European Medicines Agency

London, 23 July 2009
EMEA/517855/2009

ASSESSMENT REPORT
FOR
Xelevia

International Nonproprietary Name:
Sitagliptin

Procedure No. EMEA/H/C/762/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 is an orally active, potent, selective inhibitor of the enzyme dipeptidyl peptidase IV (DPP-4) and the first of a new therapeutic class of drugs intended to treat patients with 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. Sitagliptin was approved for marketing in the EU in 2007 and currently has therapeutic indications for second line use in combination with metformin, a PPAR-γ agonist (alone or in combination with metformin), or a sulfonylurea (alone or in combination with metformin).

The present variation was filed to seek the indication for the use of sitagliptin as monotherapy in patients with T2DM. Initially, the Marketing Authorisation Holder (MAH) proposed to amend the indication as follows: "For patients with type 2 diabetes mellitus, Xelevia is indicated to improve glycaemic control when diet and exercise alone do not provide adequate glycaemic control".

In support of the current variation application results were presented from study P049, a phase III, multicenter, double-blind, randomised study to evaluate the safety and efficacy of MK-0431 (sitagliptin) compared with metformin in patients with type 2 diabetes with inadequate glycaemic control.

Furthermore, the MAH proposed an additional modification to the currently approved indications (i.e., in the dual combination therapy with a SU deletion of "…when metformin is inappropriate due to contraindications or intolerance").

The MAH also proposed changes to sections 4.2, 4.8, and 5.1 of the SPC in order to reflect the results of the mentioned study.

2. Non-Clinical aspects

Environmental risk assessment (ERA)

The ERA submitted in the dossier for the current type II variation is an updated version of the ERA submitted by the MAH in the dossier of the initial application for Xelevia.

In Phase I the MAH calculated a $PEC_{surfacewater}$ of 0.5 µg/L under the assumption of a Fpen of 1%, which is above the trigger of 0.01 µg/L. Asthe $PEC_{surface\ water}$ is still 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. There is no indication of a bioaccumulation potential. The K_{oc} is less than 10,000 ($logK_{oc}$ = 2.88), and 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. According to these results the submission of a sediment toxicity test deemed necessary. The MAH provided the results of a sediment toxicity test according OECD 218.

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 "the results suggested that the drug substance is not toxic to sediment organisms".

The MAH was requested by the CHMP to submit a valid algae growth inhibition test (OECD 201). The MAH already committed in a previous variation procedure to provide the results of such test by July 2009.

3. Clinical aspects

3.1 Clinical efficacy

A) Main study/Methods

In support of this variation application results of one Phase III trial were submitted. Study P049 was a multicenter, double-blind, randomised, parallel-group Phase III non-inferiority study to compare the efficacy of 100 mg/d of sitagliptin with 2000 mg/d of metformin in patients with T2DM who had inadequate glycaemic control on diet and exercise alone. The study duration was 24 weeks.

Objectives

The primary objective was to demonstrate non-inferior efficacy of sitagliptin compared to metformin and to show that sitagliptin is well tolerated. The secondary objective was to show that the incidence of gastrointestinal adverse events is lower with sitagliptin than with metformin.

Patient population

Patients with T2DM who were drug-naïve or had not been treated with any antidiabetic medication for at least 4 months prior to screening were eligible. Male and female patients who were ≥18 and ≤78 years old with inadequate glycaemic control (HbA_{1c} ≥6.5% and ≤9.0%) on diet and exercise therapy alone were randomised in a 1:1 ratio to receive either sitagliptin 100 mg or metformin. 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) were excluded from participation.

Treatments

The dosing regimen for metformin included a dose titration starting at 500 mg q.d., increasing by 500 mg increments (approximately weekly) until the maximum daily dose of 1000 mg b.i.d. was achieved within 5 weeks. Patients were to remain on 1000 mg b.i.d. for the remainder of this 24-week study. Down titration was permitted for intolerance to a minimum allowed dose of 1000 mg/d. If after 6 weeks a patient was unable to tolerate at least 1000 mg of metformin daily, he/she had to be withdrawn from the study. During the active treatment period, patients not meeting progressively stricter glycaemic goals were provided glycaemic rescue therapy (glyburide [glibenclamide]) until study completion.

Concurrent lipid-lowering and antihypertensive medications as well as thyroid hormone and hormone replacement therapy had to be stable during the double-blind phase.

Endpoints and statistical analysis plan

The primary efficacy endpoint was the change from baseline in HbA_{1c}. A non-inferiority margin of 0.4% was pre-specified. Other endpoints/objectives included fasting plasma glucose (FPG), the proportion of patients meeting glycaemic goals, and insulin, proinsulin, 1,5-anhydroglucitol, and lipid levels.

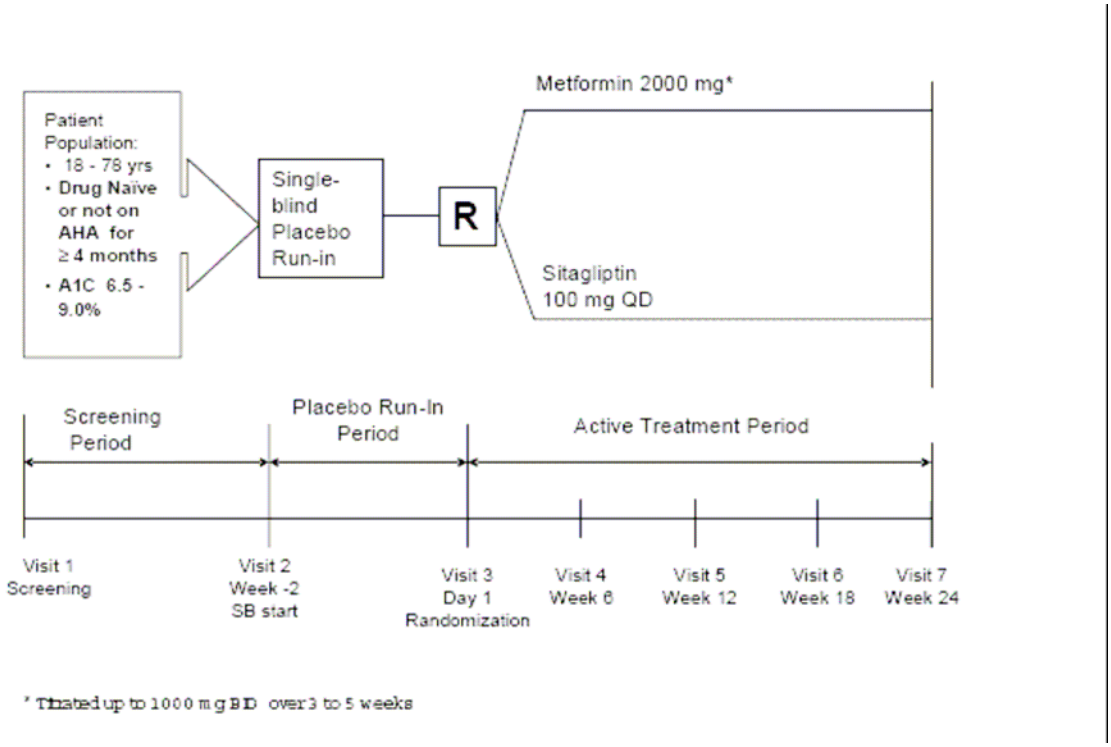
The primary analysis used the Per-Protocol (PP) population based upon international regulatory guidance regarding the primary analysis population for non-inferiority studies. For analysis of change or percent change from baseline at Week 24, the PP population required that a patient had measurements both at baseline and at Week 24 and did not have any major protocol violations. Protocol violators were identified prior to unblinding the data and excluded from the PP population. The baseline for efficacy analyses was defined as the Visit 3/Week 0/Day 1 (randomisation) measurement. The metformin treatment group was analyzed as a single group regardless of the actual dose taken. For HbA1c and FPG at Week 24, the full analysis set (FAS) population was used as a secondary analysis population. The FAS population consisted of all patients randomised who received at least one study dose, had a baseline measurement, and had at least one post-baseline measurement. The primary approach to handling missing data in the FAS population was the LOCF method.

To address the primary hypothesis, the mean change from baseline in HbA1c at Week 24 in the sitagliptin group was compared with that in the metformin group using the least-squares (LS) means of the two treatment groups as estimated via analysis of covariance (ANCOVA). The ANCOVA model included terms for treatment and baseline HbA1c value. Due to the large number of study centers and the small numbers of patients at each center, study center was not included as a factor in the analysis model.

The primary non-inferiority comparison of sitagliptin to metformin used a non-inferiority margin of 0.4%. Non-inferiority was to have been declared if the upper boundary of the 95% confidence interval of the treatment effect (sitagliptin minus metformin) was less than 0.4% in terms of HbA1c. An analysis of the proportion of individuals whose HbA1c values met glycaemic goals (<6.5% as primary; <7.0% as secondary) at Week 24 was conducted in both the PP and the FAS populations, using a logistic regression model to compare the sitagliptin group to the metformin group.

A schematic view of the study design is presented in Figure 1.

FIGURE 1: STUDY DESIGN P049



The CHMP was of the view that, in general, the design of the study is acceptable. However, the predefined non-inferiority margin of 0.4% is considered excessively large. Usually, the delta for non-inferiority is chosen on the basis of the difference in effect compared with placebo. The expected placebo-adjusted effect in this group of patients with relative low HbA1c (6.5-9) is < 0.8 % as this was the difference seen in study P021 (monotherapy) in patients with a mean baseline HbA1c of 8. In fact, mean baseline HbA1c was even lower, i.e. 7.2%, in study P049. Therefore, a lower margin would have been preferred. Furthermore, it is agreed that it was not useful to include study centre as a factor in the analysis.

Good Clinical Practice (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 2092 patients were screened, and 1034 patients were excluded. The most common reason for not being randomized was for the patient not meeting HbA1c inclusion criterion.

A total of 1058 patients participated in the study at 113 sites worldwide. One study site was identified as non-compliant with some of the requirements of GCP; for this reason, data from the 8 patients randomised at this site were deemed unreliable and were removed from all analyses (efficacy and safety).

Of the 1050 patients randomised, 917 patients completed the study. Reasons for discontinuation were generally similar between treatment groups (Table 1). Slightly more patients in the sitagliptin group (N=10, 1.9%) than in the metformin group (N=3, 0.6%) discontinued due to lack of efficacy which included patients not meeting the progressively stricter protocol-specified glycaemic criteria and/or not meeting the investigator's expectations of glycaemic improvement. More patients in the metformin group (N=19, 3.6%) than in the sitagliptin group (N=9, 1.7%) discontinued due to an adverse experience. Only one patient in the metformin group was prematurely unblinded due to an AE of increased liver enzymes.

The study report states that compliance to study drug exceeded 98% in both treatment groups.

TABLE 1: DISPOSITION OF PATIENTS

	Sitagliptin		Metformin		Total	
	n	(%)	n	(%)	n	(%)
Not Randomised					1,034	
Patients in population	532		526		1,058	
Study Disposition						
Completed	468	(88.0)	449	(85.4)	917	(86.7)
Discontinued	64	(12.0)	77	(14.6)	141	(13.3)
Adverse event	9	(1.7)	19	(3.6)	28	(2.6)
Deviation from protocol	14	(2.6)	15	(2.9)	29	(2.7)
Other	1	(0.2)	1	(0.2)	2	(0.2)
Lack of efficacy‡	10	(1.9)	3	(0.6)	13	(1.2)
Lost to follow-up	10	(1.9)	14	(2.7)	24	(2.3)
Physician decision	1	(0.2)	2	(0.4)	3	(0.3)
Trial terminated†	1	(0.2)	0	(0.0)	1	(0.1)
Withdrew consent	18	(3.4)	23	(4.4)	41	(3.9)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record. † Defined as Site Closed
‡ Includes patients not meeting the progressively stricter protocol-specified glycaemic criteria for discontinuation and /or not meeting the investigator's requirements of glycaemic improvement.

Randomised patients that were included in the per-protocol population and the full-analysis-set (FAS) population for the Week 24 analysis of change from baseline in HbA1c are presented in Table 2.

TABLE 2: PATIENT ACCOUNTING FOR THE ANALYSIS OF HBA1C AT WEEK 24

	Number (%)		
	Sitagliptin	Metformin	Total
Total Randomised	528	522	1050
Included in PP Analysis	455 (86.2)	439 (84.1)	894 (85.1)
Included in FAS Analysis	512 (97.0)	498 (95.4)	1010 (96.2)
Excluded from PP Analysis	73 (13.8)	83 (15.9)	156 (14.9)
No Treatment Data at Week 24	72 (13.6)	79 (15.1)	151 (14.4)
Major Protocol Violators	4 (0.8)	7 (1.3)	11 (1.0)
Drug Compliance <85%	4 (0.8)	7 (1.3)	11 (1.0)
Excluded from FAS Analysis	16 (3.0)	24 (4.6)	40 (3.8)
No On-Treatment Data	16 (3.0)	24 (4.6)	40 (3.8)
PP: Per Protocol.			
FAS: Full Analysis Set.			

Similar proportions of patients completed the study according to protocol and were included in the primary efficacy analysis, i.e. 86.2% and 84.1% in the sitagliptin and metformin group, respectively.

The mean age of the randomised population was 56.0 years, 46.1% were males, mean duration of diabetes was 2.4 years, and the mean baseline HbA_{1c} was 7.2%. At study entry all patients had to be on diet and exercise therapy without any antidiabetic therapy for at least four months as specified in the protocol. Thirty (30; 5.7%) and 26 (5.0%) patients in the sitagliptin and metformin group, respectively, were previously treated with an antidiabetic drug. In most cases metformin was used (3.5% in both groups). Of the randomised patients, 41.8% had baseline HbA_{1c} values <7.0% and 17.2% had baseline HbA_{1c} values ≥8.0%. The most common specific secondary diagnoses were hypertension, hyperlipidaemia and dyslipidaemia.

Slightly more patients in the sitagliptin group discontinued due to lack of efficacy, while more patients in the metformin group discontinued due to an adverse experience. There were no significant differences between groups with respect to baseline demographic and anthropometric characteristics. About 5% of patients were previously treated with antidiabetic agents, in most cases with metformin. Some patients must have received combination treatment, as the sum of percentages of individual drugs was higher than the total percentage. Seeing the mean diabetes duration of 2.4 years and the range it is surprising that only 5% of patients were pretreated, or that a patient was not treated for up to 30 years. On the other hand, HbA1c in this group of patients was rather low (7.2%) at baseline. This stresses the importance of a well chosen delta even more.

B.2. HbA1c reduction (primary endpoint)

Table 3 and Figure 2 show results of the primary efficacy analysis. Reductions in HbA_{1c} at Week 24 were observed in both treatment groups. The criterion for declaring sitagliptin non-inferior to metformin in the test of the primary hypothesis was met: the upper limit of the two-sided 95% CI for the mean difference between sitagliptin and metformin, 0.21%, was less than the prespecified non-inferiority margin of 0.40%.

Two additional supportive analyses conducted in the FAS population were also consistent with the primary analysis: ANCOVA (Table 4 and Figure 3) and the repeated measures analysis (Table 5), which were used as supplementary approaches to handle missing data.

TABLE 3: ANALYSIS OF CHANGE FROM BASELINE IN HBA1C (%) AT WEEK 24 (PER-PROTOCOL POPULATION)

Treatment	N	Baseline Mean (SD)	Week 24 Mean (SD)	Change From Baseline at Week 24	
				Mean (SE)	LS Mean (95% CI)†
Sitagliptin	455	7.22 (0.73)	6.80 (0.71)	-0.42 (0.03)	-0.43 (-0.48, -0.38)
Metformin	439	7.25 (0.69)	6.68 (0.62)	-0.57 (0.03)	-0.57 (-0.62, -0.51)
Estimated Difference				Difference in LS Means (95% CI)	
Sitagliptin vs. Metformin				0.14 (0.06, 0.21)‡	
Root Mean Square Error of Change =0.57					

† Based on analysis of covariance with terms for treatment and baseline HbA_{1c} as a covariate.
‡ Non-inferior based upon prespecified non-inferiority upper bound of 0.4.

FIGURE 2: CHANGE FROM BASELINE IN HBA1C (%) OVER TIME (LS MEAN ± SE) BY TREATMENT GROUP (PER-PROTOCOL POPULATION)

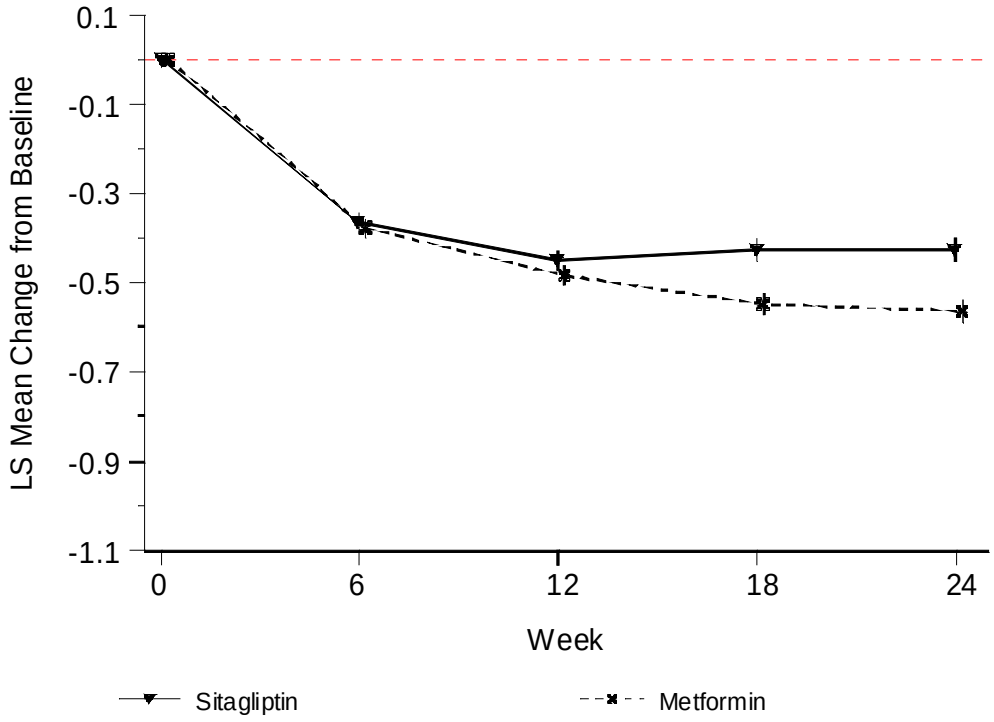


TABLE 4: ANALYSIS OF CHANGE FROM BASELINE IN HBA1C (%) AT WEEK 24 (FULL ANALYSIS SET)

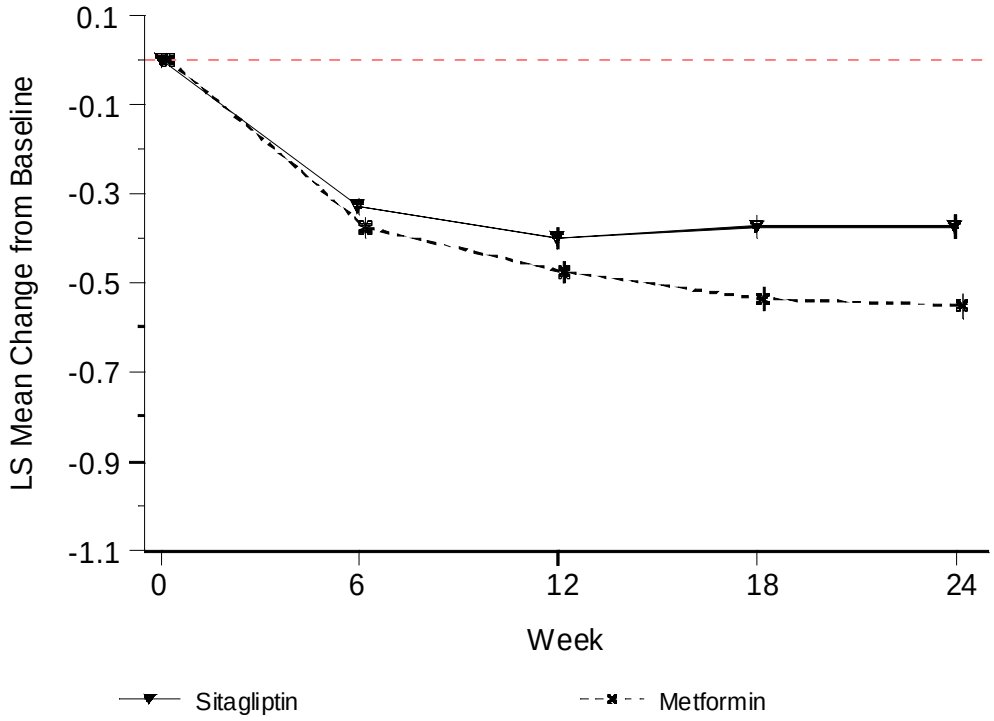
Treatment	N	Baseline Mean (SD)	Week 24 Mean (SD)	Change From Baseline at Week 24	
				Mean (SE)	LS Mean (95% CI)†
Sitagliptin	512	7.25 (0.75)	6.87 (0.84)	-0.37 (0.03)	-0.38 (-0.43, -0.32)
Metformin	498	7.25 (0.69)	6.70 (0.65)	-0.55 (0.03)	-0.55 (-0.61, -0.50)
Estimated Difference				Difference in LS Means (95% CI)	
Sitagliptin vs. Metformin				0.18 (0.10, 0.25)‡	
Root Mean Square Error of Change =0.62					

† Based on analysis of covariance with terms for treatment and baseline HbA_{1c} as a covariate.
‡ Non-inferior based upon prespecified non-inferiority upper bound of 0.4.

TABLE 5: REPEATED MEASURES ANALYSIS OF CHANGE FROM BASELINE IN HBA1C (%) (FULL ANALYSIS SET)

Treatment Group	N†	Change from Baseline at Week 24
		LS Mean (95% CI)
Sitagliptin	513	-0.39 (-0.44, -0.33)
Metformin	504	-0.56 (-0.61, -0.50)
Estimated Difference		Difference in LS Means (95% CI) at Week 24
Sitagliptin vs. Metformin		0.17 (0.09, 0.25)
† Number of patients included in the analysis.		

FIGURE 3: CHANGE FROM BASELINE IN HBA1C (%) OVER TIME (LS MEAN ± SE) BY TREATMENT GROUP (FULL ANALYSIS SET)



B.3. HbA1c goals

Proportions of patients with Week 24 HbA1c values below 6.5% (primary) and 7.0 % (secondary) in the PP population are shown in Table 6 and Table 7. Slightly greater proportions of patients in the metformin group relative to the sitagliptin group had an HbA_{1c} <6.5% and <7.0% at Week 24. Results were similar in the FAS population.

TABLE 6: PROPORTION OF PATIENTS WITH HBA_{1C} VALUE <6.5% AT WEEK 24 (PER-PROTOCOL POPULATION)

Treatment	N	Week 24 n (%)	
Sitagliptin	455	153 (33.6)	
Metformin	439	172 (39.2)	
Between Treatment Comparison	Difference in Proportion (%) (95% CI[†]) at Week 24	Relative Risk (95% CI)	Odds-Ratio[‡] (95% CI)
Sitagliptin vs. Metformin	-5.6 (-11.8, 0.8)	0.86 (0.72, 1.02)	0.69 (0.51, 0.93)

[†] Computed using the Wilson score method.
[‡] From the logistic regression model adjusting for baseline HbA_{1c}.

TABLE 7: PROPORTION OF PATIENTS WITH HBA_{1C} VALUE <7.0% AT WEEK 24 (PER-PROTOCOL POPULATION)

Treatment	N	Week 24 n (%)	
Sitagliptin	455	313 (68.8)	
Metformin	439	333 (75.9)	
Between Treatment Comparison	Difference in Proportion (%) (95% CI[†]) at Week 24	Relative Risk (95% CI)	Odds-Ratio[‡] (95% CI)
Sitagliptin vs. Metformin	-7.1 (-12.9, -1.2)	0.91 (0.84, 0.98)	0.59 (0.41, 0.83)

[†] Computed using the Wilson score method.
[‡] From the logistic regression model adjusting for baseline HbA_{1c}.

The primary and secondary efficacy results and the drop out rates due to lack of efficacy suggest that sitagliptin is less effective than metformin. The difference in HbA1c reduction between sitagliptin and metformin was 0.14 (0.06, 0.21 at 24 weeks with differences increasing over time. In the light of the overall small treatment effect, i.e. HbA1c decrease from baseline of 0.43% and 0.57% in the sitagliptin and metformin group, respectively, the chosen non-inferiority margin of 0.40% is considered too generous and the observed treatment differences cannot easily be interpreted. Proportion of patients with HbA_{1c} value <6.5% and < 7.0% at week 24 was also less (33.6 vs. 39.2% and 68.8 vs. 75.9%, respectively).

The inclusion primarily of patients with a rather low baseline HbA1c (mean 7.2%) limits the generalizability of the study results. About 50% of the screened patients were considered non-eligible mainly due to HbA1c values out of inclusion range. . Patients with higher HbA1c levels could have easily been included in this active-controlled trial.

According to the study report, 96.4% of patients in the metformin group of the PP population reached the maximum protocol-specified total daily dose of metformin of 2000 mg during the course of the study and approximately 88% were taking this dose at Week 24. This is considered adequate for a valid comparison of efficacy.

Since the difference in HbA1c appeared to widen over time, 12 month comparative monotherapy data as previously submitted for other antidiabetic agents seeking monotherapy indications would have been useful.

The assumption that sitagliptin is less effective than metformin is further supported by results from a previous study, P036, although it should be mentioned that the direct comparison of sitagliptin and metformin was not the objective of this study.
P036, was a double-blind factorial study of the co-administration of sitagliptin (MK-0431) and metformin in patients with Type 2 Diabetes Mellitus who have inadequate glycaemic control. This study has already been assessed during the evaluation for the initial Marketing Authorisation of the product. Table 8 and Figure 4 present a summary of the efficacy results suggesting that in this T2DM population - with a mean baseline HbA1c of 8.7% - sitagliptin 100 qd was similarly effective as metformin 500 mg bid but less effective than metformin 1000 mg bid.

TABLE 8:

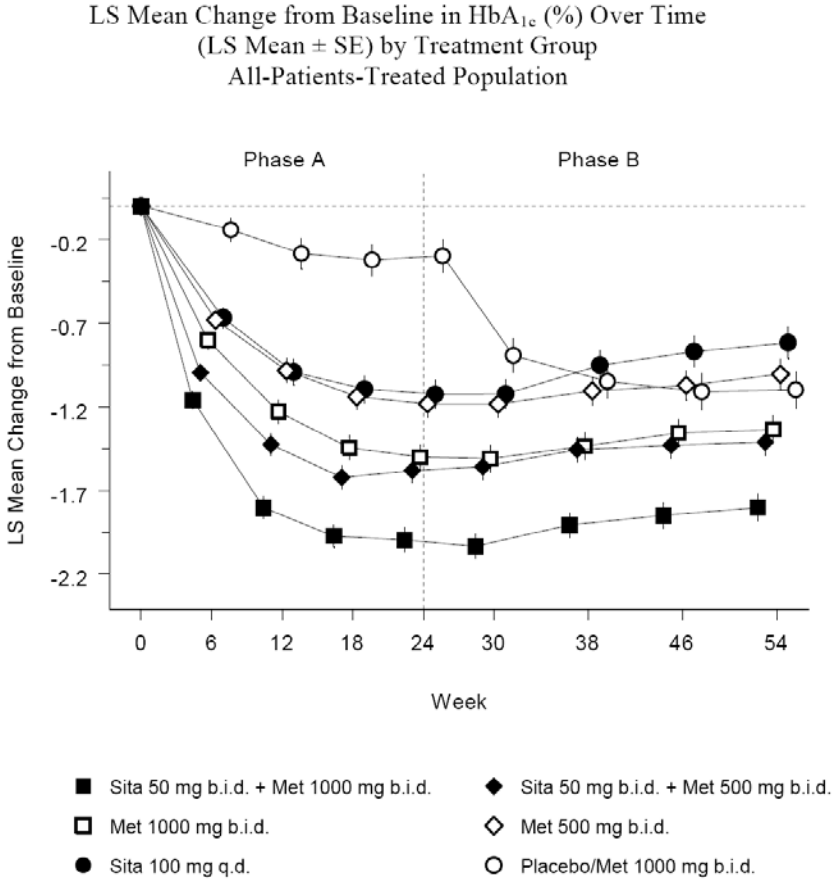
Least Squares Means for Change from Baseline at Week 54 with 95% CI
All-Patients-Treated Population

	HbA_{1c} (%)		FPG (mg/dL)	
Treatment Group	LS mean (SE)	95% CI for LS mean	LS mean (SE)	95% CI for LS mean
Sita 100 mg q.d.	-0.82 (0.10)	(-1.00, -0.63)	-16.0 (3.7)	(-23.2, -8.7)
Met 500 mg b.i.d.	-1.01 (0.09)	(-1.18, -0.83)	-29.0 (3.5)	(-35.9, -22.2)
Met 1000 mg b.i.d.	-1.34 (0.08)	(-1.50, -1.17)	-39.6 (3.3)	(-46.0, -33.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	-1.41 (0.08)	(-1.57, -1.25)	-42.5 (3.1)	(-48.6, -36.3)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	-1.80 (0.08)	(-1.96, -1.65)	-55.6 (3.1)	(-61.6, -49.6)
Placebo/Met 1000 mg b.i.d.	-1.10 (0.11)	(-1.32, -0.88)	-43.9 (4.3)	(-52.3, -35.5)

HbA_{1c} Comparing Co-administration with Individual Components	Difference in LS means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-0.41 (-0.64, -0.17)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.60 (-0.84, -0.35)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-0.47 (-0.69, -0.24)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-0.99 (-1.23, -0.74)

FPG Comparing Co-administration with Individual Components	Difference in LS means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-13.4 (-22.6, -4.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-26.5 (-36.0, -17.0)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-16.0 (-24.8, -7.2)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-39.6 (-49.1, -30.2)

FIGURE 4:



B.3. Subgroup analyses

Between-group treatment differences were generally consistent across subgroups defined by gender, race, ethnicity, baseline $HbA_{1c,}$ age, BMI, duration of diabetes and region. Between-group treatment estimates in each prespecified subgroup centered around the overall between-group treatment difference with overlapping 95% confidence intervals.

An effect of baseline HbA_{1c} level was observed within each treatment group. As baseline HbA_{1c} level increased, the (Least Squares) LS mean reduction from baseline increased for both treatment groups. LS Mean change from baseline was -0.19 (-0.27, -0.11) and -0.26 (-0.34, -0.17), respectively, for sitagliptin and metformin groups with baseline HbA1c <7.0%; -0.39 (-0.48, -0.31) and -0.61 (-0.70, -0.53) for sitagliptin and metformin groups with baseline HbA1c between 7.0% and 8.0%; -1.13 (-0.26, -0.99) and -1.24 (-1.38, -1.11) for sitagliptin and metformin groups with baseline HbA1c ≥ 8.0%.

The CHMP was of the view that data again suggest that sitagliptin is less effective than metformin.

B.4. Fasting Plasma glucose

With regards to the results of fasting plasma glucose (FPG) for the PP population at week 24, both treatment groups exhibited similar trends, beginning with a drop in the first 6 weeks followed by stable levels for the remainder of the study. Treatment with metformin resulted in a larger reduction in FPG relative to treatment with sitagliptin. The ANCOVA analysis conducted on the FAS population showed a similar trend as seen in the PP analysis.

B.5. Other efficacy parameters

Results on other efficacy parameters such as fasting insulin, proinsulin, HOMA-β, HOMA-IR and lipid panel were consistent with the findings described above, with sitagliptin slightly but not significantly less effective compared to metformin.

C) Discussion on clinical efficacy

Although the results from study P049 meet the predefined criterion for non-inferiority, all data, including data on HbA1c, responder rates, FPG and drop out rate due to lack of efficacy, do not unequivocally demonstrate non-inferior efficacy. In addition, there is some evidence from the previous study P036 that sitagliptin 100 mg/d is less effective than metformin 1000 mg bid.

Importantly, the inclusion of primarily patients with a rather low baseline HbA1c (mean 7.2%) artificially increases the probability of finding non-inferiority, because this will lead to smaller possible HbA1c reductions. Thus, patients with higher HbA1c levels should have been included to improve the assay sensitivity of this study. This would also increase the generalisability of the findings.

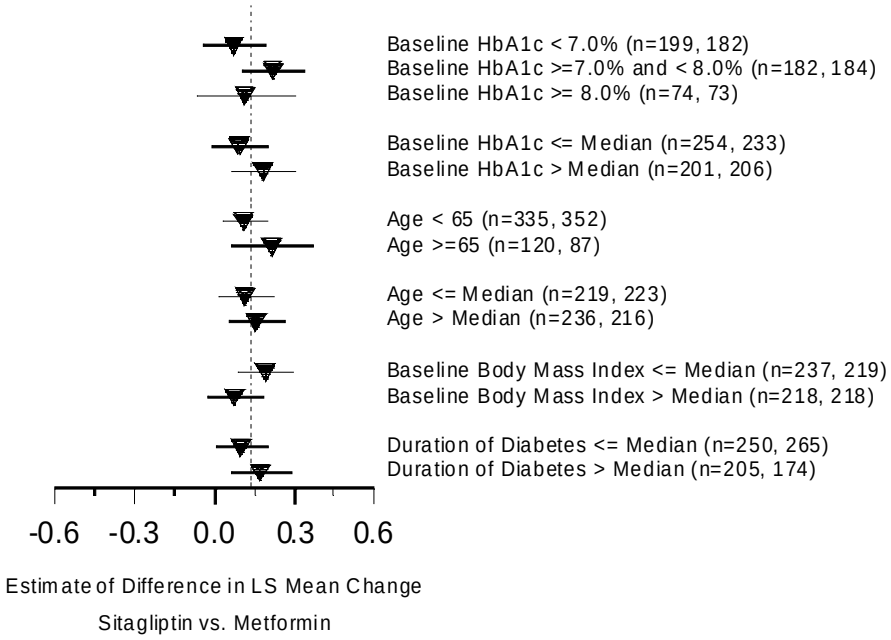
Consequently, the CHMP was of the opinion that although the upper margin of the 95% confidence interval is below 0.40 %, the results do not convincingly show that sitagliptin is non-inferior to metformin. In addition, the differences between sitagliptin and metformin appear to widen over time and 12-month comparative data would have been preferable to demonstrate maintenance of effect. Comparative data with alternatives for metformin, such as SUs, are not available for the monotherapy indication and in combination treatment with metformin non-inferior efficacy of sitagliptin compared to SU was not unequivocally proven. This was considered as a major objection.

In their response to this CHMP major objection, the MAH stated that the treatment difference in change in HbA1c between sitagliptin and metformin was similar in patients with rather low baseline HbA1c and patients with higher baseline HbA1c levels. However, the data presented suggests that the difference was greater in the group with HbA1c levels between 7.0 and 8.0%.

Based on these data the design of the study with the non-inferiority margin of 0.4%, and thus of about the same size as the observed mean sitagliptin effect (-0.43% in HbA1c from baseline), is questionable. The sensitivity of the study to demonstrate non-inferiority is questioned.

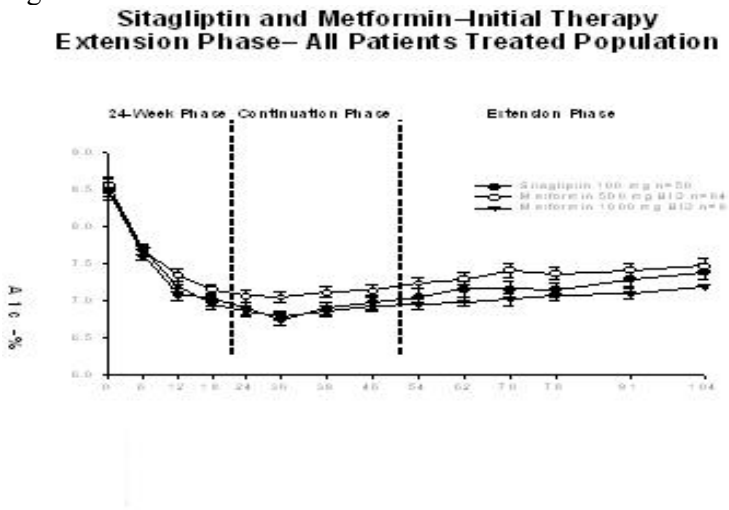
On the other hand, the HbA1c subgroup analysis revealed that the HbA1c reduction was larger with increasing baseline HbA1c values in both treatment groups as is usually observed with other glucose-lowering agents. In addition, the upper margin of the 95% CI of the treatment difference for the subgroup with baseline HbA1c > 8% was 0.3%, which provides sufficient confidence that sitagliptin is able to appropriately reduce blood glucose levels also in patients with higher baseline HbA1c.

FIGURE 5: Difference in HbA_{1c} (%) mean change from baseline at week 24 by subgroup factors (baseline HbA_{1c}, age, BMI and duration of diabetes) point estimate and 95% confidence interval sitagliptin versus metformin (per-protocol population).



As mentioned above, the CHMP noted that the difference in HbA1c appeared to widen over time, and was of the view that 12-month comparative monotherapy data would have been informative. Study P049 did not have an extension phase. However, the MAH argued that comparative data out to 2 years are available from study P036. In that study, initial therapy with the combination of sitagliptin and metformin was compared to treatment with placebo, metformin alone, and sitagliptin alone. The primary efficacy endpoint of the study was at 24 weeks. After 24 weeks, eligible patients entered a continuation phase to 54 weeks and, at 54 weeks, eligible patients remained blinded and entered an extension phase for a total of 104 weeks of study. Increasingly stricter glycaemic rescue criteria were implemented to avoid prolonged exposure to hyperglycaemia. As depicted below, for those patients in the monotherapy treatment groups who entered the extension phase (Figure 6), efficacy was maintained through 104 weeks in both the sitagliptin and metformin arms of the study, with little apparent difference in the treatment effect between the 2 medications.

Figure 6



The MAH acknowledged that metformin is the first-line agent in the treatment of T2DM. Noting the small but statistically significant between-group difference in favour of metformin in study P049, the MAH proposed a restricted monotherapy indication for sitagliptin, i.e. in patients for whom metformin is not an option due to either contraindication or intolerance.

3.2 Clinical safety

The safety analyses used the All-Patients-as-Treated (APaT) population. The APaT population included all randomised patients who received at least 1 dose of the double-blind study therapy. The metformin treatment group was analyzed as a single group regardless of the actual dose taken.

Safety and tolerability were assessed by a review of all safety parameters including adverse experiences, laboratory safety parameters, body weight and vital signs. A tiered approach was used for the analysis of safety parameters. Tier 1 adverse experiences were pre-specified and included hypoglycaemia and selected gastrointestinal (GI) events (abdominal pain [including abdominal discomfort], diarrhoea, nausea and vomiting). Inferential p-values were obtained from analyses of Tier 1 clinical adverse experiences. Comparisons of proportions of patients were performed using Fisher's exact test and confidence intervals for the between-group differences used the Wilson score method. For adverse experiences not in Tier 1 and predefined limits of change (PDLC) in laboratory variables, summary tabulations and 95% confidence intervals for between-group differences were calculated for events in Tier 2, defined as having an incidence of 1% or more in at least one treatment group; otherwise (i.e., Tier 3), only summary tabulations were generated. For monitoring the profile of continuous laboratory parameters, body weight and vital signs, summary tabulations of descriptive statistics and mean change from baseline plots over time were provided.

The secondary safety hypothesis comparing the incidence of selected GI adverse experiences between treatment groups was tested using an ordering of the GI adverse experiences. To limit the inflation of the trial-wise Type I error, a prespecified multiplicity adjustment was conducted with sitagliptin compared with metformin as follows: (1) diarrhoea compared and if significant, (2) nausea compared and if significant, (3) abdominal pain (including abdominal discomfort) compared and if significant, (4) vomiting compared. The individual tests were conducted at the two-sided 0.05 (or 0.025) level using Fisher's exact test if the primary efficacy hypothesis of non-inferiority was met (or not met).

A) Patient exposure

The mean duration of exposure was generally similar between the treatment groups. The mean duration of patient exposure to sitagliptin 100 mg was 155.7 days. For the metformin group (cumulative, on any dose to which the patient was exposed) the mean duration of patient exposure was 151.6 days.

Dose of metformin

For patients randomised to treatment with metformin, the starting dose was 500 mg/day, administered once-daily in the morning. The dose of metformin was to have been up-titrated to a maximum dose of 2000 mg/per day (administered as 1000 mg twice-daily) over the initial 5 weeks of the double-blind treatment period. The mean dose of metformin after Visit 4/Week 6 in the-per protocol (PP) population was 1903.2 mg/day. During the course of the study, 96.4% of patients in the metformin group of the PP population reached the maximum protocol-specified total daily dose of metformin of 2000 mg. At week 24 approximately 88% of patients in the metformin group in both the PP and the APaT populations were taking 2000 mg/day and only 7.7% were taking doses < 1500 mg.

B) Adverse events

The adverse experience profile is summarized by treatment group in Table 8. A slightly higher incidence of overall adverse experiences was observed in the metformin group compared with the sitagliptin group. Additionally, higher incidences of drug-related adverse experiences, adverse experiences leading to discontinuation, and drug-related adverse experiences leading to discontinuation were reported in the metformin group, primarily due to a higher rate of GI adverse experiences in this group.
The incidences of drug-related adverse experiences and drug-related adverse experiences leading to discontinuation were lower in the sitagliptin group compared with the metformin group. For all other summary measures, the incidence of adverse experiences was low and generally similar between both groups.

TABLE 8: ADVERSE EVENT SUMMARY (ALL PATIENTS AS TREATED)

	Sitagliptin		Metformin	
	n	(%)	n	(%)
Patients in population	528		522	
with one or more adverse events	198	(37.5)	215	(41.2)
with no adverse event	330	(62.5)	307	(58.8)
with drug-related† adverse events	31	(5.9)	87	(16.7)
with serious adverse events	10	(1.9)	8	(1.5)
with serious drug-related adverse events	1	(0.2)	0	(0.0)
who died	1	(0.2)	0	(0.0)
discontinued‡ due to an adverse event	9	(1.7)	19	(3.6)
discontinued due to a drug-related adverse event	3	(0.6)	12	(2.3)
discontinued due to a serious adverse event	3	(0.6)	3	(0.6)
discontinued due to a serious drug-related adverse event	1	(0.2)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

The distribution of patients with adverse experiences by system organ class (SOC) with the pre-specified analysis providing 95% CIs for the between-group differences is presented in Table 9. Adverse experiences by SOC were reported most frequently for Gastrointestinal Disorders, Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, and Nervous System Disorders. A greater incidence of Gastrointestinal Disorders adverse experiences was reported for the metformin group relative to the sitagliptin group (primarily due to increased incidences of diarrhoea and nausea). In addition to the Gastrointestinal Disorders SOC, a higher incidence of Respiratory, Thoracic and Mediastinal Disorders adverse experiences was reported in the metformin relative to the sitagliptin group (primarily due to the increased incidence of cough), for which the between-group difference around the

95% CI excluded “0”. There was a numerically lower incidence of Infection and Infestations SOC adverse experiences for the sitagliptin group.

For those SOCs with higher incidences of adverse experiences observed in the sitagliptin group compared with the metformin group, the differences between groups were small (≤2.0%), and the 95% CIs included "0". There was a small, numerically greater incidence of cardiac SOC adverse experiences reported for the sitagliptin group (2.5% vs. 1.5%); this difference was due to a range of cardiac-related adverse experiences, and the incidence of serious cardiac SOC adverse experiences was lower for the sitagliptin group relative to the metformin group. The incidence of drug-related cardiac SOC adverse experiences was higher for the sitagliptin group relative to the metformin group. Incidences of ischaemia-related cardiac adverse experiences were similar in each treatment group.

The specific adverse events which occurred with a numerically greater incidence in the sitagliptin group included hypertension, pain in extremity, constipation, and dizziness. These adverse experiences were generally mild or moderate in intensity, self-limited, not recurrent (i.e., generally reflected only 1 event and not repeated events) and resolved while patients continued on study therapy. For the adverse experiences of hypertension, the majority of patients with a reported event had pre-existing hypertension and/or increased blood pressure prior to randomisation.

B.1. Deaths, serious adverse experiences, and other important safety events

One death was reported in the sitagliptin group and none was reported in the metformin group. The death in the sitagliptin group was due to metastatic lung cancer with onset at Study Day 15. This adverse experience was not considered by the investigator to be related to study therapy.
The overall incidences of non-fatal serious adverse experiences reported to occur during the study was similar between groups: 9 patients in the sitagliptin group versus 8 in the metformin group. Specific events were distributed throughout numerous body systems. Few non-fatal serious adverse experiences resulted in discontinuation from the study: 3 in the sitagliptin group (tibia fracture, hypoglycaemia, and gastroenteritis, with the latter occurring 2 days after the patient's last dose of sitagliptin), and 3 in the metformin group (upper respiratory tract infection, malignant melanoma, and multiple endocrine adenomatosis type II). One event (hypoglycaemia occurring in a patient in the sitagliptin group) was considered drug-related.

There were 9 (1.7%) patients in the sitagliptin group compared with 19 (3.6%) patients in the metformin group who were discontinued from the study due to adverse experiences. The largest between-group difference resulted from discontinuations due to Gastrointestinal Disorders in the metformin group (1.9%) relative to the sitagliptin group (0.2%). Three patients in each group were discontinued due to non-fatal serious adverse experiences.
There were 3 (0.6%) patients in the sitagliptin group compared with 12 (2.3%) patients in the metformin group who were discontinued due to a drug-related adverse event. In the sitagliptin group, all drug-related events that resulted in discontinuation were adverse experiences of hypoglycaemia and are further described below. Of the 12 patients who were discontinued due to drug-related events in the metformin group, 10 patients discontinued due to gastrointestinal adverse experiences (including diarrhoea [6], abdominal pain [1], abdominal distension [1], dyspepsia [1], and dry mouth [1]); the other two patients discontinued for dehydration and headache.

TABLE 9: SUMMARY OF ADVERSE EXPERIENCES BY SYSTEM ORGAN CLASS (ALL PATIENTS AS TREATED)

System Organ Class	Treatment Group	n/N (%)	Difference in Proportions vs. Metformin % (95% CI)†
Blood and lymphatic system disorders	Sitagliptin Metformin	0/528 (0.0) 2/522 (0.4)	
Cardiac disorders	Sitagliptin Metformin	13/528 (2.5) 8/522 (1.5)	0.9 (-0.9, 2.8)
Congenital, familial and genetic disorders	Sitagliptin Metformin	0/528 (0.0) 3/522 (0.6)	
Ear and labyrinth disorders	Sitagliptin Metformin	4/528 (0.8) 4/522 (0.8)	
Endocrine disorders	Sitagliptin Metformin	0/528 (0.0) 1/522 (0.2)	
Eye disorders	Sitagliptin Metformin	8/528 (1.5) 8/522 (1.5)	-0.0 (-1.7, 1.6)
Gastrointestinal disorders	Sitagliptin Metformin	61/528 (11.6) 108/522 (20.7)	-9.1 (-13.6, -4.7)
General disorders and administration site conditions	Sitagliptin Metformin	12/528 (2.3) 18/522 (3.4)	-1.2 (-3.3, 0.9)
Hepatobiliary disorders	Sitagliptin Metformin	2/528 (0.4) 0/522 (0.0)	
Immune system disorders	Sitagliptin Metformin	1/528 (0.2) 5/522 (1.0)	-0.8 (-2.0, 0.3)
Infections and infestations	Sitagliptin Metformin	59/528 (11.2) 74/522 (14.2)	-3.0 (-7.1, 1.0)
Injury, poisoning and procedural complications	Sitagliptin Metformin	10/528 (1.9) 9/522 (1.7)	0.2 (-1.6, 1.9)
Investigations	Sitagliptin Metformin	15/528 (2.8) 10/522 (1.9)	0.9 (-1.0, 2.9)
Metabolism and nutrition disorders	Sitagliptin Metformin	18/528 (3.4) 22/522 (4.2)	-0.8 (-3.2, 1.6)
Musculoskeletal and connective tissue disorders	Sitagliptin Metformin	40/528 (7.6) 36/522 (6.9)	0.7 (-2.5, 3.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Sitagliptin Metformin	1/528 (0.2) 1/522 (0.2)	
Nervous system disorders	Sitagliptin Metformin	34/528 (6.4) 26/522 (5.0)	1.5 (-1.4, 4.3)
Psychiatric disorders	Sitagliptin Metformin	10/528 (1.9) 10/522 (1.9)	-0.0 (-1.8, 1.8)
Renal and urinary disorders	Sitagliptin Metformin	9/528 (1.7) 5/522 (1.0)	0.7 (-0.8, 2.3)
Reproductive system and breast disorders	Sitagliptin Metformin	8/528 (1.5) 6/522 (1.1)	0.4 (-1.2, 1.9)
Respiratory, thoracic and mediastinal disorders	Sitagliptin Metformin	10/528 (1.9) 27/522 (5.2)	-3.3 (-5.7, -1.1)
Skin and subcutaneous tissue disorders	Sitagliptin Metformin	17/528 (3.2) 13/522 (2.5)	0.7 (-1.4, 2.9)
Vascular disorders	Sitagliptin Metformin	15/528 (2.8) 6/522 (1.1)	1.7 (-0.0, 3.6)

† Based on the Wilson score method and computed only for those endpoints with at least 1% incidence in one or more treatment groups

B.2. Hypoglycaemia

Symptomatic episodes assessed as likely to be hypoglycaemia were reported by investigators as adverse experiences of hypoglycaemia; a concurrent glucose measurement was not required. However, patients were counselled to obtain fingerstick glucose values if possible when symptoms of hypoglycaemia occurred. Additional information, including available blood glucose determinations, was to have been collected for each event in order to better categorize episodes as noted below.

No patient in this study was reported to have an episode of hypoglycaemia with marked severity, i.e., with symptoms of a markedly depressed level of consciousness, loss of consciousness, or seizure.
Nine (1.7%) patients in the sitagliptin group were reported to have 17 episodes of hypoglycaemia compared to 17 (3.3%) patients in the metformin group who were reported to have 23 episodes. The between-group differences in the incidences of hypoglycaemia were not statistically significant for the comparisons of episodes of any type: episodes requiring non-medical assistance and not exhibiting marked severity, and episodes requiring medical assistance or exhibiting marked severity.

Three patients in the sitagliptin group were discontinued due to an adverse experience of hypoglycaemia; these events were considered by the investigators to be related to study therapy. Two of the 3 patients in the sitagliptin group were reported to have an event of hypoglycaemia that required medical assistance (1 of these 2 patients' events was precipitated by a missed meal); fingerstick blood glucose values associated with these events were 52 mg/dL and 54 mg/dL (2.9 mmol/dL and 3.0 mmol/dL), respectively.

B.3. Selected Gastrointestinal Adverse Experiences

The selected gastrointestinal adverse experiences prespecified for additional statistical analysis were diarrhoea, nausea, abdominal pain (including abdominal discomfort), and vomiting. The incidence was significantly lower in the sitagliptin group compared with the metformin group for diarrhoea ($p<0.001$) and nausea ($p=0.032$). In addition, there were numerically lower incidences of abdominal pain (including abdominal discomfort) and vomiting in the sitagliptin group compared with the metformin group. In addition to the prespecified gastrointestinal adverse experiences, there was also a higher incidence of dyspepsia in the metformin group.

B.4. Laboratory findings and vital signs

Across all laboratory chemistry and haematology analytes, the frequency of results meeting PDLC criteria was generally similar in the sitagliptin and metformin groups.
No clinically meaningful differences in mean changes from baseline in blood pressure and pulse rate were observed for either treatment group.
There was a mean decrease in body weight observed in both sitagliptin and metformin groups (-0.6 kg vs. -1.9 kg), with a greater decrease observed in the metformin group. No statistical analysis was performed.

C) Discussion on clinical safety

In general, both sitagliptin and metformin were well tolerated. No unexpected adverse experiences were observed. More gastrointestinal adverse experiences were seen with metformin. There was a small, numerically greater incidence of cardiac SOC adverse experiences reported for the sitagliptin group; the incidence of serious cardiac SOC adverse experiences was lower for the sitagliptin group relative to the metformin group and the incidence of drug-related cardiac SOC adverse experiences was higher for the sitagliptin group relative to the metformin group. Of note, incidences of ischaemia-related cardiac adverse experiences were similar in both treatment groups. The MAH had already committed to perform a cardiovascular outcome study at the time of marketing authorisation, which is ongoing at the moment. The most recent PSUR is covering the period 04 February 2008 to 03 August 2008. The MAH should closely monitor cases of cardiac disorders.

Although the overall incidence of hypoglycaemia or number of hypoglycaemic episodes was numerically higher for metformin, 2 patients in the sitagliptin required medical assistance for hypoglycaemia. This contradicts the assumption of strict blood-glucose dependent action of sitagliptin. Previous safety concerns regarding a sitagliptin-related propensity to infections were not confirmed in this study, which is reassuring.

No new safety issues were identified in study P049. However, long-term safety of sitagliptin still has to be established.

Additionally, the cardiovascular safety has not been established for this class of drugs. In this regards, the MAH has analyzed pooled data from 12 large Phase II / III randomized, controlled, double-blind clinical trials of sitagliptin up to 2 years in duration. According to the MAH, there were no meaningful differences in total or serious adverse experiences. Although the studies in this analysis were not designed as cardiovascular outcome trials, but rather designed as trials assessing the overall safety and efficacy of sitagliptin 100 mg/day in various treatment paradigms, no meaningful differences were observed between the two groups in the incidence rates of cardiac-related or ischemia-related adverse experiences. The MAH has started enrolling patients into a cardiovascular safety trial (P082) using adjudicated endpoints. This study expects to enrol approximately 14,000 patients and is scheduled to be completed in 2014.

D) Risk Management plan

The MAH claimed that an updated RMP will not be required for this variation. As a consequence an updated RMP was not submitted as part of this variation.

The CHMP was of the view that due to use as monothereapy the population might change, most likely to patients with less co-morbidity. However, there are no additional safety concerns with monotherapy as compared to the combination therapy. Therefore, the CHMP agreed that there is no need to update the RMP.

4. Benefit risk assessment and overall conclusion

In support of the variation, results of one trial were submitted. Study P049 was a multicenter, double-blind, randomised, parallel-group Phase III non-inferiority study to compare the efficacy of 100 mg/d of sitagliptin with 2000 mg/d of metformin in patients with T2DM who had inadequate glycaemic control on diet and exercise alone. The primary objective was to demonstrate non-inferior efficacy of sitagliptin compared to metformin on the basis of change in HbA1c (non-inferiority margin 0.4%) and to show that sitagliptin is well tolerated. The secondary objective was to show that the incidence of gastrointestinal adverse events is lower with sitagliptin than with metformin.

More patients in the sitagliptin group (10/532, 1.9%) as compared to the metformin group (1/526, 0.2%) withdrew due to lack of efficacy. The reduction in HbA1c was -0.43 in the sitagliptin group vs -0.57 % in the metformin group (difference 0.14 [-0.06, 0.21]). Responder data also suggest lower efficacy for sitagliptin (69% vs 76% with HbA1c <7.0%, sitagliptin vs metformin). In addition, metformin reduced fasting plasma glucose levels significantly more than sitagliptin (95% CI excludes 0).

The MAH claims non-inferior efficacy for sitagliptin compared to metformin. However, because patients with rather low baseline HbA1c ($\geq$ 6.5 and $\leq$9.0%) were included, the sensitivity of the study to demonstrate non-inferiority is questionable. The margin of 0.4% appears too large and is of about the same size as the mean HbA1c reduction achieved with sitagliptin. On the other hand, the HbA1c subgroup analysis revealed that HbA1c reduction was larger with increasing baseline HbA1c values in both treatment groups as observed with other glucose-lowering agents. In addition, the upper margin of the 95% CI of the treatment difference for the subgroup with baseline HbA1c > 8% was 0.3%,

which provides sufficient confidence that sitagliptin is able to appropriately reduce blood glucose levels also in patients with higher baseline HbA1c

With respect to safety, sitagliptin had a better gastrointestinal profile compared to metformin.
The MAH acknowledged that metformin is the first-line agent in the treatment of T2DM. Noting the small but statistically significant between-group difference in favour of metformin in study P049, the MAH proposed a restricted monotherapy indication for sitagliptin, i.e. in patients for whom metformin is not an option due to either contraindication or intolerance. However, main contraindications for metformin are moderate and severe renal impairment, hepatic impairment, heart failure and recent myocardial infarction. These are conditions for which there is limited experience for sitagliptin. Intolerance to metformin is mainly due to gastrointestinal side effects. Because of its better gastrointestinal tolerability, sitagliptin may be a relevant treatment alternative. It should also be recognised that in the product information of Xelevia contraindications are limited to hypersensitivity reactions and that so far no major safety issues have appeared in those patients in whom metformin is contraindicated.

For the monotherapy indication there is no direct comparison with a SU. In a comparative study with glipizide on top of metformin, sitagliptin had a significant and clinically relevant effect on glycaemic control but, due to the rather low dose of SU used in this trial, non-inferior efficacy compared to SU had not convincingly been proven. Although final conclusions are difficult to reach, it seems that, although a similar effect was noted on HbA1c, the effect of Xelevia is somewhat less, as measured by the number of discontinuations. On the other hand, as pointed out by the MAH, significantly fewer adverse experiences of hypoglycemia occurred compared to the sulfonylurea together with a more favourable effect on bodyweight.

So far, no detrimental effects of sitagliptin have been identified. A cardiovascular safety study is underway, which will monitor the long-term safety of sitagliptin in a large patient population with type 2 diabetes.

Taking all considerations together, the CHMP concluded that sitagliptin could be an alternative to SU (in patients not tolerating or with contraindications to metformin), in particular in those patients with a history of hypoglycaemia and who have weight problems.

In summary based on the above considerations, the newly proposed restricted monotherapy indication for sitagliptin, i.e. *for use as monotherapy in patients for whom metformin is not an option, due to either contraindication or intolerance* was considered acceptable.