ASSESSMENT REPORT
FOR
XELEVIA

International Nonproprietary Name:
sitagliptin

Procedure No. EMEA/H/C/II/02

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

1. Introduction

Sitagliptin phosphate, the active component of Xelevia, is a dipeptidyl peptidase-4 (DPP-4) inhibitor, developed for treatment of type 2 diabetes mellitus (T2DM). 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.

Xelevia was approved in the EU on 21 March 2007, with therapeutic indications for use in combination with metformin or a PPAR-γ agonist when treatment with metformin or the PPAR-γ agonist alone provide inadequate glycemic control.

In this Type II variation the Marketing Authorisation Holder (MAH) applied to extend the indication to add a dual oral combination therapy with a sulphonylurea (SU) and to add a triple oral combination therapy with metformin (MET) and a sulphonylurea.

In support of these indications results of one clinical trial has been submitted (Study P035).

2 Clinical aspects

2.1 Efficacy

2.1.1. Study P035

2.1.2. Study design

Study P035 was a double-blind, randomised, placebo-controlled study of sitagliptin as add-on therapy in patients with inadequate glycaemic control on glimepiride alone or in combination with metformin. The study had a 24-week double-blind placebo-controlled phase (Phase A) followed by a 30-week active comparator (pioglitazone) phase (Phase B). Male and female patients with T2DM, who were ≥18 and ≤75 years of age at the screening visit and who were either (1) not on AHA (anti-hyperglycaemic agent) or (2) on glimepiride (alone or in combination with metformin) or (3) on other AHAs (alone or in dual or triple combination therapy), were eligible to participate if they met enrolment criteria. Patients who were already on a stable dose of glimepiride (at a dose of ≥4 mg/day) alone or in combination with metformin (at a dose of ≥1500 mg/day) who had an HbA1c ≥7.5% but ≤10.5% and who met all other enrolment criteria directly entered a 2-week, single-blind placebo run-in period, and after completion were eligible to be randomised. Patients not on AHA or those on monotherapy or oral combination therapy who were not on a stable regimen of glimepiride alone or in combination with metformin entered an up to 6-week glimepiride (+/- metformin) dose titration period and then a glimepiride (+/- metformin) dose stable period of up to 10 weeks. Patients who had inadequate glycaemic control after the dose-stable period (i.e., HbA1c ≥7.5% but ≤10.5%) and who met all other enrolment criteria were eligible to be randomized after completing a 2 week single-blind placebo run-in period. Patients were stratified according to whether or not they were on metformin during the dose-stable period. Stratum 1 consisted of patients on glimepiride alone (i.e., monotherapy) and Stratum 2 consisted of patients on glimepiride and metformin in combination therapy. The protocol indicated that 50% of the randomized patient sample should be in each stratum.

Four hundred forty-one (441) patients (the entire cohort) were randomized at 73 sites worldwide to either sitagliptin 100 mg q.d. (once a day) or placebo in a 1:1 ratio for a 24-week, double-blind treatment period (Phase A). During the 24-week placebo-controlled period, patients meeting glycaemic rescue criteria were to receive rescue medication (pioglitazone) and complete Phase A but were not eligible to continue into Phase B.
Patients randomised to sitagliptin continued on sitagliptin during Phase B while those randomised to placebo were switched to pioglitazone 30 mg/day at entry into this Phase. Down-titration of glimepiride during either Phase A or B was only allowed when required to manage hypoglycaemia.

The primary efficacy endpoint was the change from baseline in HbA_{1c}; fasting plasma glucose (FPG) was a key secondary efficacy endpoint. In addition, a subset of consenting patients (and hence not a randomly selected subpopulation) underwent a 9-point meal tolerance test (MTT), which measured pre-meal and post-meal glucose, insulin, and C-peptide. The MTT was performed after 24 weeks of treatment (end of Phase A) and was also to be performed at Week 54 (end of Phase B). Patients meeting pre-specified criteria for poor glycaemic control were to receive pioglitazone as rescue therapy; a prespecified time-to-rescue analysis was performed.

Baseline characteristics (demographic, anthropometric characteristics, efficacy endpoints and duration of diabetes) were generally balanced between the treatment groups in the entire cohort, and also in each stratum. One exception was that patients in Stratum 2 (patients on glimepiride in combination with metformin) had slightly lower baseline HbA1c values, a longer duration of type 2 diabetes mellitus, and were more likely to be on combination therapy at screening compared with patients in Stratum 1 (patients on glimepiride alone).

2.1.3. Results

HbA1c

Results for HbA1c are shown in Table 1, Table 2 and Table 3. Results over time are presented in Figure 1, Figure 2 and Figure 3.

When added to glimepiride alone (Stratum 1), sitagliptin (SITA) resulted in a significant reduction in HbA1c after 24 weeks, while an increase was observed with placebo. The effect was maximal after 12 weeks, with a modest rise observed from week 12 to week 24. Difference in change from baseline between sitagliptin and placebo was –0.57 (95% CI: -0.82, -0.32) at week 24.
The same pattern was seen in Stratum 2, when sitagliptin or placebo was added to combination treatment of glimepiride + metformin. Sitagliptin addition resulted a significant reduction in HbA1c, while placebo treatment resulted in an increase in HbA1c. Between group difference was –0.89 (-1.10, -0.68) in favour of sitagliptin.

Pattern in the Entire Cohort was similar.

The sitagliptin treatment group showed a larger within-group decrease from baseline in the completers analysis than in the APT (all patients treated) analysis; however, the placebo-adjusted treatment effects were smaller in the completers analysis (-0.68, -0.50, and -0.84%) than in the APT analysis (-0.74, -0.57, and -0.89%) in the entire cohort and in Strata 1 and 2, respectively. This attenuation of the placebo-subtracted decrease in HbA1c was due to the removal of a larger number of rescued/discontinued patients from the placebo group than from the sitagliptin groups in the completers population, relative to the APT population. Rescued/discontinued patients generally had poorer HbA1c responses compared with patients who completed without rescue therapy, and thus the placebo group in the completers analysis showed a greater reduction from baseline when the imputed Week 24 values for the rescued/discontinued subset were removed.

Table 1: Analysis of Change from Baseline in HbA1c (%) at Week 24 All-Patients-Treated Population, Study P035, Entire Cohort

Treatment Group	N	Mean (SD)		Change from Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	217	8.34 (0.76)	7.88 (1.01)	-0.45 (0.06)	-0.45 (0.06)	(-0.57, -0.34)	<0.001
Placebo	208	8.37 (0.74)	8.64 (1.04)	0.28 (0.06)	0.28 (0.06)	(0.17, 0.40)	<0.001

Between Treatment Group Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	-0.74 (-0.90, -0.57)	<0.001

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment Group	<0.001
Stratum	0.035

Root Mean Square Error of Change =0.86

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

Table 2: Analysis of Change from Baseline in HbA1c (%) at Week 24 All-Patients-Treated Population, Study P035, Stratum 1

Treatment Group	N	Mean (SD)		Change from Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	102	8.41 (0.78)	8.11 (1.05)	-0.30 (0.09)	-0.30 (0.09)	(-0.48, -0.12)	0.001
Placebo	103	8.46 (0.80)	8.72 (1.14)	0.26 (0.10)	0.27 (0.09)	(0.09, 0.45)	0.004

Between Treatment Group Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	-0.57 (-0.82, -0.32)	<0.001

p-Value for ANCOVA Effects	
Baseline Value	0.003
Treatment Group	<0.001

Root Mean Square Error of Change =0.92

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

Table 3: Analysis of Change from Baseline in HbA1c (%) at Week 24 All-Patients-Treated Population, Study P035, Stratum 2

Treatment Group	N	Mean (SD)		Change from Baseline			
		Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sitagliptin 100 mg	115	8.27 (0.74)	7.68 (0.92)	-0.59 (0.08)	-0.59 (0.07)	(-0.74, -0.44)	<0.001
Placebo	105	8.28 (0.68)	8.57 (0.93)	0.30 (0.08)	0.30 (0.08)	(0.14, 0.45)	<0.001

Between Treatment Group Difference	Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Placebo	-0.89 (-1.10, -0.68)	<0.001

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment Group	<0.001

Root Mean Square Error of Change =0.80

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

Figure 1: LS Mean Change from Baseline in HbA1c (%) Over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated Population, Study P035, Entire Cohort

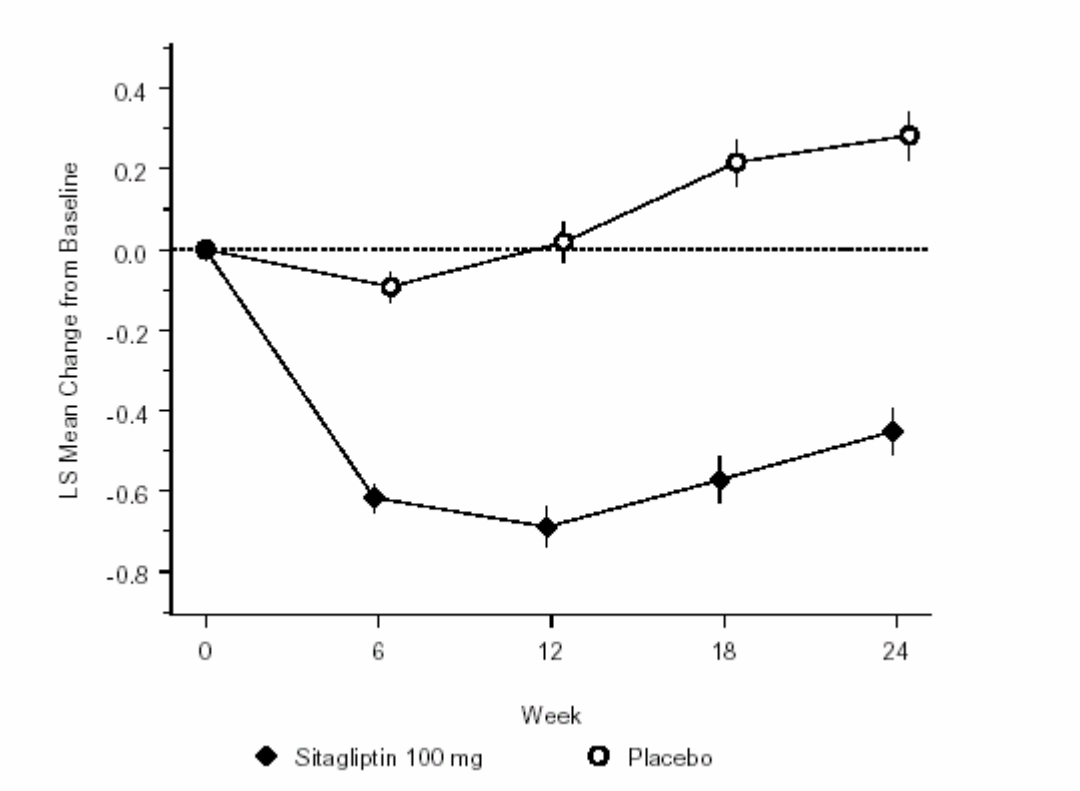


Figure 2: LS Mean Change from Baseline in HbA1c (%) Over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated Population, Study P035, Stratum 1

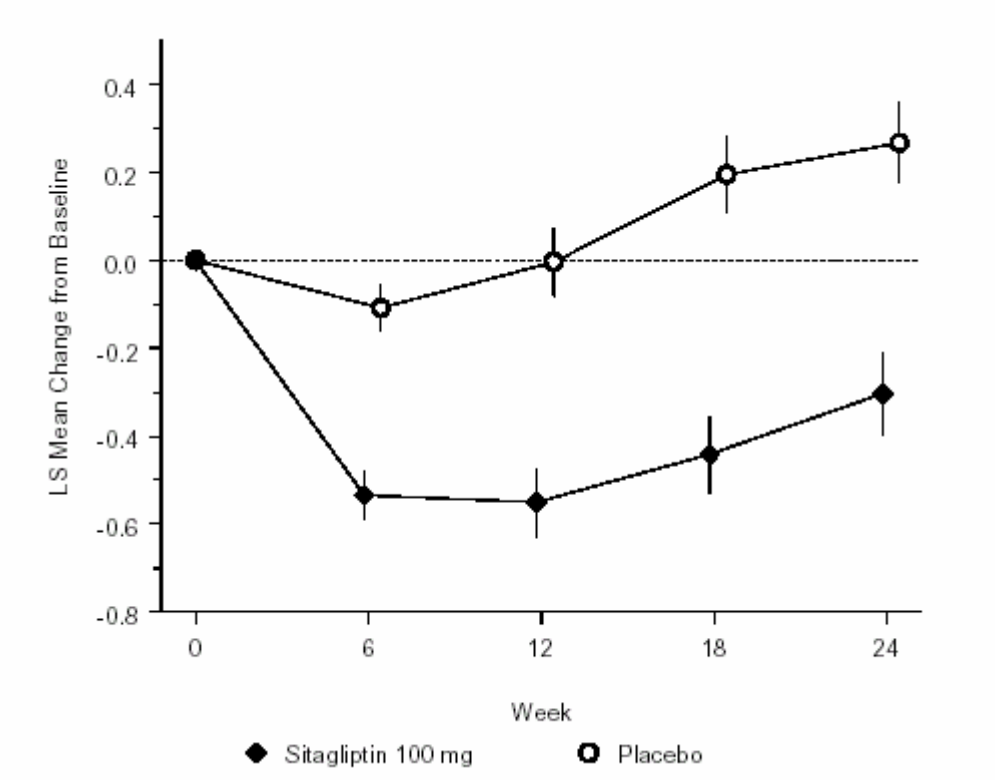
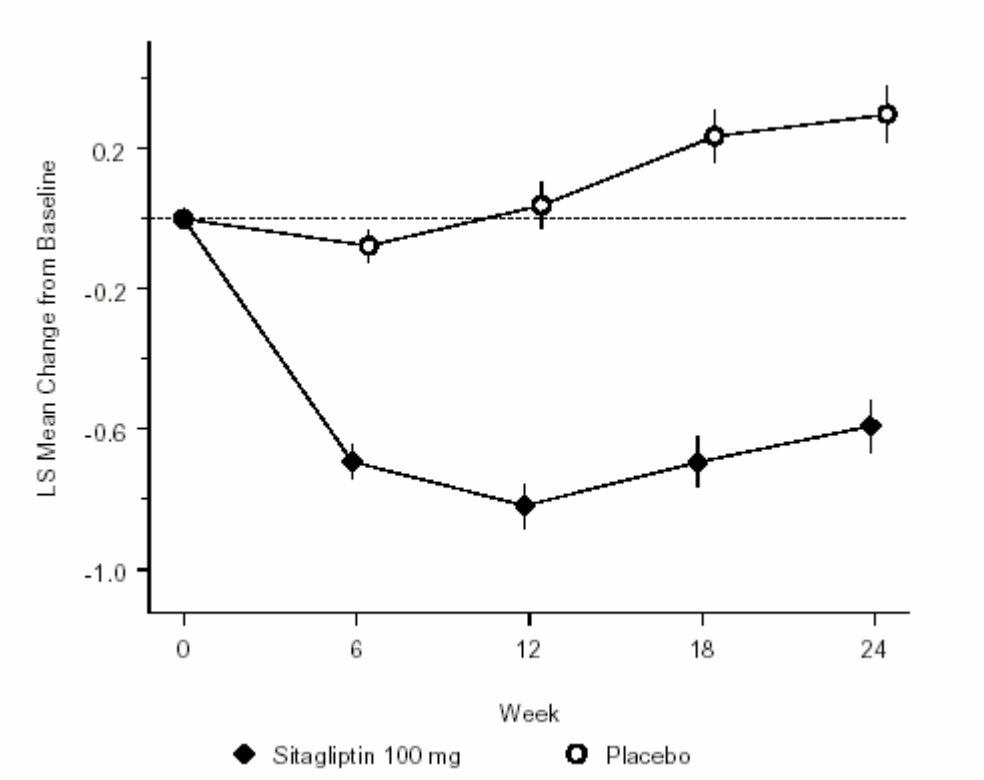


Figure 3: LS Mean Change from Baseline in HbA1c (%) Over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated Population, Study P035, Stratum 2



HbA1c goals

Analysis of the proportion of patients with HbA_{1c} values below 7.0% at Week 24 showed that sitagliptin 100 mg significantly increased the proportion of patients reaching the goal in the entire cohort (17.1% on sitagliptin 100 mg compared to 4.8% on placebo; p<0.001) and in the proportion of patients in Stratum 2 (22.6% on sitagliptin 100 mg compared to 1.0% on placebo; p<0.001), while the between-group difference in the proportion of patients in Stratum 1 (10.8% on sitagliptin 100 mg compared to 8.7% on placebo; p=0.638) was not statistically significant (Table 4). For the analyses of the < 6.5% goal, the between-group difference observed in the entire cohort (5.5% and 1.9% in sitagliptin and placebo groups, respectively; p=0.069) and in Stratum 1 (2.9% and 3.9% in sitagliptin and placebo groups, respectively; p=0.693) was not statistically significant, while in Stratum 2, a significantly (p=0.004) greater proportion of patients in the sitagliptin group than in the placebo group (7.8% vs. 0.0%) achieved this goal.

Table 4: Proportion of Patients with HbA1c Value < 7% and < 6.5% at Week 24, All-Patients-Treated Population, Entire Cohort, Stratum 1 and Stratum 2 respectively

Entire Cohort						
Treatment Group	N	n (%)		N	n (%)	
Sitagliptin 100 mg	217	37 (17.1)		217	12 (5.5)	
Placebo	208	10 (4.8)		208	4 (1.9)	
Between Treatment Group Comparison	Difference in Proportion (%) (95% CI†)	Odds-Ratio‡ (95% CI)	p-Value‡	Difference in Proportion (%) (95% CI†)	Odds-Ratio‡ (95% CI)	p-Value‡
Sitagliptin 100 mg vs. Placebo	12.2 (6.4, 18.2)	4.33 (2.04, 9.19)	<0.001	3.6 (-0.1, 7.7)	2.92 (0.92, 9.28)	0.069
Stratum 1						
	< 7%			< 6.5%		
Treatment Group	N	n (%)		N	n (%)	
Sitagliptin 100 mg	102	11 (10.8)		102	3 (2.9)	

Placebo	103	9 (8.7)		103	4 (3.9)	
Between Treatment Group Comparison	Difference in Proportion (%) (95% CI†)	Odds-Ratio‡ (95% CI)	p-Value‡	Difference in Proportion (%) (95% CI†)	Odds-Ratio‡ (95% CI)	p-Value‡
Sitagliptin 100 mg vs. Placebo	2.0 (-6.4, 10.6)	1.26 (0.48, 3.30)	0.638	-0.9 (-6.9, 4.9)	0.74 (0.16, 3.39)	0.693
Stratum 2						
	< 7%			< 6.5%		
Treatment Group	N	n (%)		N	n (%)	
Sitagliptin 100 mg	115	26 (22.6)		115	9 (7.8)	
Placebo	105	1 (1.0)		105	0 (0.0)	
Between Treatment Group Comparison	Difference in Proportion (%) (95% CI†)	Odds-Ratio‡ (95% CI)	p-Value‡	Difference in Proportion (%) (95% CI†)	Odds-Ratio‡ (95% CI)	p-Value‡
Sitagliptin 100 mg vs. Placebo	21.7 (13.7, 30.2)	34.57 (4.50, 265.51)	<0.001	7.8 (2.7, 14.2)		0.004

† Confidence Interval computed using the Wilson score method.

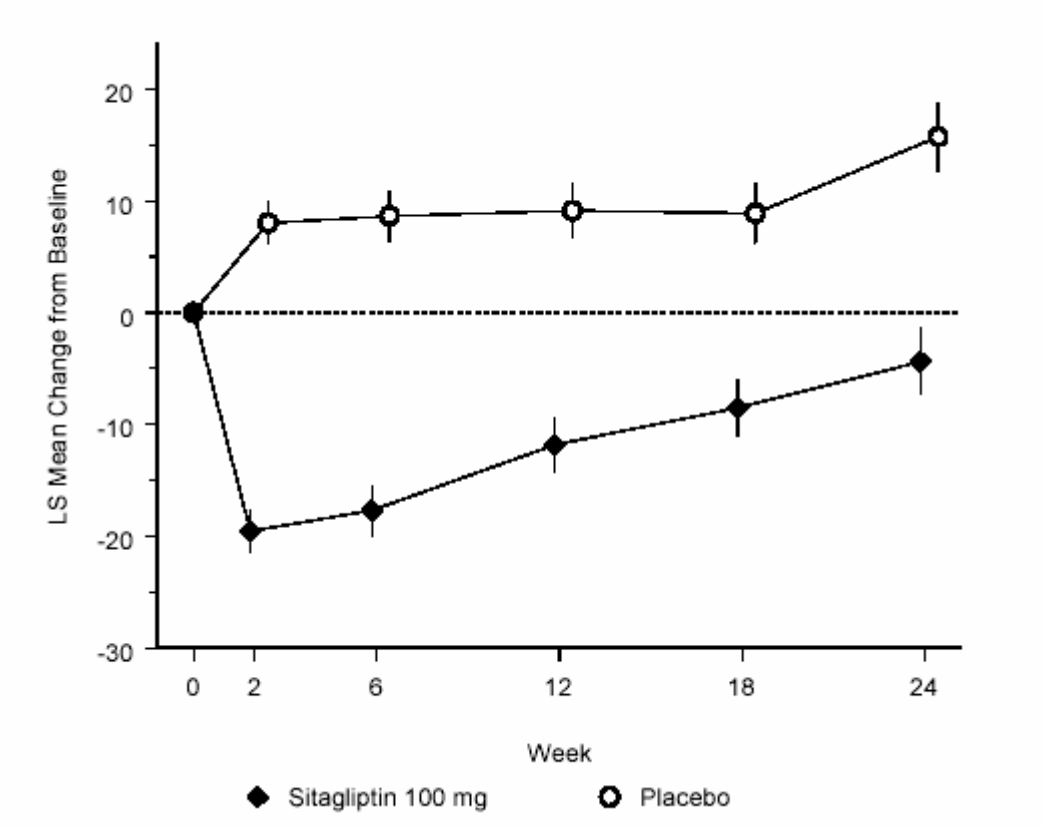
‡ From the logistic regression model, adjusting for baseline HbA1c and stratum.

Fasting plasma glucose (FPG)

Sitagliptin was more effective than placebo in lowering FPG in the entire cohort and in each stratum (Difference –20.1 [95% CI: –28.4, -11.8], -19.3 [95% CI: -31.9, -6.7], and –20.7 [95% CI: -31.7, -9.7] for the entire cohort, stratum 1 and stratum 2 respectively).

When FPG profiles over time were analysed for the entire cohort and the individual strata, a rise in FPG with sitagliptin was seen after a nadir was reached (Figure 4); a rise in the placebo group was also observed that was modestly less prominent than the rise in the sitagliptin group. The patterns within each stratum were similar to the pattern observed for the entire cohort.

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



Other efficacy endpoints

Proinsulin to Insulin Ratio HOMA-β

A statistically significant decrease in the proinsulin to insulin ratio from baseline in the sitagliptin group was observed. However, a smaller and non-statistically significant decrease was also observed in the placebo group such that the between-treatment group difference was not statistically significant. The results of HOMA-β change from baseline showed an increase for the sitagliptin group relative to the placebo group (p=0.021) at Week 24 (between-group difference of 12.0; 95% CI [1.8, 22.1]).

β-Cell Function Assessments from Frequently Sampled MTT

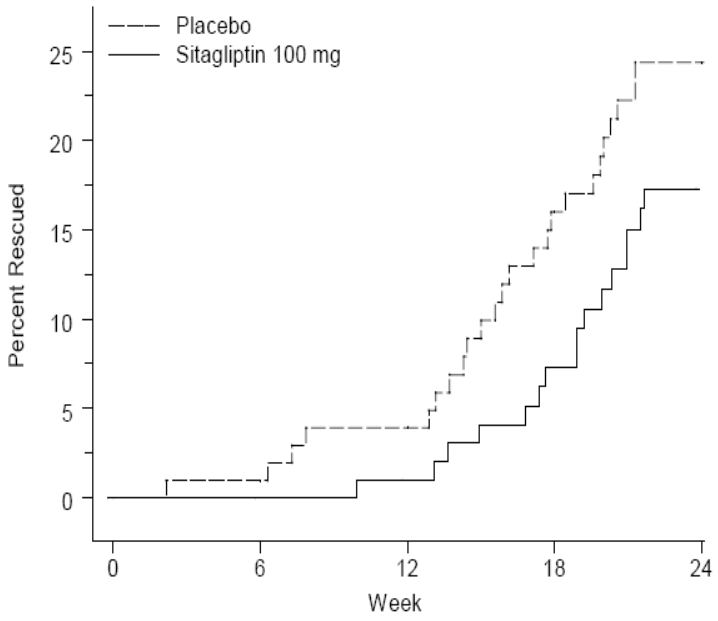
A sub-study was conducted (among patients who consented) using a frequently sampled meal tolerance test (collecting blood samples from 9 time-points) to assess changes in β-cell function with sitagliptin treatment. The analysis of data from this sub-study has not been completed.

Time-to-Rescue

Patients not meeting specific glycaemic goals after randomization during Phase A were to receive rescue therapy with open-label pioglitazone and a prespecified time to rescue was analysis was performed.. In the entire cohort and in the subset of patients in Stratum 2, a significant difference (p<0.001) was observed in the proportion of patients rescued in the sitagliptin group (12.4% and 8.2% respectively for the entire cohort and subset of patients in Stratum 2) relative to the placebo group (26.7% and 28.8%, respectively). No significant difference was observed between the two treatment groups with respect to this parameter in the subset of patients in Stratum 1 (17.3% in the sitagliptin treatment group versus 24.4% in the placebo group (difference –7.1% [-18.6, 4.4]).

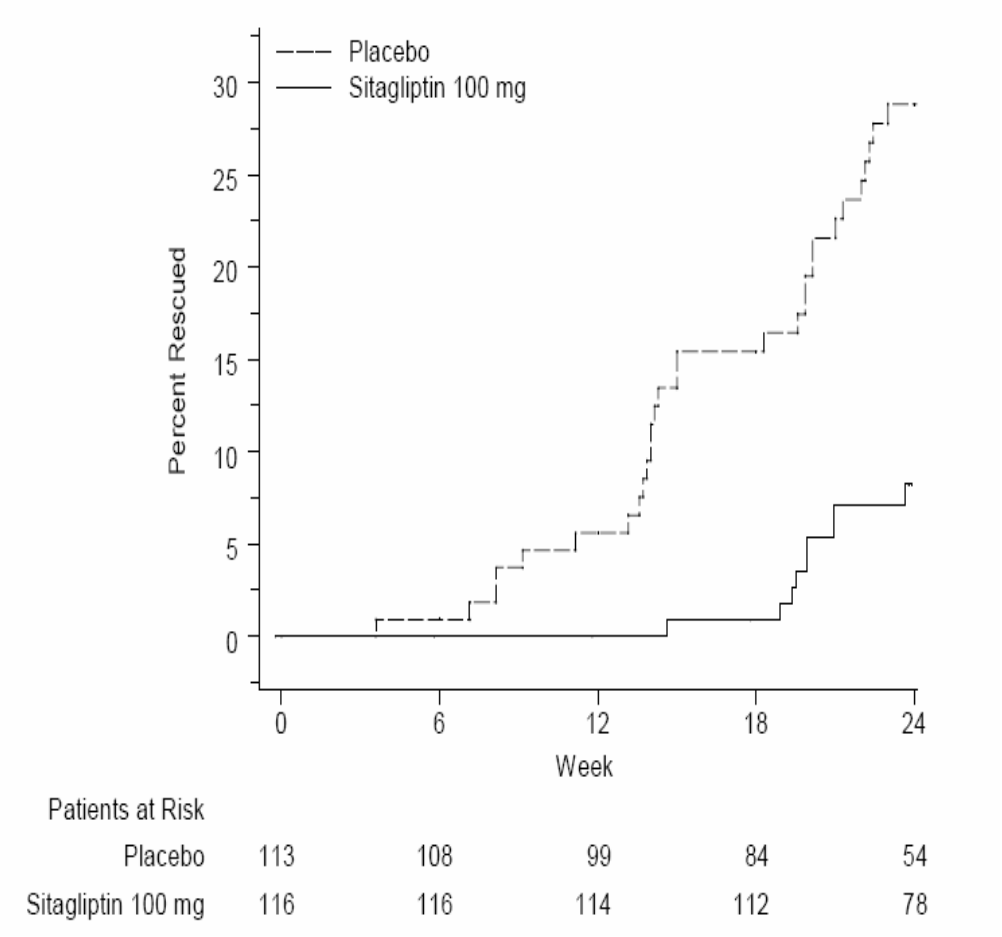
The time to rescue was later in the sitagliptin group compared with the placebo group in the entire cohort and in the subset of patients in Stratum 2. No significant difference was observed between the two treatment groups in the subset of patients in Stratum 1(Figure 5, Figure 6).

Figure 5: Patients Receiving Rescue Medication; Subset of Patients on Glimepiride Alone (Stratum 1)



Patients at Risk					
Placebo	106	101	98	83	54
Sitagliptin 100 mg	106	104	99	86	52

Figure 6: Patients Receiving Rescue Medication; Subset of Patients on Glimepiride and Metformin (Stratum 2)



Two-Hour Post-Meal Glucose (PMG)
An MTT was performed in a subset of patients who consented to participate in a 9-point MTT. Results indicated that patients treated with sitagliptin had a lower PMG, a larger increase relative to placebo in 2-hour post-meal insulin (p=0.007), 2-hour post-meal C-peptide (p<0.001), C-peptide total AUC (p=0.005), insulin 3-hour total AUC to glucose 3-hour total AUC ratio (p<0.001), and insulin total AUC to glucose total AUC ratio (p=0.013).

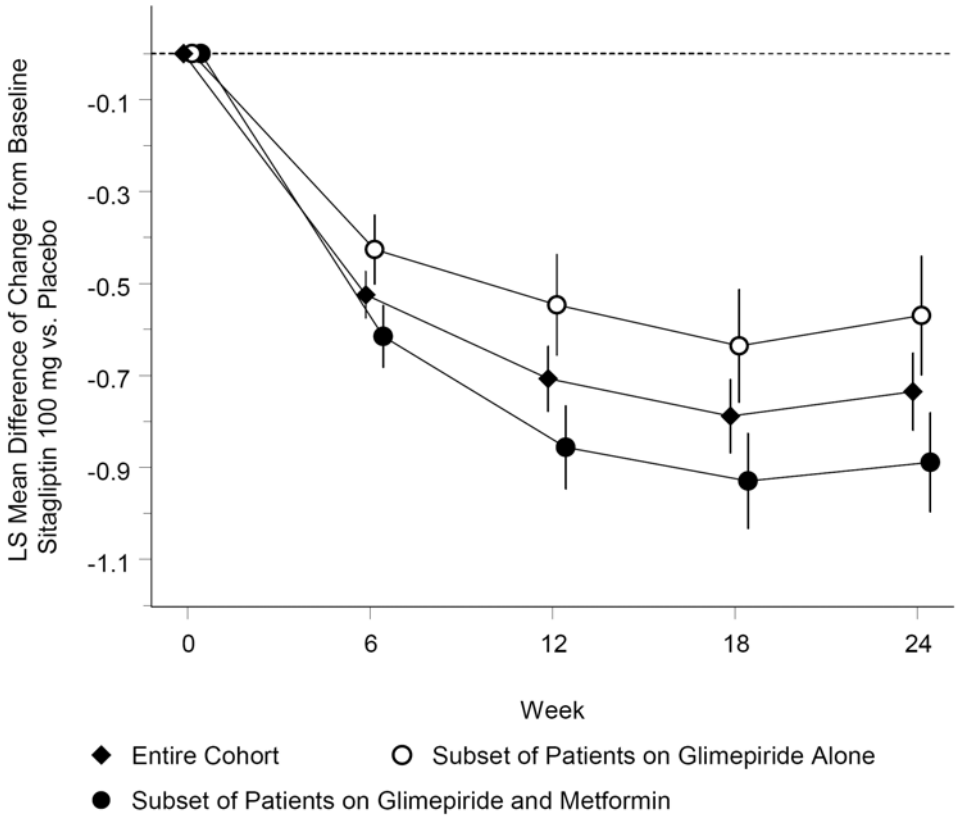
Comparison of Results in Subpopulations
The between-group differences for subgroups defined by baseline efficacy endpoint/disease-related characteristics demonstrated a notable difference between the two strata in HbA_{1c}–lowering relative to placebo by baseline HbA_{1c} category. In Stratum 2 (patients on glimepiride plus metformin), stepwise and markedly greater placebo-subtracted HbA_{1c} lowering was observed going from lower to higher baseline HbA_{1c} categories: -0.55% in patients with baseline HbA_{1c} of <8% to -1.34% in patients with baseline HbA_{1c} ≥9%. In contrast, in Stratum 1 (patients on glimepiride alone) no discernible trend in placebo-subtracted HbA_{1c}-lowering was observed with higher baseline HbA_{1c} categories. For treatment effects on HbA_{1c} by other baseline disease or glycaemic efficacy baseline characteristics, the responses were generally consistent across subgroups in the entire cohort and in the two strata, although in Stratum 2, there were few patients who were treatment naïve or who were on monotherapy.

Study P035 consisted of two Strata: in Stratum 1 patients inadequately controlled by glimepiride monotherapy received either sitagliptin or placebo; in Stratum 2 sitagliptin or placebo was added to a combination of glimepiride and metformin in patients inadequately controlled by these two agents.
The design of the study is acceptable for the CHMP, although it was discussed whether comparison with an active component (metformin) would have been desirable for stratum 1. But the CHMP

considered in this case that the placebo subtracted effects do give an appropriate estimate of the size of the effect.
In both Strata sitagliptin resulted in a decrease in HbA1c at week 24, while an increase was seen in placebo treated patients. In Stratum 1 the reduction from baseline was relatively modest (-0.3% at week 24) when compared with the results of previously submitted studies. Furthermore, HbA1c reached a nadir at week 12, and from then on increased again. For Stratum 2 results were better, but also modest and durability was also a concern. This concern is strengthened by the proportion of patients reaching goal HbA1c <7%: in Stratum 1 only 11% of patients reached that goal and the difference with placebo was not significant. In Stratum 2 22.6% of the patients reached that goal. Measures of β-cell function showed improvement with sitagliptin therapy, but these effects may be merely due to improvement of glycaemic control and may not be genuine to sitagliptin.

In their response to this concern the MAH stated that, in the assessment of the extent and durability of glycaemic response, the placebo-corrected glycaemic response to treatment is preferable to the within-group change from baseline. In study P035, the course of the within-group change from baseline in HbA1c in the sitagliptin group is impacted by a number of factors beyond the glycaemic efficacy of sitagliptin, such as stability of HbA1C at baseline, waning of background therapy, study co-interventions, such as counselling on diet and exercise and the natural history of T2DM. Placebo-correction permits proper evaluation of the impact of these factors to be sorted out from the direct effect of the drug on this endpoint and, hence, more accurately characterizes the efficacy of sitagliptin.
Based upon the approximately 0.6% decrease in HbA1c at Week 24 relative to placebo, the MAH stated that an important benefit with regard to the long-term risk of diabetes complications would be expected when sitagliptin is added to a SU agent based on the results of the UKPDS study.
Examination of the placebo-corrected change from baseline in HbA_{1c} also supports the durability of effect of sitagliptin over the 24-week treatment period. In Figure 7, placebo-subtracted difference in change from baseline in HbA_{1c} is shown for the entire cohort, stratum 1 and stratum 2. The placebo-corrected change continues to decrease after 12 weeks, reaching a nadir around Week 18, with a minimal rise in placebo-subtracted HbA_{1c} change from baseline from Week 18 through Week 24.
The rise in HbA1c after week 12 that is seen in the within group change, was observed in both the sitagliptin and placebo groups. Since this rise was similar in the two treatment groups, the MAH concluded, that it represents a trial effect, and not deterioration in response to sitagliptin.

Figure 7: LS Mean Change from Baseline in HbA1c (%) over time, Sitagliptin 100 mg vs. Placebo (LS Mean ± SE), All-Patients-Treated Population



The CHMP agreed with the MAH that the placebo-corrected response is a proper measure of the efficacy of sitagliptin in study P035. The CHMP also agreed that a number of factors, other than efficacy of sitagliptin, will influence the course of HbA1c. Waning of the response to SU might be one of these factors, and indeed might be the reason that a rise in HbA1c is seen in study P035, while a generally stable response was seen in the previously submitted studies P020 and P024, when sitagliptin was added to metformin. However, response to the total treatment regimen is also important, and the CHMP still considered that total efficacy is modest in this patient population. Although the efficacy of addition of sitagliptin to SU of Sitagliptin is modest, the CHMP is of the opinion that there might be patients who can benefit of the combination SU+sitagliptin. Therefore, the CHMP concluded that the combination treatment of Sitagliptin + SU could be approved, but for a restricted population: "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".

With regards to the triple combination therapy the MAH provided also a detailed rationale in support of using the placebo-corrected change from baseline in HbA_{1c}, rather than the within-group change in this parameter, to characterise extent of efficacy and efficacy response over time. Placebo-corrected HbA1c change from baseline was approximately 0.9% at week 24 for stratum 2 with an important potential benefit with regard to the long-term risk of diabetes complications based on the results of the UKPDS study. The placebo-subtracted difference in change from baseline in HbA_{1c} continues to decrease after 12 weeks, reaching a nadir around Week 18, with a minimal rise in placebo-subtracted HbA_{1c} change from baseline from Week 18 through Week 24. These results support the durability of sitagliptin as add-on to SU + Metformin over the 24-week treatment period. The CHMP concluded that the efficacy was better established in the triple combination therapy than when sitagliptin was added-on to SU only, although this could be related to the study population. Therefore the indication "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" was considered acceptable by the CHMP.

As a follow-up the CHMP requested the MAH to study the long-term effects of this combination. Therefore the MAH commits "to submit a plan to evaluate the durability of efficacy for the concomitant use of sitagliptin with SUs. This proposal could potentially include the large cardiovascular outcome study currently being planned." The MAH will submit their proposal in January 2008.

2.1.4. Conclusion on efficacy

It has been shown that the addition of sitagliptin to glimepiride alone or in combination with metformin, results in a significant reduction in HbA1c compared to placebo. Comparison with an active control, in particular metformin, is lacking. Discussion focused on the size and durability of the effect. The size of the effect is considered moderate, in particular when combined with glimepiride alone. Assessment of durability is impacted by a number of factors beyond the glycaemic efficacy of sitagliptin, but the placebo-subtracted response is still significant after 24 weeks.

3. Clinical safety

In the entire cohort for Study P035 clinical adverse experiences were reported for 59.5% (132 patients) in the sitagliptin treatment group and 47.0% (103 patients) in the placebo treatment group who received at least one dose of double-blind study medication. The higher incidence of adverse experiences overall appeared to be related to small differences in a range of specific adverse experiences—without a discernible pattern—and to a notable difference in the specific adverse experience of hypoglycaemia.

In the entire cohort, a total of 31 patients had one or more events of hypoglycaemia: 27 (12.2%) in the sitagliptin group and 4 (1.8%) in the placebo group ($p<0.001$ for between-group difference in proportions). There were 55 events of hypoglycaemia in the sitagliptin group, and 20 events of hypoglycaemia in the placebo group. The incidence of patients having hypoglycaemic events with sitagliptin treatment was higher in Stratum 2 than in Stratum 1. In Stratum 1, 7.5% (8 patients) and 2.8% (3 patients) in the sitagliptin and placebo groups, respectively, had one or more events of hypoglycaemia; the between-group difference was not statistically significant. In Stratum 2, 16.4% (19 patients) and 0.9% (1 patient) in the sitagliptin and placebo groups , respectively, had one or more hypoglycaemic events ($p<0.001$ for between-group difference). None of the hypoglycaemia episodes met criteria for marked severity or required medical attention, and no patients were discontinued due to hypoglycaemia. Although, the increased hypoglycaemia rate may, at least partially, be explained by the improved glycaemic control, data on another DPP-IV inhibitor suggest that this effect is dose-dependent. The higher incidence of hypoglyacemia in Stratum 2 (glimepiride and metformin) than in the Stratum 1 (glimepiride alone) of the current study is consistent with the observation that the former group of patients had better glycaemic control (HbA1c-lowering) with SITA than the latter group of patients.

Other than the higher incidence of hypoglycaemia, the incidence of drug-related adverse experiences was low, with no more than 2 patients (0.9%) reported to have any specific drug-related adverse experience in the sitagliptin group. No meaningful differences were observed for the sitagliptin compared to the placebo group in incidence of serious adverse experiences, adverse experiences leading to discontinuation (due to non-serious or serious adverse experiences), or other summary measures of clinical adverse experiences analysed.
In the entire cohort, adverse experiences by SOC (System Organ Class) were reported most frequently for Gastrointestinal Disorders, Infections and Infestations, Metabolism and Nutrition Disorders, Musculoskeletal and Connective Tissue Disorders, Nervous System Disorders, and Respiratory, Thoracic and Mediastinal Disorders.

As already observed in the dossier of the initial MAA, SITA was associated with a higher incidence of patients suffering AEs (adverse events) in the system organ classes (SOCs) "infections and infestations, musculoskeletal and connective tissue disorders, and nervous system disorders". In P035, when sitagliptin was added to the regimen of patients inadequately controlled on a sulphonylurea, there was also an increased incidence of patients suffering AEs in the SOCs "metabolism and nutrition disorders" due to an increased incidence of hypoglycaemia. A similar pattern as for SITA associated

AEs applied to drug-related AEs in the "metabolism and nutrition disorders" SOC (i.e. more patients with drug-related hypoglycaemia in the SITA group), and a trend for more patients with drug-related AEs was also observed in the "musculoskeletal and connective tissue disorders" SOC. Adverse reactions within the "infections and infestations, musculoskeletal and connective tissue disorders, and nervous system disorders" SOCs are currently the subject of further pharmacovigilance follow-up measures (e. g. risk management plan).

The incidence of laboratory adverse experiences was comparable in the SITA and placebo groups.
A statistically significant weight increase (mean 1.1 kg) relative to placebo was observed with SITA treatment in the entire cohort and in each stratum. Therefore, SITA given in combination with a SU may not be as weight neutral as in combination with e.g. metformin but the gain in body weight may also be related to the improvement in glycaemic control.

Noteworthy, patients in the SITA group had a higher prevalence in secondary diagnoses than the placebo group (i.e. a numerically higher frequency was present in 20 of 25 SOCs). In the 4 SOCs in which the incidence of AEs within that SOC was higher (with 95% CI for the between-treatment group difference not including "0") in the SITA relative to the placebo group (i. e. SOCs "infections and infestations, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, nervous system disorders"), a higher prevalence of medical history secondary diagnoses was also present in the SITA group.

3.1. Conclusion on safety

In general, sitagliptin was well tolerated. More events of hypoglycaemia were seen when sitagliptin was added to SU but they were generally of mild severity and only few patients needed a reduction in SU dose.

4. SPC and PL

Further to the new indications, the SPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 have been updated. Sections 1, 2 and 4 of the PL have been updated accordingly.

5. Risk Management Plan

Within this type II variation the MAH provided a justification that there was no need for a revised Risk Management Plan. This was considered acceptable for the CHMP as no new safety issues were identified and the current version (version 1.1) of the Risk Management Plan adequately addresses the risks related to the dual combination therapy of SITA+SU and the triple combination therapy of SITA+MET+SU.

6. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The benefit of addition of sitagliptin to SU or to SU+MET in terms of reduction of HbA1c is considered modest. However, there are patients who can benefit of the combination treatment and safety is considered acceptable.
The CHMP is therefore of the opinion that the benefit-risk is positive for a second line dual combination therapy of SITA + SU when patients have not responded to a maximal tolerated dose of sulfonylurea and when metformin is inappropriate and for a triple combination therapy of SITA +MET+SU:

- 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.