20 October 2011
EMA/43321/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Onglyza

Saxagliptin

Procedure No: EMEA/H/C/001039/II/0011

Note

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 ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Scientific discussion

1.1. Introduction

Saxagliptin is an orally 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. Saxagliptin was approved for marketing in the EU on October 1st 2009 and currently has therapeutic indications for second line use in combination with metformin, a PPAR-γ agonist, or a sulphonylurea in patients with type 2 diabetes mellitus.
The MAH submitted with this application the following extension to the indication:

> *Onglyza is indicated as add on combination therapy in adult patients aged 18 years and older with type 2 diabetes mellitus. The applicant is seeking to add to the list of combination therapies, the following: 'to improve glycaemic control in combination with insulin (with or without metformin), when this regimen alone with diet and exercise does not provide adequate glycaemic control'.*

The variation submitted is the following:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication for the use of Onglyza as add-on therapy to insulin (with or without metformin) affecting sections 4.1, 4.2, 4.4., 4.8 and 5.1 of the SmPC. The Package Leaflet has been updated accordingly. In addition, minor changes have been made throughout the Product Information.

GCP

The confirmatory clinical trial were conducted in accordance with ICH Good Clinical Practice, as declared by the MAH.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/97/2011) for the following condition(s):

- Type 2 diabetes mellitus

on the agreement of a paediatric investigation plan (PIP). At the time of submission of this application, the PIP is not yet completed as some measures were deferred.

1.2. Clinical aspects

The clinical program to evaluate the anti-hyperglycaemic activity of saxagliptin as add-on combination therapy with insulin in T2DM began with the initiation of the Phase 3b study CV181057 (study 057), a randomised, parallel, double-blind placebo-controlled multicentre trial comparing the anti-hyperglycaemic activity of saxagliptin 5 mg added on as combination therapy with insulin or to insulin in combination with metformin in subjects with T2DM who had inadequate glycaemic control. The 24-week double-blind ST treatment period was intended to provide efficacy and safety data to support the proposed indication; during the evalution of this extension of indication application, efficacy and safety results from the long term extension period of study 057 became available and were provided by the applicant, but no additional efficacy and safety aspects did emerge beyond the ST treatment results. The main study of this application is study 057, a supportive study relevant for this application (study D1680C00007) is summarized at the end of this section. In general the guideline in the therapeutic area was followed.

1.3. Clinical efficacy

3.3.1 Main study

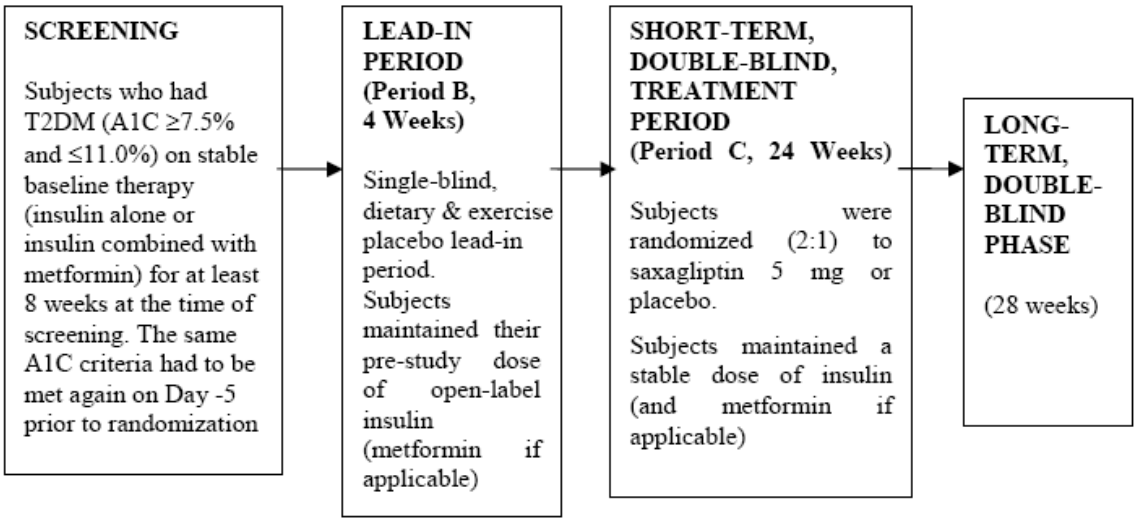
The main study of this application is Study CV181057 (study 057).

Methods

Study design

Study 057 was a Phase 3b, randomized, two-arm, parallel, double-blind, placebo-controlled multicenter trial comparing the antihyperglycaemic activity of saxagliptin added on as combination therapy with insulin or to insulin in combination with metformin in subjects with T2DM who had inadequate glycaemic control (HbA1c ≥ 7.5% and ≤ 11.0%) while on a stable dose of insulin (≥ 30 units/day, ≤ 150 units/day) or a stable dose of insulin (≥ 30 units/day, ≤ 150 units/day) in combination with a stable dose of metformin for at least 8 weeks. The ST treatment period was 24 weeks. Randomization was 2:1 (saxagliptin: placebo), and was stratified by metformin use at enrolment. The proportion of subjects using metformin was capped at 75% of total sample, to ensure sufficient participation of those on insulin monotherapy. The usual clinical dose of 5 mg once daily of saxagliptin was administered in this study. See Figure 1.

Figure 1: design of study 057



T2DM = type 2 diabetes mellitus

Study population

The population of study 057 consisted of male and female subjects with T2DM, aged between 18 and 78 years (inclusive), who had inadequate glycaemic control (defined as HbA1c levels ≥ 7.5% and ≤ 11.0%) and were on insulin alone [(≥ 30 units/day, ≤ 150 units/day) with ≤ 20% variation in total daily dose for ≥ 8 weeks prior to screening] or in combination with metformin.

Endpoints

The primary efficacy endpoint in study 057 was the change in HbA1c level from baseline until Week 24 (or the last post-baseline measurement prior to Week 24, if no Week 24 measurement was available or before rescue).
Secondary endpoints assessed at week 24 were:
• Change from baseline in AUC from 0 to 180 minutes for postprandial glucose response to an MTT;
• Change from baseline in the 120-minute postprandial glucose value during an MTT;
• Change from baseline in FPG;
• Proportion of subjects achieving a therapeutic glycaemic response (defined as HbA1c < 7%);
• Change from baseline in mean total daily insulin dose based on information recorded on the subjects' daily diary.
Other efficacy endpoints were the changes from baseline to week 24 for the postprandial glucagon AUC, postprandial C-peptide AUC, fasting glucagon, and fasting C-peptide.

Statistical analysis

With a total of 390 subjects in a 2:1 ratio to receive saxagliptin 5 mg (260 subjects) or placebo (130 subjects), there was 90% power to detect a difference in A1C mean change from baseline to Week 24 of 0.35% between saxagliptin and placebo, assuming a standard deviation of 1.0%. Assuming a drop out rate of 10%, a total of 435 subjects (290 subjects in the saxagliptin treatment arm and 145 subjects in the placebo treatment arm) were to be randomized.

Analysis populations

The Lead-in Subjects Data Set included data collected from all subjects who took at least 1 dose of placebo lead-in study medication.
The Randomized Subjects Data Set consisted of all randomized subjects who took at least 1 dose of double-blind treatment.
The Evaluable Subjects Data Set (called the "Secondary Efficacy Data Set" in the protocol) was a subset of the Randomized Subjects Data Set. It consisted of subjects who did not deviate from the

terms of the protocol in ways which could have affected the primary endpoint in a relevant way ("relevant deviation"), as specified in the pre-defined protocol deviation list prior to unblinding the study. Only the primary efficacy endpoint of change from baseline in A1C, demographics, and baseline diabetes-related characteristics were to be analyzed using the Evaluable Subjects Data Set, and only if >10% of the subjects in any treatment group were found to have a relevant deviation.
The Treated Subjects Data Set consisted of all subjects who received at least 1 dose of double-blind study drug during the short-term treatment period.

Efficacy analysis

In calculating primary and secondary endpoints in rescued subjects, endpoints (except mean total daily dose of insulin [MTDDI]) were analyzed by last observation carried forward (LOCF), as follows:

- Rescue because of increased fasting plasma glucose: For subjects rescued because of increased fasting plasma glucose (FPG) levels, measurements obtained after rescue were not considered in the analyses of the primary and secondary endpoints. Rather, the last observations prior to rescue were carried forward (LOCF).
- Rescue because of increased insulin use: For subjects rescued because of persistently increased use of insulin (MTDDI exceeding by > 20% the subject's baseline MTDDI), the last observations prior to rescue and prior to the visit with the 20% increase in MTDDI were carried forward (LOCF).

Primary endpoint

The primary efficacy endpoint was the change in HbA1c from baseline to Week 24. The primary efficacy analysis was an analysis of covariance (ANCOVA) of that endpoint (LOCF), with treatment group and metformin use at enrolment as fixed effects, and baseline value as a covariate in the model. It included subjects in the Randomized Data Set who had HbA1c assessments at baseline and post-baseline (excluding any post-rescue assessments). Within the framework of the ANCOVA model, point estimates and 95% CIs for the mean changes between the saxagliptin treatment group and the placebo treatment group were calculated. Each comparison of the saxagliptin treatment group versus the placebo treatment group was performed using a t test at α=0.05 level. The treatment-by-baseline interaction was tested and distributional assumptions were assessed.
To assess the robustness of the primary efficacy analysis, the modeling of the primary efficacy analysis was repeated in a number of sensitivity analyses.
The statistical testing of the primary and secondary efficacy endpoints proceeded in a sequential manner to control the overall type I (family-wise) error rate at the 0.05 level. The significance or non-significance of the treatment comparisons for the primary efficacy endpoint determined which statistical tests were performed to compare treatments for the secondary efficacy endpoints.

Overall, the design of the study was considered adequate to evaluate the value of saxagliptin when added to insulin. Primary and secondary endpoints were adequate The mean dose of >1800 mg is acceptable. The chosen superiority margin of 0.35% was considered rather small by CHMP but found to be acceptable in this clinical context.

Results

Disposition of subjects

Disposition of subjects is shown in Figure 2. Of the 500 subjects who entered the lead-in period, 45 did not enter the double-blind treatment period, including 2 subjects who were randomized but not treated. The most common reason for subjects discontinuing during the lead-in period was that the subjects did not meet study criteria (30 subjects, 6.0%). Of the 455 subjects who were randomized and treated with double-blind therapy, 402 (88%) subjects completed 24-weeks of treatment. A total of 304 subjects were randomized to saxagliptin and 151 were randomized to placebo. Discontinuations during the short-term treatment period were similar in both treatment groups (11.8% and 11.3%, respectively). The most common reason for discontinuation from the short-term treatment period in the saxagliptin group was subject withdrew consent (13 subjects, or 4.3%). The most common reasons for discontinuation from the placebo group were subject withdrew consent (5 subjects, or 3.3%) and lost to follow-up (5 subjects, or 3.3%). Lack of efficacy led to discontinuation in 5 subjects (3, or 1.0%, in the saxagliptin group and 2, or 1.3%, in the placebo group).

Figure 2: Disposition of subjects in study 057

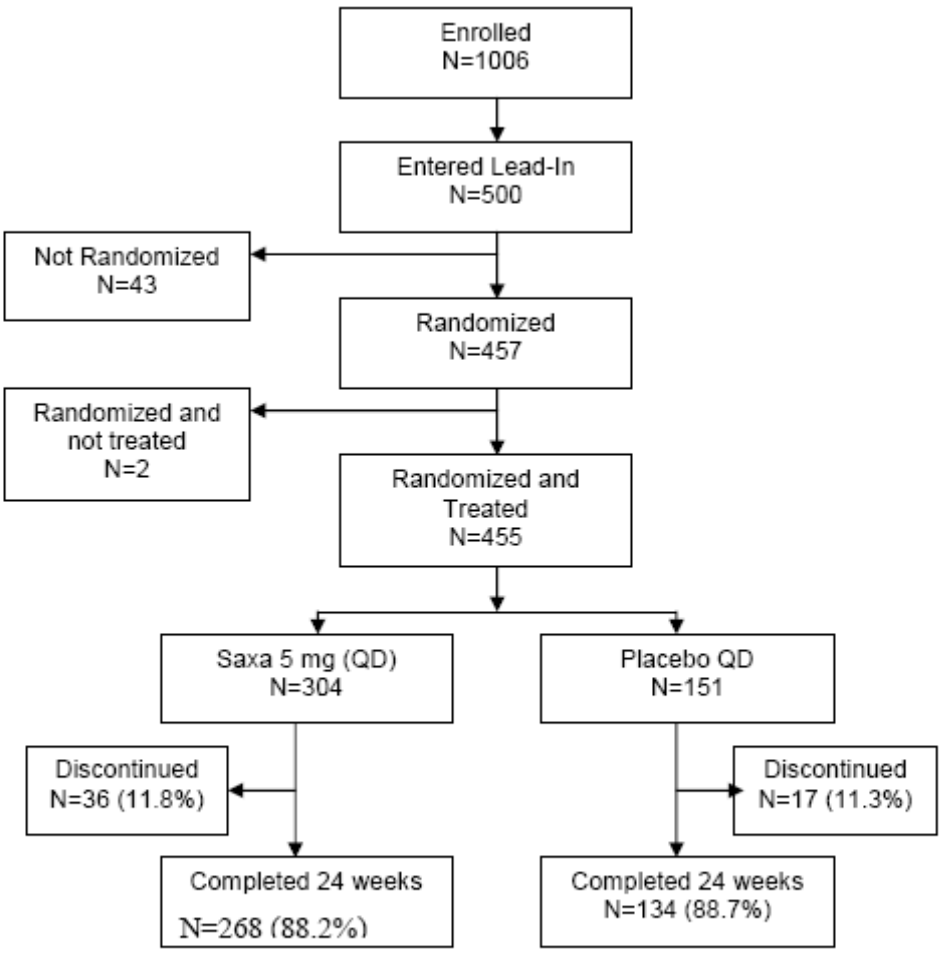


Table 1: Disposition of Subjects in Short-term Treatment Period and Primary Reason for not Completing, study 057

	Saxa 5mg + INS		Placebo + INS	
	N	%	N	%
Subjects randomised	304		151	
Subjects completing 24 weeks of treatment	268	88.2	134	88.7
Subjects not completing 24 weeks of treatment	36	11.8	17	11.3
Reason for not completing the period				
Lack of efficacy	3	1.0	2	1.3
Adverse event	6	2.0	3	2.0
Subject withdrew consent	13	4.3	5	3.3
Death	1	0.3	0	
Lost to follow-up	3	1.0	5	3.3
Poor/Non-compliance	5	1.6	1	0.7
Pregnancy	0		0	
Subject no longer meets study criteria	5	1.6	0	
Administrative reason by Sponsor	0		0	
Other	0		1	0.7

Analysis data sets for the short term treatment period are summarised in Table 2.

Table 2: Analysis Data Sets Summary for Short-term Treatment Period

	Number (%) of Subjects					
	SAXA 5MG + INS		PLACEBO + INS		Total	
	N	%	N	%	N	%
Lead-In Subjects (a)					500	
Randomized Subjects	304	(100.0)	153	(100.0)	457	(100.0)
Randomized And Treated Subjects (=Randomized Subjects data Set) (b)	304	(100.0)	151	(98.7)	455	(99.6)
Evaluable Subjects (c)	302	(99.3)	150	(98.0)	452	(98.9)
Evaluable Subjects Included In The Primary Efficacy Analysis (d)	299	(98.4)	147	(96.1)	446	(97.6)
Treated Subjects (e)	304	(100.0)	151	(98.7)	455	(99.6)

(a) Subjects who took at least one dose of lead-in medication
(b) Randomized subjects who took at least one dose of double-blind study medication
(c) Randomized subjects, excluding subjects with relevant deviations resulting in complete data exclusion
(d) Evaluable subjects, who have a baseline A1C assessment and at least 1 post-randomization A1C assessment
(e) Subjects who received at least 1 dose of double-blind study medication
Percents are based on the number of randomized subjects in each treatment group.

Demographics and baseline characteristics

Demographics and baseline characteristics are shown in Table 3 and Table 4. The 2 treatment groups were generally well balanced for demographic and baseline diabetes characteristics. Of the 455 randomized and treated subjects, 41.3% were men and 78.0% were white; the mean age was 57.2 years (range 18 to 77 years). Most (84.6%) subjects were diagnosed with T2DM ≥5 years before the start of the study with a mean duration of diabetes of 12.0 years. The mean baseline HbA1c was 8.66% (range, 7.3% to 11.4%).
Demographic characteristics were also examined for the 314 subjects taking metformin and the 141 subjects not taking metformin. Among subjects taking metformin 41.7% were male, 76.4% were white, and the mean age was 56.7 years (range 18 to 77 years). Among subjects not taking metformin 40.4% were male, 81.6% were white, and the mean age was 58.4 years (range 29 to 77 years). Overall, baseline diabetes characteristics were generally similar between those taking metformin and those not taking concomitant metformin.

Table 3: Demographics for ST treatment period, study 057

	Saxa 5mg + INS N=304		Placebo + INS N=151		Total N=455	
Age						
n	304		151		455	
Mean	57.2		57.3		57.2	
Min, Max	18	77	30	77	18	77
Age categorisation, n (%)						
<65	233	(76.6)	118	(78.1)	351	(77.1)
≥65	71	(23.4)	33	(21.9)	104	(22.9)
≥75	6	(2.0)	3	(2.0)	9	(2.0)
Gender, n (%)						
Male	120	(39.5)	68	(45.0)	188	(41.3)
Female	184	(60.5)	83	(55.0)	267	(58.7)
Race, n (%)						
White	237	(78.0)	118	(78.1)	355	(78.0)
Black/African American	13	(4.3)	9	(6.0)	22	(4.8)
Asian	40	(13.2)	19	(12.6)	59	(13.0)
Other	14	(4.6)	5	(3.3)	19	(4.2)
Geographical Region, n (%)						
North America	59	(19.4)	33	(21.9)	92	(20.2)
Latin America	58	(19.1)	31	(20.5)	89	(19.6)
Europe	125	(41.1)	56	(37.1)	181	(39.8)
Asia/Pacific	36	(11.8)	15	(9.9)	51	(11.2)
Africa	26	(8.6)	16	(10.6)	42	(9.2)
Weight (kg)						
n	304		151		455	
Mean	87.65		86.21		87.17	
Min, Max	51.0	140.6	55.2	136.0	51.0	140.6
Body Mass Index (kg/m^2)						
n		304		151		455
Mean		32.57		31.76		32.30
Min, Max	21.7	45.5	21.5	44.9	21.5	45.5

Table 4: Baseline disease characteristics for ST treatment period, study 057

	Saxa 5mg + INS N=304		Placebo + INS N=151		Total N=455	
Duration of Type 2 Diabetes (years)						
n	304		151		455	
Mean (SD)	11.8	(6.93)	12.2	(7.37)	12.0	(7.07)
Min, Max	0.7	35.1	0.2	36.8	0.2	36.8
Baseline A1c						
n	304		151		455	
Mean (SD)	8.67	0.896	8.64	0.855	8.66	0.882
Min, Max	7.3	11.2	7.3	11.4	7.3	11.4
Categorised Baseline A1c (%) n (%)						
< 8	76	(25.0)	38	(25.2)	114	(25.1)
8 - < 9	126	(41.4)	65	(43.0)	191	(42.0)
≥ 9	102	(33.6)	48	(31.8)	150	(33.0)
Fasting plasma glucose (mg/dL)						
n	303		150		453	
Mean (SD)	173.5	(54.34)	173.1	(55.76)	173.4	(54.75)
Min, Max	50	382	55	359	50	382
Insulin type n (%)						
Intermediate acting & long acting	9	(3.0)	8	(5.3)	17	(3.7)
Intermediate acting & pre-mixed insulin	4	(1.3)	4	(2.6)	8	(1.8)
Intermediate acting insulin alone	54	(17.8)	32	(21.2)	86	(18.9)
Long acting & pre-mixed insulin	3	(1.0)	2	(1.3)	5	(1.1)
Long acting insulin alone	52	(17.1)	29	(19.2)	81	(17.8)
Pre-mixed insulin alone	182	(59.9)	76	(50.3)	258	(56.7)
Metformin Dose (mg) in patients using metformin						
(n)	205		104		309	
Mean (SD)	1805.4	(655.18)	1861.1	590.88	1824.1	633.85
Median	2000.0		1775.0		2000.0	
Min, Max	250,	3000	850,	3000	250,	3000

Overall, there were no differences between treatment groups in percentages of patients who completed the study and percentage of withdrawals. In addition, there were no relevant differences between treatment groups in demographics and baseline disease characteristics. Most patients were White (78%), 20% were from North America, 20% from Latin America, 40% from Europe, 11% from Asia. Baseline disease characteristics were typical for T2DM patients.

Primary efficacy endpoint

The primary and secondary efficacy endpoints in study 057 are summarized by treatment group in Table 5. Overall, study 057 showed that saxagliptin added on to insulin (or to insulin combined with metformin) improves glycaemic control in subjects with T2DM. There was a statistically significant reduction in adjusted mean change in HbA1c from baseline to Week 24 in the saxagliptin treatment group compared with placebo ($p<0.0001$). The adjusted mean change from baseline was -0.73% (95% CI [-0.83, -0.62]) for the saxagliptin treatment group and -0.32% (95% CI [-0.46, -0.17]) for placebo. The difference in the adjusted mean change from baseline versus placebo was -0.41% (95% CI [-0.59, -0.24]).

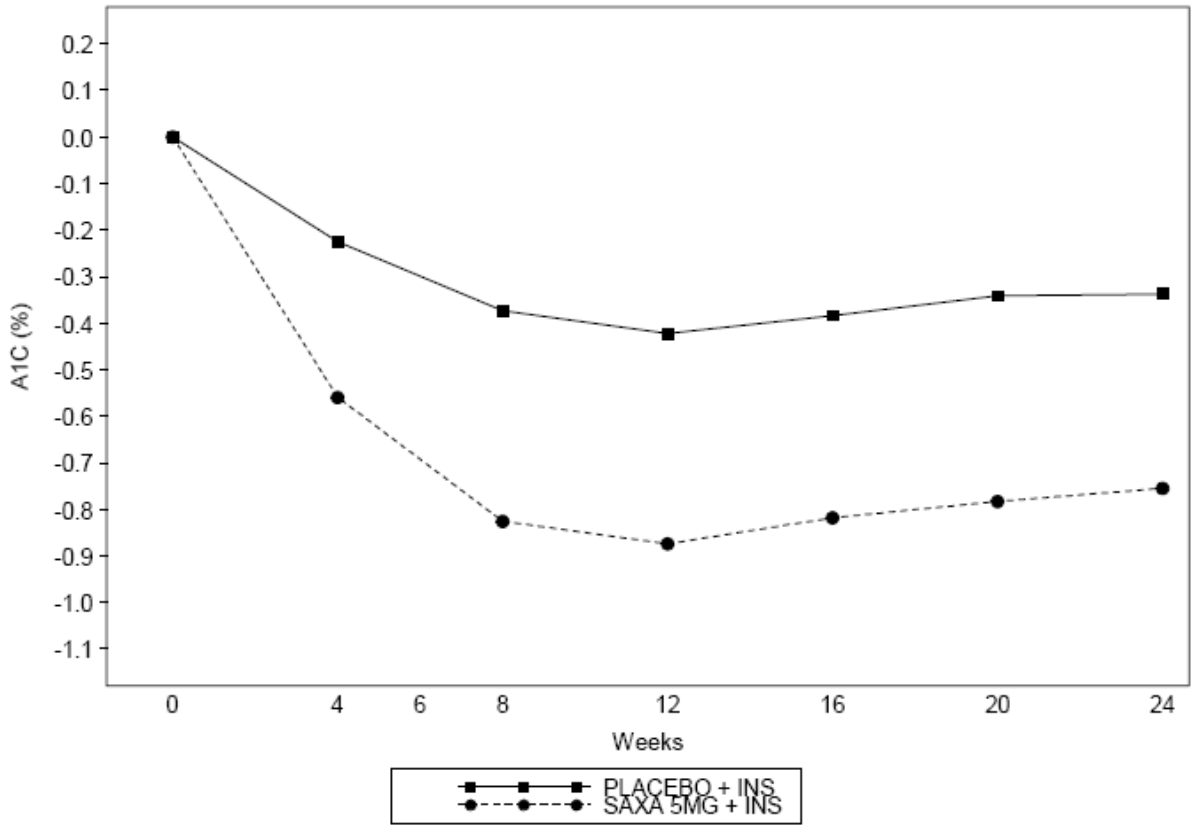
Table 5: Primary and secondary efficacy endpoints at week 24 (LOCF), study 057

	Saxa 5mg + Ins N=304	Pla + Ins N=151
HbA1c (%)		
n	300	149
Adj mean change from baseline (CI)	-0.73 (-0.83, -0.62)	-0.32 (-0.46, -0.17)
Adj mean difference (CI)	-0.41 (-0.59, -0.24)	
P-value	< 0.0001	
PPG AUC (mg*min/dL)		
n	258	122
Adj mean change from baseline (CI)	-4548.5 (-5900.7, -3196.4)	-718.8 (-2649.0, 1211.4)
Adj mean difference (CI)	-3829.8 (-6122.4, -1537.1)	
P-value	0.0011	
120-min PPG (mg/dL)		
n	262	129
Adj mean change from baseline (CI)	-27.2 (-35.7, -18.6)	-4.2 (-16.1, 7.8)
Adj mean difference (CI)	-23.0 (-37.2, -8.7)	
P-value	0.0016	
FPG (mg/dL)		
n	300	149
Adj mean change from baseline (CI)	-10.1 (-15.72, -4.44)	-6.1 (-13.89, 1.77)
Adj mean difference (CI)	-4.0 (-13.32, 5.28)	
P-value	0.3958	
Subjects achieving HbA1c <7% [a]		
n/N (%)	52/300 (17.3)	10/149 (6.7)
Difference from control (CI)	10.6 (4.7, 16.5)	
Mean Total Daily Dose of Insulin (Unit) [a]		
n	299	151
Adj mean change from baseline (CI)	1.7 (0.3, 3.0)	5.0 (3.1, 6.9)
Adj mean difference (CI)	-3.3 (-5.6, -1.1)	

[a] The absence of statistical significance on the prior secondary endpoint (FPG) precluded formal assessment of this secondary endpoint for statistical significance.
Adj = adjusted; AUC = area under the curve; CI = confidence interval; FPG = fasting plasma glucose; Ins = insulin; Pla = placebo; PPG = postprandial glucose; Saxa = saxagliptin; SE = standard error

Changes over time are shown in Figure 3. For saxagliptin, a reduction from baseline was observed at Weeks 4 and 8 and became progressively greater to Week 12; this reduction was maintained through Week 24. For placebo, smaller reductions were observed from Weeks 4 to 12 and values stabilized after that point through Week 24.

Figure 3: HbA1c mean change from baseline (LOCF) over time during ST treatment period, Study 057



Similar results were obtained when examining HbA1c change from baseline results at Week 24 regardless of rescue. The adjusted mean change from baseline HbA1c (regardless of rescue) was - 0.76% (95% CI [-0.87, -0.66]) for the saxagliptin treatment group and -0.40% (95% CI [-0.54, -0.25]) for placebo. The difference in the adjusted mean change from baseline versus placebo was -0.37% (95% CI [-0.54, -0.19]).

When examining HbA1c data obtained prior to a 10% change in insulin dose, there was a reduction in adjusted mean change in HbA1c from baseline to Week 24 in the saxagliptin treatment group compared with placebo. The adjusted mean change from baseline was -0.71% (95% CI [-0.81, - 0.61]) for the saxagliptin treatment group and -0.25% (95% CI [-0.40, -0.11]) for placebo. The difference in the adjusted mean change from baseline versus placebo was -0.46% (95% CI [-0.63, -0.29]). These results were consistent with those obtained for the main analysis.

Results for changes from baseline in HbA1c at Week 24 (LOCF) were similar in subjects with and without metformin use at baseline. Among subjects with metformin use at baseline, the adjusted mean change from baseline was -0.79% (95% CI [-0.91, -0.67]) for the saxagliptin treatment group and -0.38% (95% CI [-0.55, -0.21]) for placebo. The difference in the adjusted mean change from baseline versus placebo was -0.41% (95% CI [-0.62, -0.20]). Among subjects with no metformin use at baseline, the adjusted mean change from baseline was -0.67% (95% CI [-0.84, - 0.49]) for the saxagliptin treatment group and -0.25% (95% CI [-0.51, 0.00]) for placebo. The difference in the adjusted mean change from baseline versus placebo was -0.41% (95% CI [-0.72, -0.10]).

Secondary endpoints

Results for secondary endpoints were in line with those of the primary endpoint.

At Week 24, there was a statistically significant reduction in change from baseline in postprandial glucose AUC during an MTT in the saxagliptin treatment group compared with placebo (p=0.0011) (Table 5). The difference in the adjusted mean change from baseline versus placebo was -3829.8 (95% CI [-6122.4, -1537.1]). There was also a statistically significant reduction in 120-minute postprandial glucose concentration when examining results for change from baseline to Week 24 (p=0.0016) (Table 5). The difference in the adjusted mean change from baseline versus placebo was -23.0 mg/dL (-1.3 mmol/L) (95% CI [-37.2, -8.7 mg/dL; -2.1, -0.5 mmol/L]).

Saxagliptin was associated with a numerically greater decrease in adjusted mean change from baseline in FPG compared with placebo (-4.02 mg/dL, -0.2 mmol/L), but this difference was not statistically significant (p= 0.3958; 95% CI [-13.32, 5.28 mg/dL; -0.7, 0.3 mmol/L])(Table 5). When examining data obtained prior to a 10% change in insulin dose in a post-hoc sensitivity analysis, the reduction in adjusted mean change in FPG from baseline to Week 24 was greater in the saxagliptin treatment group compared with the placebo group. The difference in the adjusted mean change from baseline versus placebo was -12.94 mg/dL (-0.7 mmol/L) (95% CI [-22.27, -3.61 mg/dL; -1.2, -0.2 mmol/L]).
A greater proportion of subjects treated with saxagliptin achieved a therapeutic glycaemic response (defined as HbA1c < 7.0%) adjusted for baseline HbA1c relative to placebo (17.3% versus 6.7%) (Table 1). The difference in the proportions of subjects achieving HbA1c < 7% versus placebo was 10.6% (95% CI [4.7, 16.5]). The absence of statistical significance on the prior secondary endpoint (FPG) precluded formal assessment of this secondary endpoint for statistical significance. However, the 95% CI for the difference for the proportions in the 2 treatment groups did not include 0. The difference in the proportions of subjects achieving HbA1c < 7% was higher in the saxagliptin group than the placebo group regardless of whether subjects were receiving metformin (saxagliptin: 19.4%; placebo: 7.8%) or were not receiving metformin (saxagliptin: 12.8%; placebo: 4.3%).
Mean total daily insulin dose increased from baseline to Week 24 (LOCF) in both treatment groups. The adjusted mean increase from baseline in MTDDI was lower in the saxagliptin group (1.7 units; 95% CI [0.3, 3.0]) than the placebo group (5.0 units; 95% CI [3.1, 6.9]) at Week 24 (Table 5). The difference in the adjusted mean change from baseline in the total daily dose of insulin versus placebo was -3.3 units (95% CI [-5.6, -1.1]). The absence of statistical significance on the prior secondary endpoint (FPG) precluded formal assessment of this secondary endpoint for statistical significance. However, the 95% CI for the difference in the insulin dose in the 2 treatment groups did not include 0.

Other efficacy endpoints

The difference in the adjusted mean change from baseline in fasting C-peptide at Week 24 (saxagliptin versus placebo) was 0.05 ng/mL (95% CI [-0.18, 0.29]).
The difference in the adjusted mean change from baseline in postprandial C-peptide AUC at Week 24 (saxagliptin versus placebo) was 5.1 ng*min/mL (95% CI [-50.1, 60.4]).
The difference in the adjusted mean change from baseline in fasting glucagon at Week 24 (saxagliptin versus placebo) was -4.53 pg/mL (95% CI [-10.01, 0.95]).
The difference in the adjusted mean change from baseline postprandial glucagon AUC at Week 24 (saxagliptin versus placebo) was -1640.2 pg*min/mL (95% CI [-2649.1, -631.2]).
The proportion of subjects who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified glycaemic criteria during the short-term treatment period was numerically lower in the saxagliptin group at every time point. At Week 24, 22.7% of the saxagliptin treated patients and 31.8% of the placebo treated patients had discontinued (difference -9.1%; 95% CI [-18.7, 0.7]).

Physical measurements

Overall, there were numerical increases in mean body weight (LOCF) across both treatment groups. Baseline mean body weight was 87.71 kg for saxagliptin treated subjects and 86.21 kg for placebo treated subjects. At Week 24, the adjusted mean change in body weight (LOCF) was 0.39 kg (95% CI [0.10, 0.69]) for the saxagliptin group and 0.18 kg (95% CI [-0.23, 0.59]) for the placebo group. The difference in the adjusted mean change from baseline versus placebo was 0.22 kg (95% CI [-0.27, 0.70]).
Mean BMI values also increased (LOCF) across both treatment groups. Baseline mean BMI was 32.58 kg/m2 for saxagliptin treated subjects and 31.76 kg/m2 for placebo treated subjects. At Week 24, the adjusted mean change in BMI (LOCF) was 0.16 kg/m2 (95% CI [0.05, 0.27]) for the saxagliptin group and 0.05 kg/m2 (95% CI [-0.11, 0.20]) for the placebo group. The difference in the adjusted mean change from baseline versus placebo was 0.11 kg/m2 (95% CI [-0.07, 0.30]).

Summary of main outcome parameters

Overall, both primary and secondary parameters indicate that the addition of saxagliptin to patients treated with insulin was effective. The results were similar in subjects with and without metformin use at baseline.However, the effect was modest. For HbA1c, the adjusted mean difference from placebo was -0.41. This was also expressed in the proportion of patients achieving therapeutic glycaemic response (HbA1c < 7%): 17.3 vs 6.7% for the saxagliptin and insulin group, respectively. Even though

the treatment effect was modest, the study demonstrated that saxagliptin + insulin produced a statistically significant reduction in HbA1c compared to placebo + insulin after 24 weeks of double-blind treatment, with a treatment difference of 0.41%.
The placebo group had a reduction in A1C of 0.32%, likely attributable to dietary and exercise factors, some of which may have extended beyond randomisation.
A small increase in body weight was seen in both groups (0.39 kg vs 0.18 kg in the saxagliptin vs placebo group, respectively).
During the evalution of this extension of indication application, efficacy results from the long term extension period of study 057 became available and were provided by the applicant and did show that reductions from baseline A1C seen in the saxagliptin + insulin group compared with the placebo + insulin group were sustained to Week 52; results were consistent for subjects using metformin and not using metformin at baseline. Increases from baseline in mean total daily dose of insulin were seen in both treatment groups through Week 52, with a numerically smaller increase in the saxagliptin group.
Both treatment groups experienced small numerical increases in weight, of similar magnitude, through Week 52.

Clinical studies in special populations

No strong interactions ($p < 0.1$) of treatment by subgroup were noted for subgroup analyses of change from baseline in HbA1c at Week 24 (LOCF) by metformin use, baseline HbA1c, duration of diabetes, race, gender, age, BMI, or geographic region (see Table 6).

Table 6: Changes in HbA1c at Week 24, evaluation in subgroups, study 057

	Saxa 5mg + INS	Placebo + INS
Metformin use		
Metformin (N)	206	103
HbA1c: Adjusted mean change from Baseline (%)	-0.79	-0.38
Difference from Control (95% CI)	-0.41 (-0.62, -0.20)	
No Metformin (N)	94	46
HbA1c: Adjusted mean change from Baseline (%)	-0.67	-0.25
Difference from Control (95% CI)	-0.41 (-0.72, -0.10)	
Baseline HbA1c		
Baseline HbA1c < 8.0% (N)	76	36
HbA1c: Adjusted mean change from Baseline (%)	-0.68	-0.27
Difference from Control (95% CI)	-0.41 (-0.77, -0.06)	
Baseline HbA1c ≥ 8.0% -<9.0% (N)	122	65
HbA1c: Adjusted mean change from Baseline (%)	-0.69	-0.29
Difference from Control (95% CI)	-0.40 (-0.66, -0.13)	
Baseline HbA1c ≥ 9% (N)	102	48
HbA1c: Adjusted mean change from Baseline (%)	-0.89	-0.46
Difference from Control (95% CI)	-0.42 (-0.73, -0.12)	
Duration of diabetes		
Duration of diabetes ≤ 1.5 yr (N)	5	5
HbA1c: Adjusted mean change from Baseline (%)	-0.17	-0.55
Difference from Control (95% CI)	0.38 (-0.72, 1.49)	
Duration of diabetes ≤ 3yr (N)	19	12
HbA1c: Adjusted mean change from Baseline (%)	-0.53	-0.19
Difference from Control (95% CI)	-0.33 (-0.98, 0.31)	
Duration of diabetes > 3 -< 5 yr (N)	26	12
HbA1c: Adjusted mean change from Baseline (%)	-0.72	-0.56
Difference from Control (95% CI)	-0.15 (-0.76, 0.45)	
Duration of diabetes > 5 yr (N)	255	125
HbA1c: Adjusted mean change from Baseline (%)	-0.74	-0.30
Difference from Control (95% CI)	-0.44 (-0.63, -0.25)	
Duration of diabetes ≥ 10 yrs (N)	167	93
HbA1c: Adjusted mean change from Baseline (%)	-0.80	-0.32
Difference from Control (95% CI)	-0.48 (-0.70, -0.25)	
Race		
White (N)	234	116
HbA1c: Adjusted mean change from Baseline (%)	-0.81	-0.37
Difference from Control (95% CI)	-0.44 (-0.64, -0.24)	
Black. African American (N)	13	9
HbA1c: Adjusted mean change from Baseline (%)	-0.47	-0.08
Difference from Control (95% CI)	-0.38 (-1.13, 0.37)	
Asian (N)	39	19
HbA1c: Adjusted mean change from Baseline (%)	-0.54	-0.08
Difference from Control (95% CI)	-0.46 (-0.94, 0.03)	
Other (N)	14	5
HbA1c: Adjusted mean change from Baseline (%)	-0.67	-1.10
Difference from Control (95% CI)	0.43 (-0.47, 1.34)	
Gender		
Female (N)	181	81
HbA1c: Adjusted mean change from Baseline (%)	-0.77	-0.33
Difference from Control (95% CI)	-0.45 (-0.68, -0.21)	
Male (N)	119	68
HbA1c: Adjusted mean change from Baseline (%)	-0.72	-0.36
Difference from Control (95% CI)	-0.36 (-0.63, -0.10)	
Age		
Age < 65 yr (N)	230	117
HbA1c: Adjusted mean change from Baseline (%)	-0.73	-0.31
Difference from Control (95% CI)	-0.42 (-0.62, -0.22)	
Age ≥ 65 yr (N)	70	32
HbA1c: Adjusted mean change from Baseline (%)	-0.73	-0.35

	Saxa 5mg + INS	Placebo + INS
Difference from Control (95% CI)	-0.38 (-0.75, -0.01)	
Age ≥ 75 yr (N)	5	3
HbA1c: Adjusted mean change from Baseline (%)	-0.57	-0.66
Difference from Control (95% CI)	0.09 (-1.18, 1.37)	
BMI		
BMI < 30 (N)	106	61
HbA1c: Adjusted mean change from Baseline (%)	-0.76	-0.25
Difference from Control (95% CI)	-0.50 (-0.78, -0.23)	
BMI ≥ 30 (N)	194	88
HbA1c: Adjusted mean change from Baseline (%)	-0.75	-0.40
Difference from Control (95% CI)	-0.35 (-0.57, -0.12)	
Geographic Region		
North America (N)	59	33
HbA1c: Adjusted mean change from Baseline (%)	-0.64	-0.15
Difference from Control (95% CI)	-0.49 (-0.86, -0.12)	
Latin America (N)	58	29
HbA1c: Adjusted mean change from Baseline (%)	-1.15	-0.52
Difference from Control (95% CI)	-0.63 (-1.02, -0.24)	
Europe (N)	122	56
HbA1c: Adjusted mean change from Baseline (%)	-0.69	-0.41
Difference from Control (95% CI)	-0.29 (-0.56, -0.01)	
Asia/Pacific (N)	35	15
HbA1c: Adjusted mean change from Baseline (%)	-0.58	0.06
Difference from Control (95% CI)	-0.64 (-1.17, -0.12)	
Africa (N)	26	16
HbA1c: Adjusted mean change from Baseline (%)	-0.65	-0.56
Difference from Control (95% CI)	-0.09 (-0.63, -.46)	

For some subgroups (duration of diabetes ≤1.5 yr and race "other") the effect in the saxagliptin group was smaller than in the placebo group. However, in these subgroups the number of patients was small and the 95% CIs were large.
With respect to the geographic region, the difference from control was -0.29 in Europe, vs -0.64 in Asia, -0.49 in North America and -0.63 in Latin America. There is a large difference in response to placebo, with no effect in Asia, and the largest effect (-0.52) in Latin America. This was raised as a concern by the CHMP, and in response the MAH has submitted further details on the number of European patients recruited from the EU and the number of patients outside the EU. The efficacy results of these both groups are compared. Although the placebo-corrected mean reductions were numerically smaller for EU subjects than in the overall population (also in the individual geographic regions as presented in the ST CSR) and the 95% CI of the placebo-corrected reduction was wide, there was no evidence of a treatment-by-region interaction in this new analysis (p=0.262). A difference in placebo-corrected response between Asian and European patients or Asian and White patients had previously also been observed with another DPP-4 inhibitor.

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Supportive study: Study D1680C00007 (study 07)

To supplement study 057, this submission also includes data from study D1680C00007 (study 07), a Phase 3b clinical study that investigated the efficacy, safety, tolerability, and PK of saxagliptin 2.5 mg compared to placebo in adult subjects with type 2 diabetes and renal impairment (moderate, severe, and end-stage). Study 07 was designed to test the hypothesis that saxagliptin 2.5 mg once daily in renally impaired subjects with type 2 diabetes is effective and well tolerated. Because the intent was to evaluate the effects of the selected dose of saxagliptin in a subject population as broad as possible to reflect general treatment practices, subjects receiving treatment with oral antidiabetics (OADs) and/or insulin were permitted to enrol in the study. Results of this study have previously been submitted and assessed in regulatory applications introducing the 2.5 mg strength and posology in patients with moderate or severe renal impairment (EMEA/H/C/10039/X/04-II/08). In short: Study 07 was a 12-week study with a 40 week extension. At baseline, the majority of subjects was using other

antihyperglycaemic medications, including insulin and oral blood glucose lowering drugs. Numbers of patients using insulin were 70/85 (82.4%) in the saxagliptin group versus 55/85 subjects (64.7%) in the placebo group. Mean insulin dose was 50.73 IU in the saxagliptin group and 41.68 IU in the placebo group. At week 12, HbA1c was reduced in both treatment groups. The reduction was statistically significantly greater with saxagliptin group than with placebo. Insulin dose decreased slightly from baseline in the saxagliptin group but remained relatively constant in the placebo group. In general, saxagliptin 2.5 mg was well tolerated. In subjects receiving insulin, the incidence of AEs and SAEs was higher than in patients not treated with insulin (AEs: 77.5% vs 64.3% in the saxagliptin group insulin vs non-insulin; 70.2% vs 71.4% in the placebo group insulin vs non-insulin. SAEs: 28.2% vs 21.4% in the saxagliptin group and 31.6% vs 21.4% in the placebo group). In these groups too, incidence in the saxagliptin group was higher as compared with placebo. The CHMP concluded that the benefit/risk of this study and the Type II variation was positive. Results of study 07 will not be further discussed in this Assessment Report.

3.3.2 Conclusion on the clinical efficacy

The addition of saxagliptin to patients treated with insulin resulted in a modest decrease of HbA1c. The maximum was reached at week 12 and was maintained trough week 24. The mean placebo corrected decrease was -0.41%. Secondary endpoints were in line with this result.
Results were similar in subjects with and without metformin use at baseline.
In both groups a relative large percentage of patients discontinued because of lack of glycaemic control (22.7% vs 32.8 in the saxagliptin and placebo group, respectively).
There were differences in effect according to geographic region. These differences were due to a difference in placebo response, with no effect of placebo in Asian patients and the largest effect in Latin America patients. In European patients the placebo-corrected decrease in HbA1c was very modest: -0.29%. However, there was no evidence of a treatment-by-region interaction in an additional analysis requested by CHMP during the evaluation. Also, a difference in placebo-corrected response between Asian and European patients or Asian and White patients has been observed with another DPP-4 inhibitor. In study 057, there was no significant difference in placebo-corrected HbA1c between White patients and Asian patients, perhaps because of the inclusion of Latin American patients who had both a large response on placebo and on saxagliptin.

1.4. Clinical safety

Patient exposure

In study 057, a total of 455 subjects (saxagliptin: 304; placebo: 151) received double-blind study medication during the 24-week ST period. The mean duration of exposure to study medication was 161.6 days (standard deviation [SD] 31.06) in the saxagliptin group and 161.9 days (SD 29.46) in the placebo group. A total of 402 of these 455 subjects (88.4%) completed 24 weeks of treatment.
See also Figure 2 and Table 1.

Adverse events

Saxagliptin added to insulin therapy was well tolerated with a safety profile comparable to that of placebo. The incidence of AEs, SAEs, and AEs leading to discontinuation was similar between the 2 treatment groups (Table 7).
The overall incidence of AEs during the short-term treatment period (prior to rescue), excluding all events of hypoglycaemia, was 52.3% in subjects receiving saxagliptin compared with 55.6% in subjects receiving placebo. Table 8 presents AEs (excluding events of hypoglycaemia) that occurred in ≥ 2% of subjects. In the saxagliptin group the 3 most common events were urinary tract infection, upper respiratory tract infection, and headache whereas in the placebo group the 3 most common events were influenza, urinary tract infection, and pain in extremity. When examining AEs regardless of rescue status, the overall incidence of AEs, excluding all events of hypoglycaemia, was 53.9% in subjects receiving saxagliptin compared with 57.6% in subjects receiving placebo. This incidence reflects the addition of 8 subjects (5 in the saxagliptin group and 3 in the placebo group) with AEs post rescue (and not prior to rescue). The types of AEs reported regardless of rescue status were comparable to those noted prior to rescue; most were unlikely or unrelated to study drug treatment and mild or moderate in intensity.

Table 7: Overall summary of adverse events during short-term treatment period, prior to rescue, study 057

	Saxa 5mg + Ins N = 304		Pla + Ins N = 151	
At least one adverse event	173	(56.9)	90	(59.6)
At least one related adverse event	43	(14.1)	26	(17.2)
Deaths	1	(0.3)	0	
At least one serious adverse event	12	(3.9)	6	(4.0)
At least one related serious adverse event	2	(0.7)	0	
Discontinuation due to serious adverse event	0		0	
Discontinuation due to adverse event	4	(1.3)	3	(2.0)

Table 8: Most Common Adverse Events (Incidence >=2%) - Summary by system Organ Class and Preferred Term During Short-term Treatment Period, Prior to Rescue- Treated subjects, study 057

System Organ Class (SOC) (%) Preferred Term (PT) (%)	SAXA 5MG + INS N=304	PLACEBO + INS N=151
TOTAL SUBJECTS WITH AN EVENT	159 (52.3)	84 (55.6)
INFECTIONS AND INFESTATIONS	79 (26.0)	44 (29.1)
urinary tract infection	18 (5.9)	9 (6.0)
upper respiratory tract infection	14 (4.6)	6 (4.0)
bronchitis	10 (3.3)	3 (2.0)
influenza	9 (3.0)	10 (6.6)
nasopharyngitis	8 (2.6)	7 (4.6)
GASTROINTESTINAL DISORDERS	41 (13.5)	21 (13.9)
constipation	8 (2.6)	4 (2.6)
diarrhoea	8 (2.6)	6 (4.0)
gastritis	7 (2.3)	2 (1.3)
NERVOUS SYSTEM DISORDERS	36 (11.8)	17 (11.3)
headache	13 (4.3)	5 (3.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	34 (11.2)	21 (13.9)
arthralgia	8 (2.6)	2 (1.3)
back pain	6 (2.0)	4 (2.6)
pain in extremity	5 (1.6)	9 (6.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	21 (6.9)	8 (5.3)
oedema peripheral	6 (2.0)	4 (2.6)

The incidence of AEs, SAEs, and AEs leading to discontinuation was similar between the 2 treatment groups. The safety profile of saxagliptin was comparable to that of placebo. There were no unexpected adverse events.

Serious adverse events and deaths

One death, as a result of myocardial infarction, was reported during the 24-week ST period. The investigator judged the event of myocardial infarction to be very severe in intensity and considered the event not to be related to the study medication. The patient had a history of cardiovascular disease.
Other SAEs (prior to rescue) were reported for a similar proportion of subjects in the saxagliptin (12 patients, 3.9%) and placebo (6 patients, 4.0%) groups. No SAE was reported for more than 1 subject during the ST treatment period and most SAEs were considered by the investigator to be not likely related or unrelated to study drug treatment.

Two subjects in the saxagliptin group had SAEs that were considered to be related to study drug treatment: 1 subject with chest pain and 1 subject with 2 episodes of severe hypoglycaemia. Three saxagliptin-treated subjects and no placebo-treated subjects had cardiovascular-related SAEs prior to rescue: myocardial infarction that led to death (see "Deaths" above), acute coronary syndrome, and acute myocardial infarction. There was 1 subject with a SAE of breast cancer post-rescue leading to discontinuation during the ST treatment period in the saxagliptin group.

There were 3 subjects in the saxagliptin group and none in the placebo group with a cardiac event. One of these patients died. All patients had a history of cardiovascular disease or hypercholesterolemia. No action was taken in relation to the study drug. None of these events was considered related to the study drug by the investigator. Although these cases are serious, there is insufficient information to draw a conclusion on any relation with saxagliptin. In any case, cardiac event are closely monitored and reported in 6 monthly periodc safety update reports. Moreover, the MAH is conducting a 5-year cardiovascular outcomes study to evaluate the effect of saxagliptin on the incidence of CV death, myocardial infarction, or ischaemic stroke in subjects with T2DM.

Adverse events leading to discontinuation

Seven subjects (4 [1.3%] in the saxagliptin group and 3 [2.0%] in the placebo group) discontinued from study due to AEs during the ST treatment period (prior to rescue). Additionally, 1 subject discontinued due to an AE that began during the lead-in period (creatinine renal clearance decreased. In the saxagliptin group, there were two patients in the SOC "investigations" (glomerular filtration rate decreased), one patients with "gastrointestinal disorders" (diarrhoea, dyspepsia), and one patient with hypoglycaemia. Hypoglycaemia began on Day 125 and resolved within 5 days. In the placebo group, there were two patients in the SOC "investigations" (blood creatine phosphokinase increased, blood creatinine increased, creatinine renal clearance decreased), and one with upper abdominal pain. Most AEs leading to discontinuation of treatment were reported to be of mild or moderate intensity.
When examining subjects regardless of rescue status, there was 1 additional subject in the saxagliptin group with an AE that led to discontinuation from study. This subject had a post-rescue SAE of breast cancer (considered by the investigator not to be related to study medication).

Adverse events of special interest

AEs of **hypoglycaemia** were recorded and analysed separately from other AEs. Confirmed hypoglycaemia was defined by a fingerstick glucose value ≤50 mg/dL (2.8 mmol/L) with associated hypoglycaemia symptoms. The overall frequency of confirmed hypoglycaemic events with associated symptoms during the ST treatment period was 5.3% in the saxagliptin group and 3.3% in the placebo group. Most of these confirmed hypoglycaemic events with associated symptoms were mild or moderate in intensity.
A total of 56 (18.4%) subjects in the saxagliptin group and 30 (19.9%) subjects in the placebo group experienced any hypoglycaemic AE during the ST treatment period and prior to rescue. These included hypoglycaemia in 15.8% and 17.2% of subjects, and blood glucose decreased in 2.6% and 6.0% of subjects, respectively. Most hypoglycaemic events were of mild or moderate intensity. One subject in the saxagliptin group required medical assistance for her hypoglycaemia.

The proportion of subjects who had AEs included in the SOC Skin and Subcutaneous Tissue Disorders was the same in the saxagliptin and placebo groups (2.0%). The SOC Skin and subcutaneous Tissue Disorder AEs occurring in ≥ 2 subjects were skin ulcer in 2 (0.7%) subjects in the saxagliptin group and rash in 2 (1.3%) subjects in the placebo group.

A similar proportion of subjects had AEs prior to rescue in the SOC Infections and Infestations (saxagliptin: 26.0%; placebo: 29.1%). These AEs most common AEs in this SOC included urinary tract infection, upper respiratory tract infection, and influenza.

One (0.3%) subject in the saxagliptin group and no subject in the placebo group had an AE of Lymphopenia.

One (0.3%) subject in the saxagliptin group and 1 (0.7%) subject in the placebo group had an AE of thrombocytopenia prior to rescue. For the subject in the saxagliptin group, the investigator reported a non-serious AE of thrombocytopenia for a platelet count of 39 x103 c/µL (39 x109 c/L). The study medication was interrupted due to the thrombocytopenia, the platelet count returned to normal at the next measurement, the event of thrombocytopenia resolved, and the study medication was restarted.

The investigator judged the event to be moderate in intensity and possibly related to the study medication.

One (0.3%) subject in the saxagliptin group and no subject in the placebo group had an AE of pedal oedema. This AE was mild in intensity, and considered by the investigator not to be related to study drug treatment, and was still continuing as of last contact with the subject.

Three (1.0%) saxagliptin-treated subjects and no placebo-treated subjects had cardiovascular-related PT (preferred term) events prior to rescue: a SAE of acute coronary syndrome, a SAE of acute myocardial infarction, and a SAE of myocardial infarction that led to death. All 3 events were submitted to the adjudication committee and confirmed by reviewers. None of these AEs were considered by the investigator to be related to study medication.

Two (0.7%) subjects in the saxagliptin group and no subject in the placebo group had hypersensitivity AEs. One subject had an AE of hypersensitivity (reported term of allergy symptoms) that was moderate in intensity, considered by the investigator not to be related to study drug treatment, and was still ongoing as of last contact with the subject. One subject had an AE of urticaria that was mild in intensity, considered by the investigator to possibly be related to study drug treatment, and resolved within 5 days.

No subject had an AE matching the pre-specified preferred terms for pancreatitis.

Five subjects, 2 (0.7%) subjects in the saxagliptin group and 3 (2.0%) subjects in the placebo group had fracture AEs (Supplemental Table S.6.5.14). These included foot fracture in the 2 subjects in the saxagliptin group and 1 subject each with hand fracture, humerus fracture, and lower limb fracture in the placebo group. None of these fractures were considered by the investigator to be related to study drug treatment and all resolved within 32 days.

In the SOC Gastrointestinal disorders, there was no apparent difference between treatment groups, saxagliptin group 41 (13.5%) subjects and placebo group 21 (13.9%) subjects. Gastrointestinal-related AEs by PT reported by ≥ 2% of subjects in either treatment group during the ST period were constipation (2.6% versus 2.6% in the saxagliptin and placebo groups, respectively), diarrhoea (2.6% versus 4.0%, respectively), and gastritis (2.3% versus 1.3%, respectively).

Overal, analysis of adverse events of special interest did not reveal unexpected adverse events. There was no difference in the incidence of hypoglycaemia between the saxagliptin group and the placebo group.
However, skin ulcer and neuropathic ulcer observed in less than 2% in the saxagliptin group were raised as a concern by the CHMP. The MAH therefore provided further clarification that the cases in study 057 represent isolated reports of skin ulceration. There were 3 (1.0%) subjects who reported skin or neuropathic ulcers in the saxagliptin treatment group and none in the placebo group. These ulcers were mild in intensity, did not lead to discontinuation, and resolved during saxagliptin therapy. Section 4.4 of the current SmPC contains text regarding skin disorder, including ulceration and the current text was considered sufficient by the CHMP.

Laboratory findings

There were no marked abnormalities (MAs) reported for decreased platelets or decreased neutrophils. For saxagliptin treated subjects, marked abnormalities were reported in 1 (0.3%) subject each for decreased hemoglobin and decreased hematocrit and for 1 (0.7%) subject in the placebo group for decreased leukocytes. Decreased lymphocytes (lymphopenia) was noted for 3 (1.0%) subjects in the saxagliptin group and 1 (0.7%) subject in the placebo group. Increased eosinophils were noted for 7 (2.4%) subjects in the saxagliptin group and 6 (4.0%) subjects in the placebo group.

Alkaline phosphatase levels elevated >1.5 x ULN were noted for 9 (3.0%) subjects in the saxagliptin group and 3 (2.0%) subjects in the placebo group, and there were no subjects with alkaline phosphatase levels >3 x baseline and >ULN. Markedly abnormal elevated ALT (>3 x ULN) was reported for 2 (0.7%) subjects in the saxagliptin group and 1 (0.7%) in the placebo group. One (0.3%) subject in the saxagliptin group had markedly abnormal elevated total bilirubin (>2 mg/dL [34.2 µmol/L] or >1.5 x ULN). However, no subject had ALT >3 x ULN and a total bilirubin >1.5 x ULN or ALT >3 x ULN and a total bilirubin >2 mg/dL (34.2 µmol/L).
Four (1.3%) subjects in the saxagliptin group and 1 (0.7%) subject in the placebo group had elevated creatine kinase (CK) > 5 x ULN and were reported as AEs in 3 cases. In most cases these elevations

represented a single high value and CK levels had returned to within normal limits (or were much lower) by the last recorded value.

The most frequent urinary marked abnormality was urinary WBCs (measured quantitatively), which was present in 26 (25.2%) subjects in the saxagliptin group and 6 (13.3%) subjects in the placebo group. Marked abnormalities of haematuria (measured via dipstick) were seen in 11 (3.7%) subjects in the saxagliptin group and 1 (0.7%) subject in the placebo group. Few subjects had marked abnormalities of urinary protein (4 [1.4%] saxagliptin subjects and no placebo subject) or urinary RBCs (6 [12.8%] saxagliptin subjects and no placebo subjects) during the ST treatment period.

Vital signs

Of the 180 subjects who had normal ECG tracings at baseline, 16 (12.5%) who received saxagliptin and 2 (3.8%) who received placebo had abnormal tracings at Week 24. A varying spectrum of ECG abnormalities was noted over all treatment groups. A review of the ECG abnormality descriptions indicated that none of the changes was of clinical relevance.
No clinically meaningful changes from baseline were observed for systolic and diastolic blood pressures or heart rate in either treatment group during the double blind treatment period.

3.4.1 Conclusion on clinical safety

Overall saxagliptin was well tolerated. There were no unexpected or new adverse events.
The overall incidence of AEs during the short-term treatment period (prior to rescue), excluding all events of hypoglycaemia, was 52.3% in subjects receiving saxagliptin compared with 55.6% in subjects receiving placebo. Including rescue, the incidence was 53.9% and 57.6% respectively.
In the saxagliptin group the 3 most common events were urinary tract infection, upper respiratory tract infection, and headache whereas in the placebo group the 3 most common events were influenza, urinary tract infection, and pain in extremity.
Patients on saxagliptin had no more hypoglycaemia than placebo treated patients.
There was one death due to myocardial infarction and two other cardiovascular-related SAEs in the saxagliptin group, all considered unrelated to study medication. Patients had already a cardiovascular history and/or hypercholesterolemia. Information is insufficient to draw any conclusion on a relation with saxagliptin usage. In any case, cardiac events are closely monitored and reported in 6-monthly periodc safety update reports. Moreover, the MAH is conducting a 5-year cardiovascular outcomes study to evaluate the effect of saxagliptin on the incidence of CV death, myocardial infarction, or ischaemic stroke in subjects with T2DM.
During the evalution of this extension of indication application, efficacy results from the long term extension period of study 057 became available and were provided by the applicant and did show that proportions of subjects reporting AEs, serious AEs, and discontinuations for AEs were similar across both treatment groups during the extension period. No additional efficacy and safety aspects have emerged.

Risk management plan

A new RMP version had been provided as part of a recent PSUR submission, which was assessed and concluded. This RMP version was already updated to include exposure data from study CV181057 as well as data on identified and potential risks and therefore also contains important identified and potential risks for saxagliptin in the context of the change in indication with this type II variation. The applicant hereby provided a justification for not submitting an update of the current RMP as part of this extension of indication application, which was considered acceptable by the CHMP.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.
No additional risk minimisation activities were required beyond those included in the product information

Changes to the Product Information

Following the assessment of this extension of indication application, the CHMP endorsed the following changes to the SmPC and to the Package Leaflet (bold underlined = new text, strikethrough = deleted text):

Section 4.1 Therapeutic indications of the SmPC

- **in combination with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.**

Section 4.2 Posology and method of administration of the SmPC

Posology

Add-on combination therapy

The recommended dose of Onglyza is 5 mg once daily as add-on combination therapy with metformin, **insulin,** a thiazolidinedione or a sulphonylurea.

Section 4.4 Special warnings and precautions for use of the SmPC

General
Onglyza should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Onglyza is not a substitute for insulin in insulin-requiring patients.

Use with **medicinal products known to cause hypoglycaemia**
Sulphonylureas **and insulin** are known to cause hypoglycaemia. Therefore, a lower dose of sulphonylurea **or insulin** may be required to reduce the risk of hypoglycaemia when used in combination with Onglyza.

Section 4.8 Undesirable effects of the SmPC

When used as add-on to insulin (with or without metformin), the overall incidence of reported hypoglycaemia was 18.4% for Onglyza 5 mg and 19.9% for placebo.

Section 5.1 Pharmacodynamic properties of the SmPC

Saxagliptin add-on combination therapy with insulin (with or without metformin)
A total of 455 patients with type 2 diabetes participated in a 24-week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin in combination with a stable dose of insulin (baseline mean: 54.2 Units) in patients with inadequate glycaemic control (HbA1c ≥ 7.5% and ≤ 11%) on insulin alone (n=141) or on insulin in combination with a stable dose of metformin (n=314). Saxagliptin 5 mg add-on to insulin with or without metformin provided significant improvements after 24 weeks in HbA1c and PPG compared with placebo add-on to insulin with or without metformin. Similar HbA1c reductions versus placebo were achieved for patients receiving saxagliptin 5 mg add-on to insulin regardless of metformin use (−0.4% for both subgroups). Improvements from baseline HbA1c were sustained in the saxagliptin add-on to insulin group compared to the placebo add-on to insulin group with or without metformin at Week 52. The HbA1c change for the saxagliptin group (n=244) compared to placebo (n=124) was -0.4% at Week 52.

Table 3 Key efficacy results of Onglyza 5 mg per day in placebo-controlled monotherapy trials and in add-on combination therapy trials

	Mean baseline HbA1c (%)	Mean change[2] from baseline HbA1c (%) at Week 24	Placebo-corrected mean change in HbA1c (%) at Week 24 (95% CI)
MONOTHERAPY STUDIES			
• Study CV181011 (n=103)	8.0	-0.5	-0.6 (-0.9, -0.4)[3]
• Study CV181038 (n=69)	7.9	-0.7 (morning)	-0.4 (-0.7, -0.1)[4]
(n=70)	7.9	-0.6 (evening)	-0.4 (-0.6, -0.1)[5]
ADD-ON/COMBINATION STUDIES			
• Study CV181014: add-on to metformin (n=186)	8.1	-0.7	-0.8 (-1.0, -0.6)[3]
• Study CV181040: add-on to SU[1] (n=250)	8.5	-0.6	-0.7 (-0.9, -0.6)[3]
• Study CV181013: add-on to TZD (n=183)	8.4	-0.9	-0.6 (-0.8, -0.4)[3]
• Study CV181039: initial combination with metformin[6]			
Overall population (n=306)	9.4	-2.5	-0.5 (-0.7, -0.4)[7]
Baseline HbA1c ≥ 10% stratum (n=107)	10.8	-3.3	-0.6 (-0.9, -0.3)[8]
• **Study CV181057: add-on to insulin (+/-metformin)**			
Overall population (n=300)	**8.7**	**-0.7**	**-0.4 (-0.6, -0.2)[3]**

n=Randomized patients (primary efficacy-intention-to-treat analysis) **with data available**.
[1]Placebo group had uptitration of glibenclamide from 7.5 to 15 mg total daily dose.
[2] Adjusted mean change from baseline adjusted for baseline value (ANCOVA).
[3] p<0.0001 compared to placebo.
[4] p=0.0059 compared to placebo.
[5] p=0.0157 compared to placebo.
[6] Metformin was uptitrated from 500 to 2000 mg per day as tolerated.
[7] Mean HbA1c change is the difference between the saxagliptin+metformin and metformin alone groups (p<0.0001).
[8] Mean HbA1c change is the difference between the saxagliptin+metformin and metformin alone groups.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Onglyza in one or more subsets of the paediatric population in the treatment of type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

The Package Leaflet has been updated accordingly. In addition minor changes have been made throughout the Product Information.

The CHMP agreed with the changes to the Annexes requested by the MAH listed above.

2. Benefit Risk Balance

Benefits

Beneficial effects

The efficacy and safety of the addition of saxagliptin to insulin was investigated in one clinical study (057). This was a randomised, double-blind, placebo controlled trial in 455 patients, insufficiently controlled by insulin or insulin plus metformin. After screening and lead-in, patients were randomised in a 2:1 ratio to receive saxagliptin 5 mg qd or placebo for 24 weeks.
The addition of saxagliptin to patients treated with insulin resulted in a decrease of HbA1c. The maximum was reached at week 12 and was maintained trough week 24. The mean placebo corrected decrease was -0.41%. Secondary endpoints were in line with this result. Results were similar in subjects with and without metformin use at baseline.
Mean total insulin dose increased from baseline to week 24 in both groups. However, the mean increase was lower in the saxagliptin group (1.7 units) than in the placebo group (5.0 units).
After this short term period, patients entered a long-term phase of 28 weeks, the data of which had been provided by the applicant during the evaluation and did not show any additional efficacy aspects; the observed decrease of HbA1c in particular was sustained thought week 52.
Overall, both primary and secondary parameters indicate that the addition of saxagliptin to patients treated with insulin was effective. The effect was modest with an HbA1c adjusted mean difference from placebo of -0.41% but the study demonstrated nevertheless a statistically significant reduction, and the effect size in this population with advanced T2DM was still considered to be of clinical relevance by the CHMP.

Uncertainty in the knowledge about the beneficial effects

In both groups a relative large percentage of patients discontinued because of lack of glycaemic control (22.7% vs 32.8 in the saxagliptin and placebo group, respectively).
The placebo group had a considerable reduction in HbA1c of 0.32%, likely attributable to dietary and exercise factors, some of which may have extended beyond randomisation.
There were differences in effect according to geographic region. The adjusted mean change in HbA1c from baseline was -0.69% in Europe, -0.64% in North America, -1.15% in Latin America, and -0.58% in Asia. The response in the placebo group was -0.41% in Europe, -0.15% in North America, -0.52% in Latin America and 0.06% in Asia. This resulted in a difference from control of -0.29% in Europe, vs -0.49% in North America, -0.63% in Latin America and -0.64% in Asia. However, there was no evidence of a treatment-by-region interaction (p=0.262) and a difference in placebo-corrected response between Asian and European patients had previously also been observed with another DPP-4 inhibitor.

Risks

Unfavourable effects

In general saxagliptin was well tolerated. There were no unexpected or new adverse events.
The overall incidence of AEs during the short-term treatment period (prior to rescue), excluding all events of hypoglycaemia, was 52.3% in subjects receiving saxagliptin compared with 55.6% in subjects receiving placebo. In the saxagliptin group the 3 most common events were urinary tract infection, upper respiratory tract infection, and headache whereas in the placebo group the 3 most common events were influenza, urinary tract infection, and pain in extremity.
Patients on saxagliptin had no more hypoglycaemia than placebo treated patients.
Data submitted during the evaluation for the extension period through week 52 of study 057 did not show any different findings compared to the short term period.

Uncertainty in the knowledge about the unfavourable effects

There was one death due to myocardial infarction and two other cardiovascular-related SAEs in the saxagliptin group, all considered unrelated to study medication. Patients had already a cardiovascular history and/or hypercholesterolemia. Nevertheless, cardiac safety is specifically monitored in 6-monthly periodic safety update reports and further addressed in the context of a cardiovascular outcome study performed by the MAH.

Balance

Importance of favourable and unfavourable effects

The addition of saxagliptin resulted in a decrease in HbA1c for the whole population.
However, in both groups a relative large percentage of patients discontinued because of lack of glycaemic control (22.7% vs 32.8 in the saxagliptin and placebo group, respectively).
There were no differences in the size of the effect between races, but there were differences between geographic regions. These were mainly due to differences in placebo-response, with no response in Asian people and a decrease of HbA1C of -0.41% in European patients. This resulted in a relatively small placebo-corrected numerical decrease of -0.29% in the European population of the study. In this heavily treated population with advanced diabetes the effect size was nevertheless still considered to be clinically relevant by the CHMP.
Saxagliptin was in general well tolerated, with no unexpected findings, and no more side effects than the placebo treated patients. Although the three cardiac adverse events were serious, their relation with saxagliptin, if any, is not established. Therefore, cardiovascular adverse events are being closely monitored and further addressed in a dedicated outcome study.

Benefit-risk balance

The effect of adding saxagliptin on HbA1c was modest, especially in European patients, however was still considered to be relevant for the patient group involved. Treatment was not associated with an increase in events of hypoglycaemia, and the increase of daily insulin dose was slightly less in the saxagliptin group. Saxagliptin was well tolerated.

Discussion on the benefit-risk assessment

Saxagliptin, when added to an existing insulin treatment, resulted in further reductions of HbA1c, without showing any unexpected consequences in its safety profile.
The overall B/R of saxagliptin added to insulin is positive.

3. Conclusion

On 20 October 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the SmPC and PL.