sites outside the community, was carried out in accordance with the ethical standards of Directive 2001/20/EC.

B) Results

B.1. Patient disposition, baseline data and demographics

A total of 742 patients were screened, from which 464 were screen failures. The most common reason for not being randomised was failure to meet HbA1c inclusion criteria (46.8% of patients not randomized). The next most common reason for patients not being randomized was because of laboratory values (other than HbA1c) meeting protocol exclusion criteria (17.7% of patients not randomized). These included the following parameters: creatinine ≥ 1.4 mg/dL (123.8 μmol/L) for males or ≥ 1.3 mg/dL (114.9 μmol/L) for females, an elevated ALT or AST >2-fold the upper limit of normal (ULN), TSH <0.3 mIU/L or >5 mIU/L, or triglycerides >600 mg/dL (6.78 mmol/L).

Two hundred seventy eight (278) patients with T2DM with inadequate glycaemic control on a PPARγ agonist (rosiglitazone) in combination with metformin were randomized in the study at 41 sites worldwide. One study site was identified as non-compliant with some of the requirements of Good Clinical Practice (GCP). For this reason, the patient data from the 16 patients randomized at that site were deemed unreliable and were removed from all analyses (efficacy and safety). This concerns 11 patients in the sitagliptin group and 5 patients in the placebo group. Therefore, the analyses were performed on a total of 262 randomised patients.

A high number of patients were screened. However, many patients were excluded, mainly because they were ineligible. Therefore, the resulted population is a highly selected patient group on dual therapy.

Table 1: Patient Accounting in the Analysis of HbA1c at Week 18

	Number (%†)		
	Sitagliptin 100 mg	Placebo	Total
Total Patients Randomized	170	92	262
Included in FAS Analysis	168 (98.8)	88 (95.7)	256 (97.7)
Included in Week 18 Completers	155 (91.2)	79 (85.9)	234 (89.3)
Excluded from FAS Analysis	2 (1.2)	4 (4.3)	6 (2.3)
No Baseline Data	1 (0.6)	0 (0.0)	1 (0.4)
No On-treatment Data	1 (0.6)	4 (4.3)	5 (1.9)
FAS Patients Excluded from Week 18 Completers Analysis	13 (7.6)	9 (9.8)	22 (8.4)
Rescued Prior to Week 18	5 (2.9)	2 (2.2)	7 (2.7)
No Treatment Data at Week 18	8 (4.7)	7 (7.6)	15 (5.7)

†Percentages calculated as 100*(Number/Total patients randomized).
FAS = Full Analysis Set.

Data Source: [16.4.2.4; 16.4.2.11]

A total of 219 (83.6%) patients completed the study. A higher percentage of patients completed the study in the sitagliptin group compared to the placebo group. Reasons for discontinuation were generally similar between treatment groups with a higher percentage of patients in the placebo treatment group discontinuing due to lack of efficacy. During the conduct of this study, a report was published suggesting an association of rosiglitazone with an increased risk of cardiovascular events; subsequently, seven patients (3 patients in the sitagliptin treatment group (1.7%) and 4 patients in the placebo treatment group (4.3%) discontinued due to concerns over the use of rosiglitazone).

Demographic and anthropometric traits were generally similar across treatment groups. In addition, baseline disease characteristics, including duration of disease, and baseline HbA1c and FPG were also similar across treatment groups.

The mean age of the randomized population was 54.5 years, 57.6% were males, mean duration of diabetes was 9.3 years, and the mean baseline HbA1c was 8.8%. There were more Asian (34.1%) in the sitaglipitin group then in the placebo group (26.1%) and more Hispanic in the placebo (10.9%) than in the sitaglipitin group (7.6%).

At study entry, all patients were on dual combination therapy with: a PPARγ agonist and metformin, a sulfonylurea and metformin, or a PPARγ agonist and a sulphonylurea, as required by the protocol.

Of the randomized patients 23.4% had baseline HbA1c values <8.0% and 43.3% had baseline HbA1c values ≥9.0%.

Two hundred and fifty-nine (98.9%) of the 262 randomized patients had at least 1 secondary diagnosis other than T2DM. Metabolism and nutrition disorders, vascular disorders, musculoskeletal and connective tissue disorders and nervous system disorders were the most common categories by SOC of secondary diagnoses.

The most common specific secondary diagnoses were hypertension (sitagliptin 63.5% vs 59.8% in placebo group), hypercholesterolaemia (sitagliptin 24.1% vs 19.6% in placebo group), hyperlipidaemia (sitagliptin 22.9% vs 27.2% in placebo group), dyslipidaemia (sitagliptin 24.1% vs 19.6% in placebo group and obesity (sitagliptin 19.4% vs 18.5% in placebo group). There were no clinically important differences among treatment groups in the frequency or type of secondary diagnoses.

All of the 262 randomized patients had prior therapies (i.e., took at least 1 medication from 30 days prior to the screening visit [Visit 1] up until the day before randomization). The most common prior drug therapeutic categories in the sitagliptin and placebo treatment groups were drugs used for

diabetes, agents acting on the renin-angiotensin system, serum lipid-reducing agents and analgesics. There were no clinically important differences between treatment groups.

Two hundred and fifteen (82.1%) patients took concomitant therapies (i.e., took at least 1 medication post-randomization). The most common concomitant drug therapeutic categories were for anti-bacterials for systemic use, analgesics, and anti-inflammatory and anti-rheumatic products. There were no meaningful differences between treatment groups in the use of concomitant medications post-randomization.

B.2. HbA1c reduction (primary endpoint)

- **Primary Endpoint HbA1c at Week 18**

Table 2 displays Week 18 HbA1c results for the Full Analysis Set (FAS) population. The reduction observed with sitagliptin was statistically significantly greater than that observed with placebo. The analysis of HbA1c conducted in the completers population at Week 18 supported the conclusion for the primary analysis.

Table 2: Analysis of Change from Baseline in HbA1c (%) at Week 18 (Full Analysis Set)

		Mean (SD)		Change from Baseline			
Treatment Group	N	Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	168	8.81 (0.99)	7.78 (1.11)	-1.04 (0.07)	-1.03 (0.07)	(-1.17, -0.90)	<0.001
Placebo	88	8.73 (1.00)	8.45 (1.26)	-0.29 (0.10)	-0.31 (0.09)	(-0.50, -0.13)	0.001

Between Treatment Group Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	-0.72 (-0.95, -0.49)	<0.001

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment	<0.001
Diabetes Pharmacotherapy at Screening (Visit 1)	0.251

Root Mean Square Error of Change =0.87

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

Data Source: [16.4.2.4]

- **Secondary Analysis Endpoint: HbA1c at Week 54**

Consistent with the analysis at Week 18, a significantly greater reduction from baseline in HbA1c was observed at Week 54 with sitagliptin relative to that observed with placebo (nominal p<0.001, Table 3).

Table 3: Analysis of Change from Baseline in HbA1c (%) at Week 54 (Full Analysis Set)

		Mean (SD)		Change from Baseline			
Treatment Group	N	Baseline	Week 54	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	168	8.81 (0.99)	7.76 (1.17)	-1.06 (0.09)	-1.05 (0.08)	(-1.21, -0.89)	<0.001
Placebo	88	8.73 (1.00)	8.48 (1.30)	-0.25 (0.11)	-0.28 (0.11)	(-0.50, -0.05)	0.015

Between Treatment Group Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	-0.77 (-1.04, -0.50)	<0.001

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment	<0.001
Diabetes Pharmacotherapy at Screening (Visit 1)	0.630

Root Mean Square Error of Change =1.04

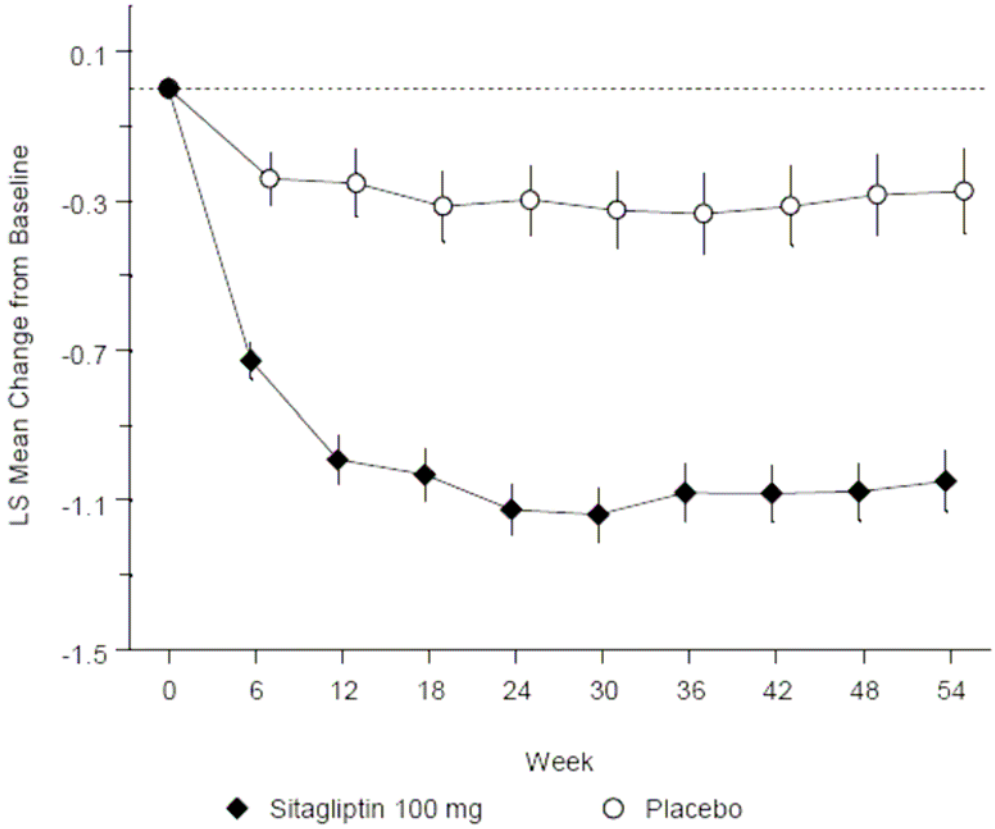
CI = Confidence Interval; LS = Least Squares; SD = Standard Deviation; SE = Standard Error.

Data Source: [16.4.2.4]

The analysis of HbA1c conducted in the completers population at Week 54 showed a greater reduction from baseline as compared with the analysis of the FAS population within both the sitagliptin and placebo groups. The between group difference in the least squares (LS) mean change from baseline was smaller in the completers population than in the FAS population and was no longer statistically significant. It is noted, however, that the completers population was defined by post-randomization events: many more placebo patients than sitagliptin patients underwent glycaemic rescue or discontinued, and as a result, the baseline HbA1c level of the placebo group was lower than the one of the sitagliptin group.

The profile of LS mean changes from baseline in HbA1c over time (Figure 2) shows a progressive reduction that reached a plateau at Week 24 in the sitagliptin group and remained stable through Week 54. In the placebo group, there was a reduction at Week 6 in LS mean change from baseline, which remained stable through Week 54.

Figure 2: LS Mean Change from Baseline in HbA1c (%) Over Time (LS Mean ± SE) by Treatment Group (Full Analysis Set)



The CHMP concurred that there is a significant HbA1c reduction in the sitagliptin group compared to placebo at week 18 and week 54 in the FAS analysis set and in the completers analysis.

- **HbA1c Goal < 7%**

The results of analysis of proportions of patients with Week 18 HbA1c values below 7.0% are shown in Table 4 in the FAS population. The odds of achieving a Week 18 HbA1c level <7.0% were statistically significantly higher in the sitagliptin group than in the placebo group (nominal p=0.003). The results of the analyses of HbA1c goal attainment of <7.0% at Week 54 (Table 5) or at both Week 18 and Week 54 (Table 6) are consistent with the results observed at Week 18. The same conclusions can be drawn for the results of analyses for the completers population.

Table 4: Proportion of Patients with HbA1c Value < 7.0% and < 6.5% at Week 18 (Full Analysis Set)

HbA1c <7%			
Treatment	N	n (%)	
Sitagliptin 100 mg	168	37 (22.0)	
Placebo	88	8 (9.1)	
Between Treatment Comparison	Difference in Proportion (%) (95% CI†)	Odds-Ratio‡ (95% CI)	p-Value‡
Sitagliptin 100 mg vs. Placebo	12.9 (3.3, 21.1)	3.85 (1.58, 9.37)	0.003
HbA1c < 6.5%			
Sitagliptin 100 mg	168	12 (7.1)	
Placebo	88	4 (4.5)	
Between Treatment Comparison	Difference in Proportion (%) (95% CI†)	Odds-Ratio‡ (95% CI)	p-Value‡
Sitagliptin 100 mg vs. Placebo	2.6 (-4.6, 8.2)	1.86 (0.56, 6.17)	0.309

† Confidence Interval computed using the Wilson score method

‡ From the logistic regression model, adjusting for baseline HbA1c and prior anti-hyperglycaemic medication status

CI = Confidence Interval.

Table 5: Proportion of Patients with HbA1c Value < 7.0% at Week 54 (Full Analysis Set and Completers)

Full Analysis Set: HbA1c < 7%		
Treatment	N	n (%)
Sitagliptin 100 mg	168	44 (26.2)
Placebo	88	12 (13.6)
Completers: HbA1c < 7%		
Treatment	N	n (%)
Sitagliptin 100 mg	114	37 (32.5)
Placebo	40	11 (27.5)

Table 6: Proportion of Patients with HbA1c Value < 7.0% at Week 18 and Week 54 (Full Analysis Set)

Treatment	N	n (%)
Sitagliptin 100 mg	168	25 (14.9)
Placebo	88	5 (5.7)

The baseline HbA1c value was a significant covariate ($p<0.001$) because patients with higher baseline values tended to have greater reduction in HbA1c from baseline. However, there were no apparent differences in the between treatment effects across the different baseline HbA1c levels.

The results of analysis of proportions of patients with HbA1c values below 7.0% at week 18, at week 54 and week 18 and 54 show a lot of variation. Only 14.9% of the patients in the sitagliptin group showed a HbA1c < 7% at both visits. The CHMP, during its January 2009 meeting requested that the MAH should explain these results. The CHMP also requested that the MAH should demonstrate the complete statistical values like it was done for the 18 weeks at week 54 and week 18 and week 54.

In its responses to the CHMP request, the MAH argued that the percentages of patients at the HbA1c goal of <7.0% was statistically significant higher in the sitagliptin group compared with the placebo group at Week 18 and at Week 54. Similarly, the difference between groups in the percentage of patients meeting this goal at both Week 18 and Week 54 was also statistically significant in favour of sitagliptin. Although some patients on sitagliptin who met the HbA1c <7.0% goal at Week 18 did not meet this goal at Week 54 (n=12; 7.1%), a larger number of patients (n=19; 11.3%) who did not meet the goal at Week 18 did meet the goal at Week 54.

The MAH further justified that there is a relation (correlation coefficient = 0.70, p<0.001) between results at Week 18 and Week 54. This is consistent with the maximum effect occurring at or near the Week 18 time point.

On the view of the results the CHMP was of the opinion that the effect of sitagliptin on HbA1c level goal <7.0% is modest; although differences are statistically significant, confidence intervals are very wide. Nevertheless, the CHMP agreed that there might be patients who can benefit from addition of sitagliptin to metformin and pioglitazone.

A relatively high proportion of patients had high baseline HbA1c values in this population. The results of the summary statistics for HbA1c change by HbA1c at baseline at week 18 are shown in Table 7.

Table 7:

Summary Statistics for HbA1c Change from Baseline (%) at Week 18
By HbA1c at Baseline
(Full Analysis Set)

		Baseline	On Treatment	Change from Baseline		
Treatment Group	N	Mean (SD)	Mean (SD)	Mean (SE)	Median	Range
Baseline HbA_{1c} < 8.0%						
Sitagliptin 100 mg	34	7.56 (0.30)	6.81 (0.67)	-0.75 (0.11)	-0.75	-2.00 to 1.10
Placebo	25	7.55 (0.29)	7.50 (0.60)	-0.05 (0.11)	-0.10	-1.20 to 1.40
8.0% ≤ Baseline HbA_{1c} < 9.0%						
Sitagliptin 100 mg	61	8.39 (0.31)	7.52 (0.76)	-0.86 (0.09)	-0.90	-2.00 to 2.30
Placebo	25	8.45 (0.26)	8.25 (0.96)	-0.20 (0.18)	-0.30	-2.10 to 2.40
9.0% ≤ Baseline HbA_{1c} < 10.0%						
Sitagliptin 100 mg	48	9.40 (0.30)	8.08 (0.72)	-1.31 (0.10)	-1.40	-2.90 to 0.60
Placebo	29	9.44 (0.25)	8.84 (1.22)	-0.60 (0.25)	-0.50	-3.90 to 1.40
Baseline HbA_{1c} ≥ 10.0%						
Sitagliptin 100 mg	25	10.44 (0.35)	9.11 (1.38)	-1.32 (0.28)	-1.30	-4.30 to 1.90
Placebo	9	10.53 (0.30)	10.37 (0.75)	-0.17 (0.21)	-0.20	-1.10 to 0.80
SD=Standard Deviation; SE=Standard Error.						

The Week 54 data were additionally submitted by the MAH. The HbA1c level decrease was greater with higher baseline HbA1c levels. These results were in line with the Week 18 data.

B.3. Secondary Endpoints

- **Two-Hour Post-Meal Glucose (2-hour PMG) at week 18**

Table 8 displays 2-hour PMG results for the FAS population at Week 18. Decreases in 2-hour PMG relative to baseline were observed in both groups, with a statistically significantly greater decrease in the sitagliptin group than in the placebo group.

The analysis of 2-hour PMG conducted in the completers population at week 18 supported the conclusion for the primary analysis.

- **Two-Hour PMG at Week 54**

A significantly greater reduction in 2-hour PMG was observed with sitagliptin at Week 54 than that observed with placebo (see Table 9).

Table 8: Analysis of Change from Baseline in 2-Hour Post-Meal Glucose (mg/dL) at Week 18 (Full Analysis Set)

		Mean (SD)		Change from Baseline			
Treatment Group	N	Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	142	257.8 (63.1)	196.9 (54.6)	-60.9 (4.7)	-59.9 (3.7)	(-67.1, -52.6)	<0.001
Placebo	75	249.5 (57.5)	231.9 (47.8)	-17.6 (6.0)	-22.0 (5.1)	(-32.1, -12.0)	<0.001

Between Treatment Group Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	-37.9 (-50.2, -25.5)	<0.001

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment	<0.001
Diabetes Pharmacotherapy at Screening (Visit 1)	0.042

Root Mean Square Error of Change =43.7
CI = Confidence Interval; LS = Least Squares; SD = Standard Deviation; SE = Standard Error.

Table 9: Analysis of Change from Baseline in 2-Hour Post-Meal Glucose (mg/dL) at Week 54 (Full Analysis Set)

		Mean (SD)		Change from Baseline			
Treatment Group	N	Baseline	Week 54	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	147	256.6 (64.3)	204.5 (57.1)	-52.1 (5.0)	-50.7 (4.2)	(-59.1, -42.4)	<0.001
Placebo	77	247.7 (58.1)	235.8 (56.7)	-11.9 (7.6)	-16.6 (5.9)	(-28.2, -5.0)	0.005

Between Treatment Group Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	-34.1 (-48.4, -19.9)	<0.001

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment	<0.001
Diabetes Pharmacotherapy at Screening (Visit 1)	0.172

Root Mean Square Error of Change =51.0
CI = Confidence Interval; LS = Least Squares; SD = Standard Deviation; SE = Standard Error.

The analysis of 2-hour PMG conducted in the completers population at Week 54 showed greater within group decreases from baseline in both treatment groups and smaller between group difference in LS mean reduction from baseline compared to the analysis of the FAS population due to the same reason as the endpoint of HbA1c.

- **Fast Plasma Glucose (FPG) at Week 18**

Table 10 displays Week 18 FPG results for the FAS population. A statistically significantly greater decrease in mean change from baseline in FPG was observed in the sitagliptin group relative to the placebo group.

The analysis of FPG conducted in the completers population at Week 18 supported the conclusion from the FAS analysis.

Table 10: Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dl) at Week 18 (Full Analysis Set)

Treatment Group	N	Mean (SD)		Change from Baseline			
		Baseline	Week 18	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	169	182.1 (38.8)	151.8 (36.0)	-30.3 (2.9)	-30.7 (2.4)	(-35.5, -26.0)	<0.001
Placebo	89	183.5 (42.6)	172.7 (41.9)	-10.7 (3.6)	-11.7 (3.4)	(-18.3, -5.1)	<0.001

Between Treatment Group Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	-19.0 (-27.2, -10.9)	<0.001

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment	<0.001
Diabetes Pharmacotherapy at Screening (Visit 1)	0.016

Root Mean Square Error of Change =31.3

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

Data Source: [16.4.2.4]

- **FPG at Week 54**

Similarly, a significantly greater reduction in FPG was observed with sitagliptin at Week 54 relative to that observed with placebo for the FAS population (nominal p<0.001, Table 11). The repeated measures analysis used as a secondary approach to handling missing data supported the conclusion for the primary analysis.

Table 11: Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dl) at Week 54 (Full Analysis Set).

Treatment Group	N	Mean (SD)		Change from Baseline			
		Baseline	Week 54	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	169	182.1 (38.8)	154.5 (38.1)	-27.6 (3.0)	-28.0 (2.7)	(-33.3, -22.8)	<0.001
Placebo	89	183.5 (42.6)	174.0 (46.5)	-9.5 (4.2)	-10.7 (3.7)	(-18.0, -3.3)	0.004

Between Treatment Group Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	-17.4 (-26.4, -8.4)	<0.001

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment	<0.001
Diabetes Pharmacotherapy at Screening (Visit 1)	0.013

Root Mean Square Error of Change =34.6

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

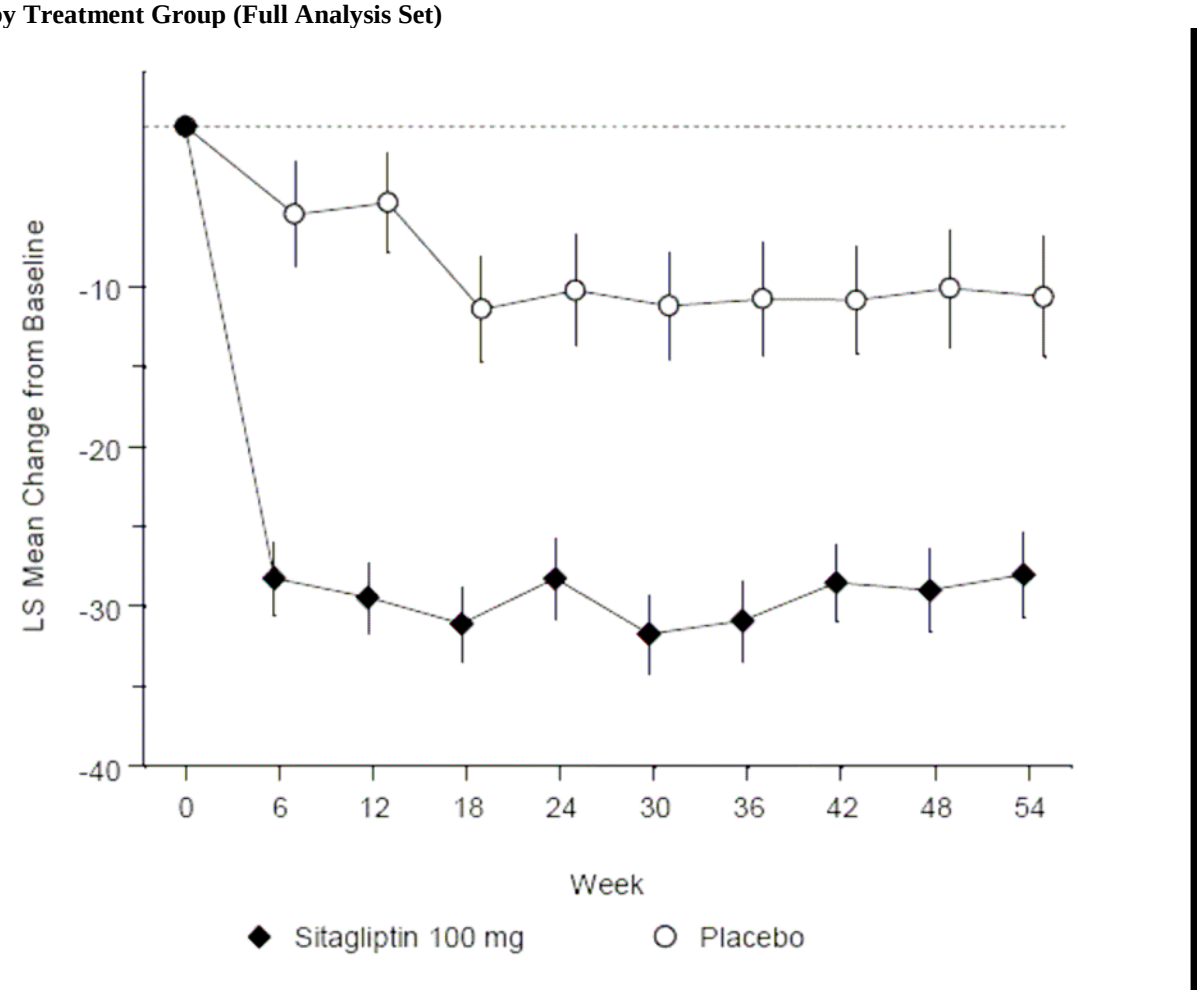
The analysis of FPG conducted in the completers population at Week 54 shows greater decreases from baseline within both the sitagliptin and placebo groups and smaller between group difference on the reduction from baseline as compared to the analysis of the FAS population due to the same reason as the endpoint of HbA1c.

- **Durability of FPG Effect**

The profiles of mean change from baseline in FPG over time (Figure 3) showed reduction in mean FPG in the sitagliptin group at Week 6, with a reduction through Week 54. There was a reduction in the placebo group and the FPG level was stabilized from Week 18 through Week 54.

The coefficient of durability (COD), defined here as the slope of the time profile of mean change from baseline in the outcome variable (FPG), was derived using the LS Means produced by the ANCOVA models. The estimation of COD provides a quantitative assessment for the rate of deterioration of a treatment after reaching its peak efficacy. A treatment with larger COD tends to be less to Week 54 and its 95% CI were provided. Standard errors for the COD were computed by bootstrapping subjects within treatment groups. There was no statistically significant between-group difference in the COD (nominal p=0.612).

Figure 3: LS Mean Change from Baseline in Fasting Plasma Glucose (mg/dL) Over Time (LS Mean ± SE) by Treatment Group (Full Analysis Set)



There is a statistically significantly greater decrease in 2-hour PMG relative to baseline in the sitagliptin group than in the placebo group at 18 weeks and at 54 weeks in the FAS analysis and in the completers analysis. The reduction in FPG is smaller but also significant.

B.4. Tertiary endpoints

Other parameters such as Measures of Beta-Cell Function and Insulin Secretion (like Proinsulin/Insulin Ratio, HOMA B, 2-hour post-meal C-peptide, 2-hour proinsulin to insulin ratio, 2-hour post-meal insulin, 2-hour post-meal proinsulin, insulinogenic index and AUC endpoints) are supportive to the primary endpoints results

B.5. Time to Rescue

The medical risk of inadequate glycaemic control was considered and efforts to limit this risk were implemented in the study protocol. To ensure that patients were not exposed to poorer control for an undue period of time, strict glycaemic rescue and discontinuation criteria were included in the study design. Because of the length of the placebo-controlled double-blind treatment period, progressively stricter glycaemic rescue/discontinuation criteria were implemented, so that patients with poorer

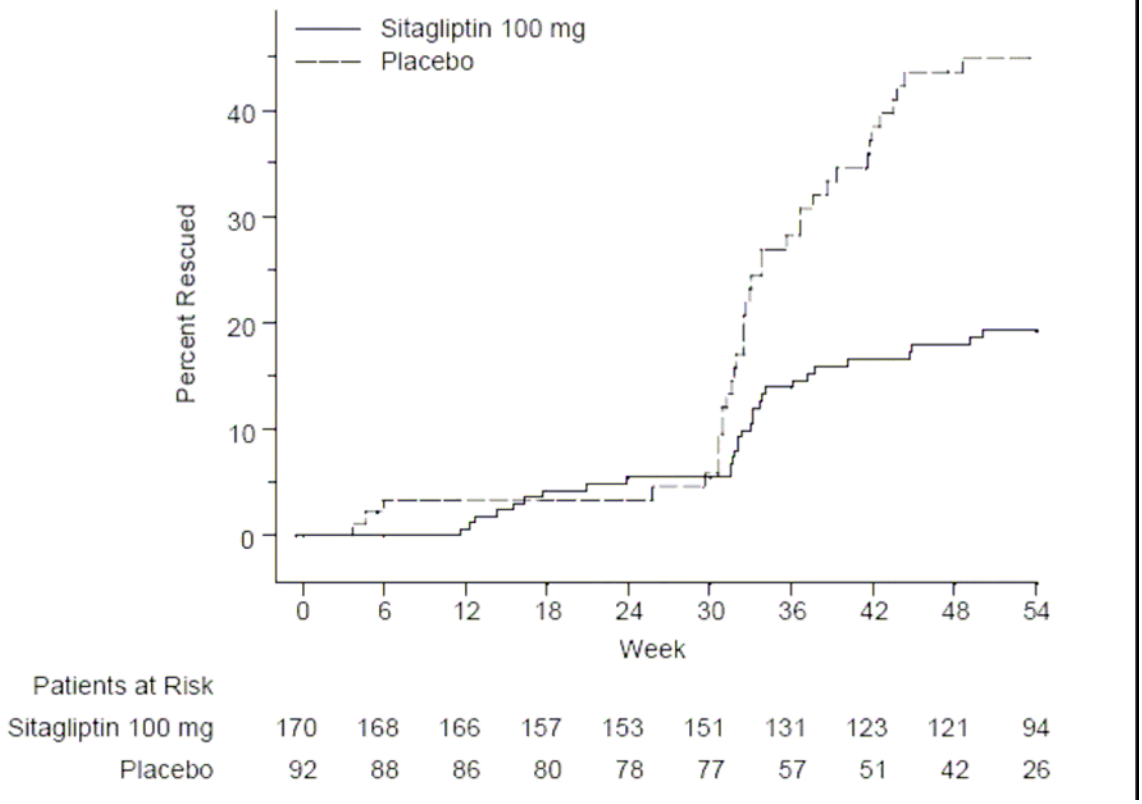
glycaemic control were rescued early in the double-blind treatment period. Indeed, rescue could have been initiated immediately after the patient entered the double-blind period if the patient's FPG reflected deterioration of control. In addition, all patients received initial and continued counselling for diet and exercise, which may lead to improvements in glycaemic control.

The study design included rescue therapy with a sulfonylurea (generally glipizide) in patients with poor glycaemic control. Rescue therapy was provided to allow patients to benefit from continued participation in the study and to support the collection of a larger database of safety and tolerability information while avoiding prolonged exposure to poor glycaemic control. Patients who were rescued were included in the glycaemic/lipid analysis and primary safety analysis up until the initiation of rescue therapy. A secondary analysis of safety included data regardless of the initiation of rescue therapy.

Figure 4 presents results for the analysis of time to receiving glycaemic rescue medication. A significantly smaller proportion of patients in the sitagliptin treatment group initiated rescue therapy by Week 54 compared to patients in the placebo treatment group. The numbers of patients at risk (i.e., patients who were not rescued) at each specified calendar week are also provided in Figure 4.

The progressive increase in the proportion of patients rescued in both treatment groups after Week 30 was due to the implementation of progressively stricter rescue criteria. Specifically, the rescue criterion from baseline through Week 9 was an FPG value >280 mg/dL; the rescue criterion after Week 9 through Week 24 was an FPG value >240 mg/dL; the rescue criterion after Week 24 was an HbA1c value >8.5%.

Figure 4: Patients receiving rescue medication



Patients at Risk										
Sitagliptin 100 mg	170	168	166	157	153	151	131	123	121	94
Placebo	92	88	86	80	78	77	57	51	42	26

3.2 Clinical safety

A) Clinical adverse experiences

Over the 54-week treatment period, slightly higher incidences of overall adverse experiences were observed in the sitagliptin group compared to the placebo group (75.3% and 70.7% respectively). These were not indicative of isolated increases but rather reflective of a number of slightly higher incidences of specific AEs across a number of body systems. In addition, slightly higher incidences of serious adverse experiences were observed in the sitagliptin group compared to the placebo group (8.2% and 3.3% respectively), but no serious adverse experience was reported in more than 2 patients in a treatment group and none was considered by the investigator to be related to study drug.

Slightly higher incidences of drug-related adverse experiences were also observed in the sitagliptin group (15.3% and 10.9% respectively) compared to the placebo group. For all summary measures, the 95% confidence interval (CI) around the between-group difference included "0". The number of patients discontinued due to adverse experiences was low and similar in both treatment groups, and no patients were discontinued in either treatment group due to a drug-related adverse experience. No deaths were reported in this study.

The results of the clinical adverse experience profile and summary analyses for the secondary safety analysis (all data included) are not meaningfully different from those in the primary safety analysis (excluding data after initiation of glycaemic rescue therapy).

Adverse experiences by System Organ Class (SOC) were reported most frequently for Infections and Infestations, Gastrointestinal Disorders, and Musculoskeletal and Connective Tissue Disorders. The incidences of adverse experiences grouped by SOC were generally comparable between the two treatment groups. Over 54 weeks, a higher incidence of adverse experiences was reported for patients in the sitagliptin group (9 (5.3%) patients) compared with the placebo group (1 (1.1%) patient) in the Cardiac Disorders SOC. Other SOCs for which a numerically higher incidence of adverse experiences was observed in the sitagliptin treatment group and with a between-group difference >2% include: Eye Disorders; General Disorders and Administration Site Conditions; Infections and Infestations; Injury, Poisoning, and Procedural Complications; Metabolism and Nutrition Disorders; and Respiratory, Thoracic, and Mediastinal Disorders SOCs. For all SOCs, the observed between-group differences in the incidence of adverse experiences were generally similar to those observed at Week 18 and the 95% CI included "0". Specific adverse experiences are discussed in the following section.

The above-mentioned increase in incidence of cardiac disorders observed during the use of sitagliptin was noted by the CHMP, who requested that these types of events be closely monitored. The MAH was requested to submit this complete data set in the upcoming PSURs.

A.1. Hypoglycemia

Over the 54 weeks, hypoglycemia was observed in 7 patients (4.1%) in the sitagliptin group who had 10 episodes in total. In the placebo group only one patient (1.1%) with one episode of hypoglycemia was reported. All episodes of hypoglycemia were considered mild in intensity, none required either non-medical or medical assistance, and no patients were discontinued due to the adverse experience of hypoglycemia. Events of hypoglycemia in the sitagliptin group were considered by the investigator to be related to the study medication in 4 of the patients and not related in the other 3 patients. The episode of hypoglycaemia in 1 patient in the placebo group was considered not related to the study drug by the investigator.

A.2. Body Weight

An increase from baseline in body weight at Week 18 was noted in both groups (sitagliptin 0.4 kg; placebo 0.1 kg); not statistically significant (p=0.362). At 54 weeks, the increase in body weight from baseline was 1.8 kg for the sitagliptin group, versus 1.2 kg for the placebo group. No statistically significant (p=0.372) between-group difference was observed for body weight increase at Week 54.

A.3. Gastro-intestinal Side Effects

Over 54 weeks, the incidences of the pre-specified gastrointestinal adverse experiences (abdominal pain, nausea, vomiting, and diarrhea) were numerically higher in the placebo treatment group compared with the incidences observed in the sitagliptin group.

A.4. Other

Adverse experiences of headache, independent of relationship with the study drug, were reported for 10 (5.9%) patients in the sitagliptin treatment group compared with 4 (4.3%) patients in the placebo treatment group. Of those, adverse experiences of headache in 4 (2.4%) patients in the sitagliptin group and none in the placebo group were considered by the investigator to be possibly related to the study drug. Two of these events resolved while the patient was on study medication. The other two (reported as adverse experiences) were ongoing at study completion. Adverse experiences in these four patients were mild in intensity and did not result in interruption or discontinuation of the study drug.

B) Laboratory tests

For most laboratory parameters, mean changes over time and frequency of values meeting Pre-defined Laboratory Criteria (PDLC) were similar in the sitagliptin treatment group compared to the placebo group. Over the 54-week treatment period, similar incidences of laboratory adverse experiences overall and laboratory drug-related adverse experiences were observed in both treatment groups. No laboratory serious adverse experiences were reported. One patient in the sitagliptin group was discontinued due to a laboratory drug-related adverse experience of decreased white blood cells. There were no discontinuations due to laboratory adverse experiences in the placebo group.

C) Risk Management plan

There was no change in the pharmacovigilance and risk minimisation activities as defined in the RMP as it existed at the time of submission. An update to the RMP was submitted in June 2009.

3.4. Changes to the Product Information

The CHMP agreed with the introduction of the new wordings in the Summary of Product Characteristics and Package Leaflet, as detailed below.

The text underlined has been introduced in this variation and the text strikethrough has been deleted.

3.4.1 Changes to the Summary of Product Characteristics (SPC)

Section 4.1 (Therapeutic indications)

"For patients with type 2 diabetes mellitus in whom use of a PPARγ agonist (i.e. a thiazolidinedione) is appropriate, Xelevia 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"*

Section 4.4 (Special warnings and precautions for use)

"*In clinical trials of Xelevia as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia (i.e. metformin and/or ~~pioglitazone~~a PPARγ agonist),…*"

Section 4.8 (Undesirable effects)

"*In ~~9~~ 10 large clinical trials of up to 2 years in duration, over 29~~7~~00 patients have received treatment with Xelevia 100 mg per day alone or in combination with metformin, a sulphonylurea (with or without metformin) or a PPARγ agent (with or without metformin). In a pooled analysis of 9 of these trials, the rate of discontinuation due to adverse experiences considered drug-related was 0.8 % with 100 mg per day and 1.5 % with other treatments. No adverse reactions considered as drug-related were reported in patients treated with sitagliptin occurring in excess (> 0.2 % and difference > 1 patient) of that in patients treated with control. In an additional combination study with a PPARγ agent (rosiglitazone) and metformin, no patients were discontinued due to adverse experiences considered as drug-related.*"

(…)

"Table 1. The frequency of adverse reactions identified from placebo-controlled clinical studies

Adverse Reaction	***Frequency of adverse reaction by treatment regimen***				
	Sitagliptin with Metformin[1]	***Sitagliptin with a Sulfonylurea[2]***	***Sitagliptin with ~~Metformin and~~ a Sulfonylurea and Metformin[3]***	***Sitagliptin with a PPARγ Agent (pioglitazone)[4]***	***Sitagliptin with a PPARγ Agent (rosiglitazone) and Metformin[5]***
Time-point	***24-week***	***24-week***	***24-week***	***24-week***	***18-week***
Investigations					
blood glucose decreased	*Uncommon*				
Nervous system disorders					
headache					*Common*
somnolence	*Uncommon*				
Gastrointestinal disorders					
diarrhoea	*Uncommon*				*Common*
nausea	*Common*				
flatulence				*Common*	
constipation			*Common*		
upper abdominal pain	*Uncommon*				
vomiting					*Common*

Metabolism and nutrition disorders					
*hypoglycaemia**		*Very common*	*Very common*	*Common*	*Common*
General disorders					
peripheral oedema				*Common*	*Common*†

* *In clinical trials of Xelevia as monotherapy and sitagliptin as part of combination therapy with metformin and/or a PPARγagent, rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo.*

† *Observed in the 54-week analysis."*

(…)

"5 *In this study of sitagliptin 100 mg once daily in combination with rosiglitazone and metformin, which continued through 54 weeks, the incidence of adverse reactions considered as drug-related in patients treated with the sitagliptin combination compared to treatment with the placebo combination was 15.3 % and 10.9 %, respectively. Other drug-related adverse reactions reported in the 54-week analysis (frequency common) in patients treated with the sitagliptin combination occurring in excess (> 0.2 % and difference > 1 patient) of that in patients treated with the placebo combination were: headache, cough, vomiting, hypoglycaemia, fungal skin infection, and upper respiratory tract infection."*

Section 4.9 (Overdose)

"In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days."

Section 5.1 (Pharmacodynamic properties)

"In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations."

"Overall, sitagliptin improved glycaemic control when given as monotherapy, when used in combination with metformin (initial or add-on therapy), in combination with a sulphonylurea (with or without metformin), ~~and~~ in combination with a thiazolidinedione, and in combination with a thiazolidinedione and metformin…."

"A 54-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of rosiglitazone and metformin. The addition of sitagliptin to rosiglitazone and metformin provided significant improvements in glycaemic parameters at the primary timepoint of Week 18, with improvements sustained through the end of the study. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo (1.9 vs. 1.3 kg)."

"Table 2. HbA_{1c} results in placebo-controlled monotherapy and combination therapy studies*

Study	*Mean baseline HbA1c (%)*	*Mean change from baseline HbA1c (%)†*	*Placebo-corrected mean change in HbA1c (%)† (95 % CI)*
Sitagliptin 100 mg once daily added to ongoing rosiglitazone + metformin therapy (N=170)			
Week 18	*8.8*	*-1.0*	*-0.7‡ (-0.9, -0.5)*
Week 54	*8.8*	*-1.0*	*-0.8‡ (-1.0, -0.5)*

‡ HbA_{1c} (%) at week 24.

3.4.2 Changes to the Package Leaflet (PL)

Section 4 (Possible side effects)

"Some patients have experienced the following side effects while taking Xelevia in combination with rosiglitazone and metformin:
Common: headache, cough, diarrhoea, vomiting, low blood sugar, fungal skin infection, upper respiratory infection, swelling of the hands or legs."

4. Overall conclusion and benefit-risk assessment

Study P052 was a multicenter, double-blind, randomized, parallel-group Phase III study to compare the efficacy of sitagliptin 100 mg with placebo in patients with T2DM who had inadequate glycaemic control on combination therapy with metformin (at a dose of ≥1500 mg/day) and rosiglitazone (at a dose of ≥4 mg/day). The study was designed to include patients on different types of dual medication. Patients with T2DM on dual combination therapy with metformin and a PPARγ agonist, a PPARγ agonist and a sulfonylurea agent, or metformin and a sulfonylurea agent were eligible. Prior to randomisation patients switched from their own therapy to metformin and rosiglitazone and the dose was titrated. The wash-out/titration period for metformin and PPARγ agonist was long enough. The mean duration of diabetes was relatively long with 9.3 years and mean HbA1c levels were relatively high (8.8%) in this study population.

Furthermore, to ensure that patients were not exposed to poorer control for an undue period of time, strict glycaemic rescue and discontinuation criteria were included in the study design. Between 18 and 30 weeks the rescue criteria were based on FPG levels >13.32 mmol/L. The sitagliptin and placebo group were more or less the same regarding glycaemic rescue therapy. Starting from Week 24, the rescue criteria changed to a longer-term measurement method: HbA1c >8.5%. After week 30 a strong difference between the two groups occurred.

In study P052, sitagliptin as add-on therapy in patients with inadequate control on metformin and rosiglitazone provided improvement in glycaemic control compared with placebo. Least square means for change from baseline at week 54 with 95% CI Full-Analysis-Set Population for HbA1c (%): -0.77 (-1.04, -0.50) for FPG (mg/dL): -17.4 (-26.4, -8.4) and for 2-hourPMG (mg/dL) -34.1 (-48.4, -19.9) for sitagliptin compared vs placebo. There was a trend that patients with higher baseline HbA1c values had a greater mean decrease from baseline in HbA1c in both sitagliptin group and placebo group.

Add-on therapy with sitagliptin resulted in greater proportions of patients achieving the glycaemic goal of HbA1c <7% compared to placebo. The percentage of patients achieving HbA1c< 7% at week 54 (26.2%) was higher than at week 18 (22%), however the percentage of patients achieving HbA1c< 7% at week 18 and week 54 was only 14.9%. Results were variable and confidence intervals were wide. Nevertheless, there might be patients who can benefit from addition of sitagliptin to metformin and PPARγ agonist treatment.

The overall exposure and safety population examined was sufficient. A higher percentage of patients completed the study in the sitagliptin group compared to the placebo group. Reasons for discontinuation were generally similar between treatment groups with a higher percentage of patients in the placebo treatment group discontinuing due to lack of efficacy.

Over the 54-week treatment period slightly higher incidences of serious adverse experiences, slightly higher incidences of overall adverse experiences and slightly higher incidences of drug-related adverse experiences were observed in the sitagliptin group compared to the placebo group (8.2% vs 3.3% and 75.3% vs 70.7% and 15.3% vs 10.9% respectively). No unexpected adverse events and no deaths were reported.

The overall number of patients reported to have clinical adverse experiences of hypoglycaemia during the study was low and the between-group difference in the incidence of adverse experiences was not statistically significant. The few hypoglycaemia events reported in this study with sitagliptin were mild, none required assistance for treatment, and none caused interruption or discontinuation of study drug.

Over 54 weeks, the incidences of the pre-specified gastrointestinal adverse experiences (abdominal pain, nausea, vomiting, and diarrhoea) were numerically higher in the placebo treatment group compared with the incidences observed in the sitagliptin group.

After 54 weeks body weight increased 1.8 kg in the sitagliptin group and 1.2 kg in the placebo group. The difference between groups was not statistically significant.

In conclusion, sitagliptin 100mg caused a very small, but statistically significant reduction in mean HbA1c in respect to baseline HbA1c. There was a statistically significant decrease in postprandial glucose levels in the sitagliptin group. In the sitagliptin group, a greater proportion of patients achieved the glycaemic goal of HbA1c <7%, however this effect seems to be variable over time. The numbers of hypoglycaemic events during the use of sitagliptin was low.

Benefits
Mean HbA1c reduction was small in respect to baseline HbA1c, but significant. A significant decrease of postprandial glucose was measured. More patients in the sitagliptin group reached HbA1c <7%, although the percentage was modest and less patients in the sitagliptin group needed rescue therapy from week 24 onwards. There were few hypoglycaemic events.

Risks
No unexpected adverse events were observed.

Balance
The benefit/risk for Xelevia to include the indication for the triple combination therapy with a PPARγ agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist is considered positive.