EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2012
EMA/70628/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Invented name Komboglyze

Procedure No. EMEA/H/C/002059/II/0004

Marketing authorisation holder (MAH): Bristol-Myers Squibb / AstraZeneca EEIG

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb / AstraZeneca EEIG submitted to the European Medicines Agency on 12 April 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Komboglyze	saxagliptin / metformin hydrochloride	See Annex A

The following variation was requested:

Variation(s) 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

The MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to extend the indication for combination of Komboglyze with insulin (i.e., triple combination therapy). The Package Leaflet was proposed to be updated in accordance. Furthermore, the MAH took this opportunity to correct minor typographical errors in the SmPC and the Package Leaflet.

Rapporteur: Pieter de Graeff

1.2. Steps taken for the assessment

Submission date:	12 April 2012
Start of procedure:	22 April 2012
Rapporteur's preliminary assessment report circulated on:	13 June 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 July 2012
MAH's responses submitted to the CHMP on:	9 August 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	7 September 2012
CHMP opinion:	20 September 2012

2. Scientific discussion

2.1. Introduction

Saxagliptin phosphate 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.

Komboglyze is a fixed dose combination product consisting of saxagliptin + metformin. Komboglyze was approved in the EU on 24 November 2011.The MAH submitted a clinical Type II Variation to extend the indication of Komboglyze as follows:

> *Komboglyze is also indicated in combination with insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control.*

The clinical program to support the use of Komboglyze in combination therapy with insulin was developed in accordance with the 2002 'Notes for Guidance on Clinical Investigations of Medicinal Products in the Treatment of Diabetes Mellitus' (CPMP/EWP/1080/00, May 2002).

This submission consisted of 1 pivotal Phase 3b controlled clinical study, CV181057 (Study 57), which evaluated saxagliptin as add-on therapy to insulin with or without metformin. Study 57 included a 24-week double-blind short-term (ST) period plus an additional 28-week long term (LT) extension period.

The data of study 57 was already submitted previously in support of a variation of Onglyza for the use of saxagliptin in combination with insulin, with or without metformin (see Type II variation EMEA/H/C/001039/II/0011, CHMP positive opinion dated 20 October 2011). The European Commission Decision was granted on 22 November 2011.

This application is therefore based to a considerable part on the data already submitted by the MAH for Onglyza (saxagliptin) as part of the extension of indication as add-on to insulin (variation EMEA/H/C/001039/II/0011). The MAH also included in this submission the long-term data that were submitted during the evaluation of Onglyza variation II/011. For Onglyza the indication was as add-on therapy to insulin both with or without metformin. Therefore within this submission for Komboglyze, the combination with metformin is particularly emphasized.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision on the granting of a product-specific waiver for saxagliptin/metformin (P/240/2009).

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 conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/83/EC.

2.2. Clinical efficacy aspects

The clinical program to evaluate the anti-hyperglycaemic activity of saxagliptin as add on combination therapy with insulin in T2DM is supported by data from the Phase 3b study CV181057 (study 57). Study 57 was a randomized, parallel, double-blind placebo controlled, multicenter trial that compared the anti-hyperglycaemic activity of saxagliptin 5 mg added 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 provides efficacy and safety data to support the

proposed indication; the 28-week LT extension for this study provides additional supportive efficacy and safety data from 402 subjects.

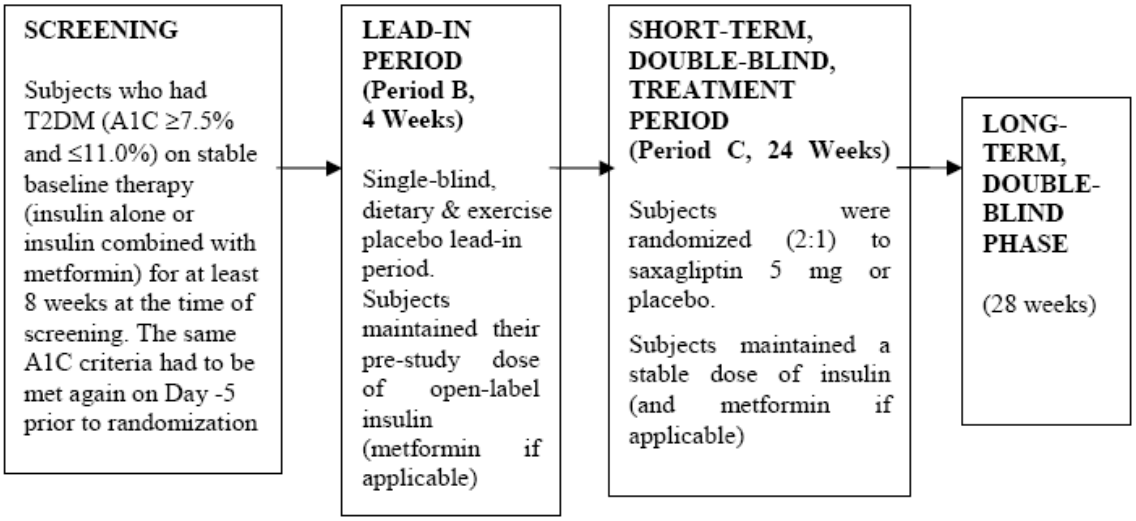
2.2.1. Methods – analysis of data submitted

The main study for this application is study 057.

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 as combination therapy with insulin or to insulin in combination with metformin in subjects withT2DM 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. The 24-week double-blind ST treatment period provides efficacy and safety data to support the proposed indication; the 28-week LT extension for this study provides additional supportive efficacy and safety data from 402 subjects. 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 asHbA1c < 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 analysed 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 analysed 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

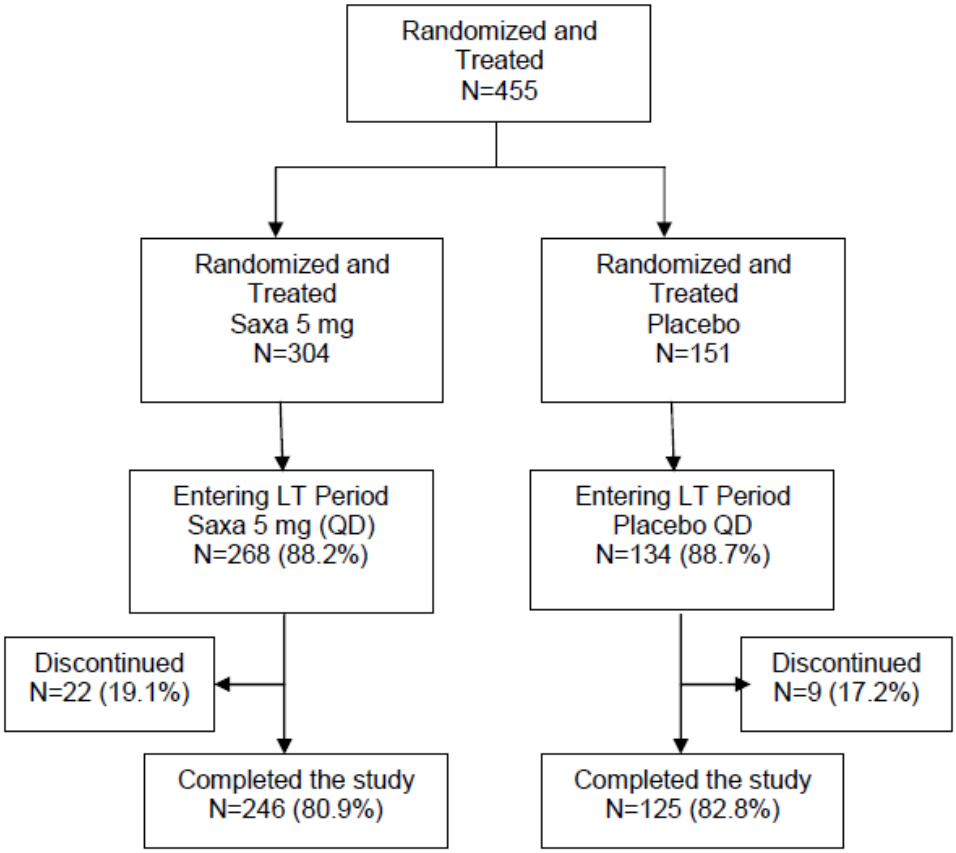
The primary efficacy endpoint was the change in HbA1c from baseline to Week 24. The primary efficacy analysis was an analysis of covariance (ANCOVA) of that endpoint (LOCF), with treatment group and metformin use at enrolment as fixed effects, and baseline value as a covariate in the model. It included 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 modelling 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.

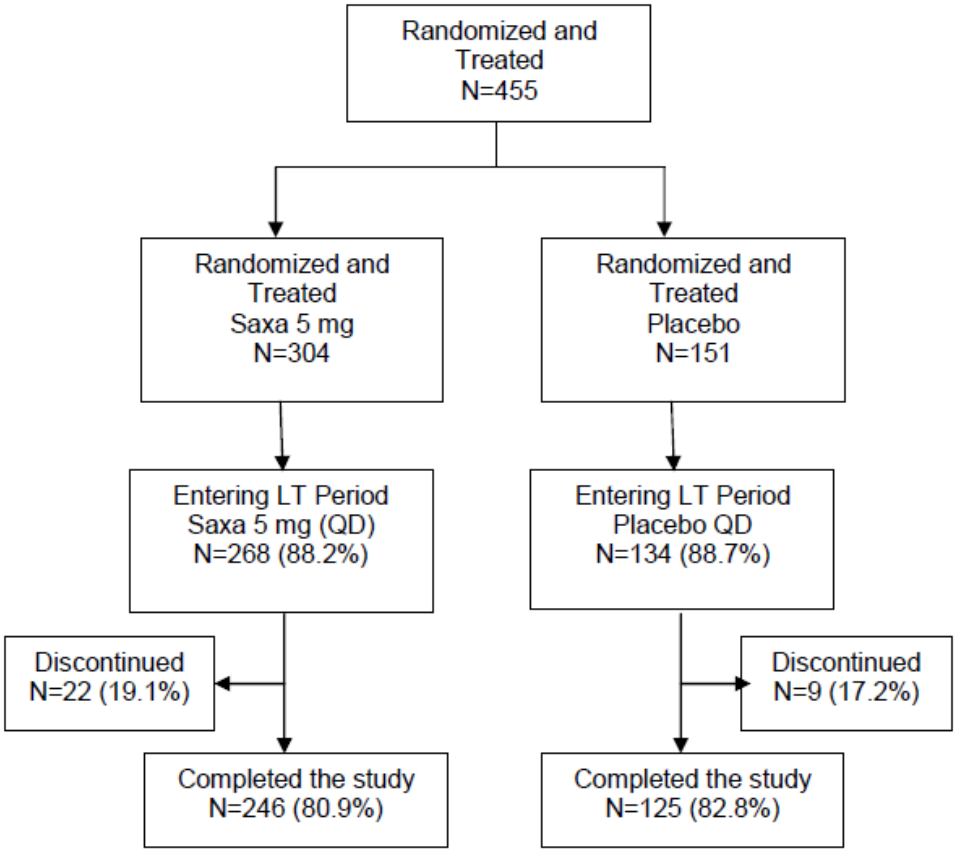
Overall, the design of the study was considered adequate to evaluate the value of saxagliptin when added to insulin. Primary and secondary endpoints were adequate. The inclusion criterion of metformin dose ≥ 1500 mg/day is consistent with that used in previous studies of saxagliptin and other antidiabetic agents and is acceptable. 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



Note: The denominator of each % is the number of randomized and treated subjects.
LT = long term; QD = once daily; SAXA = saxagliptin

Figure 2, Table 1 and Table 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). Discontinuations during the LT-treatment period were also similar (8.2 versus 6.7% in the saxagliptin resp. placebo group).



Note: The denominator of each % is the number of randomized and treated subjects.
LT = long term; QD = once daily; SAXA = saxagliptin

Figure 2: Disposition of subjects in study 057

Table 1: Disposition of Subjects in Short-term and Long-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
Subjects entering the LT period	268	88.2	134	88.7
Reasons for discontinuation of the study	22	8.2	9	6.7
Lack of efficacy	2	0.7	0	
Adverse event	4	1.5	0	
Subject withdrew consent	3	1.1	2	1.5
Death	0		0	
Lost to follow-up	1	0.4	1	0.7
Poor/Non-compliance	5	1.9	2	1.5
Pregnancy	1	0.4	0	
Subject no longer meets study criteria	5	1.9	4	3.0
Administrative reason by Sponsor	0		0	
Other	1	0.4	0	

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

For the analysis of ST+LT period "Randomized Subjects", "Randomized And Treated Subjects" and "Treated Subjects" were used.

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
Percentages 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

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. Sixty-eight per cent (68%) of patients were metformin users.

According to the inclusion criteria, baseline HbA1C was supposed to be ≥ 7.5% and ≤ 11.0% and the MTDDI ≥ 30 units/day, ≤150 units/day. However, according to Table 4, patients had baseline HbA1C values ranging from 7.3- 11.4%, and in the saxagliptin group the minimum insulin dose was 19 units.

During the extension of indication procedure with Onglyza (variation II/011), the MAH was requested by the CHMP to explain the differences observed, and stated that here could be slight differences in HbA1c between screening or Day -5 and baseline, resulting in a baseline value just outside the required range, and that all randomised subjects but 1 had baseline mean total daily dose of insulin (MTDD1) values within the specified range of >=30 to <= 150 units/day. These answers were considered acceptable by the CHMP.

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]).

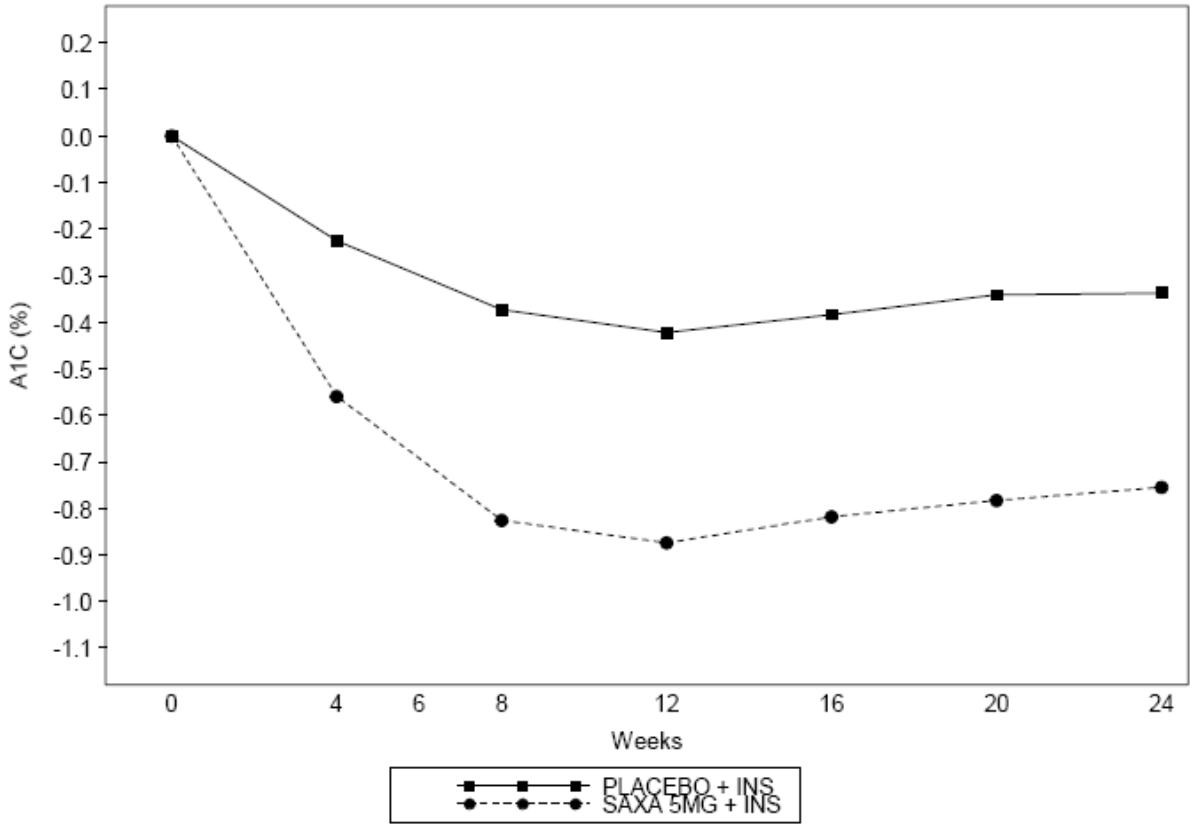
Table 5: Primary and secondary efficacy endpoints at week 24 (LOCF), study 057

	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.

Change from baseline in HbA1c in subgroups based on metformin use (ST treatment period)

Results for changes from baseline in HbA1c at Week 24 (LOCF) were similar in subjects with and without metformin use at baseline (see Table 6). 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]). Changes over time are shown in Figure 4.

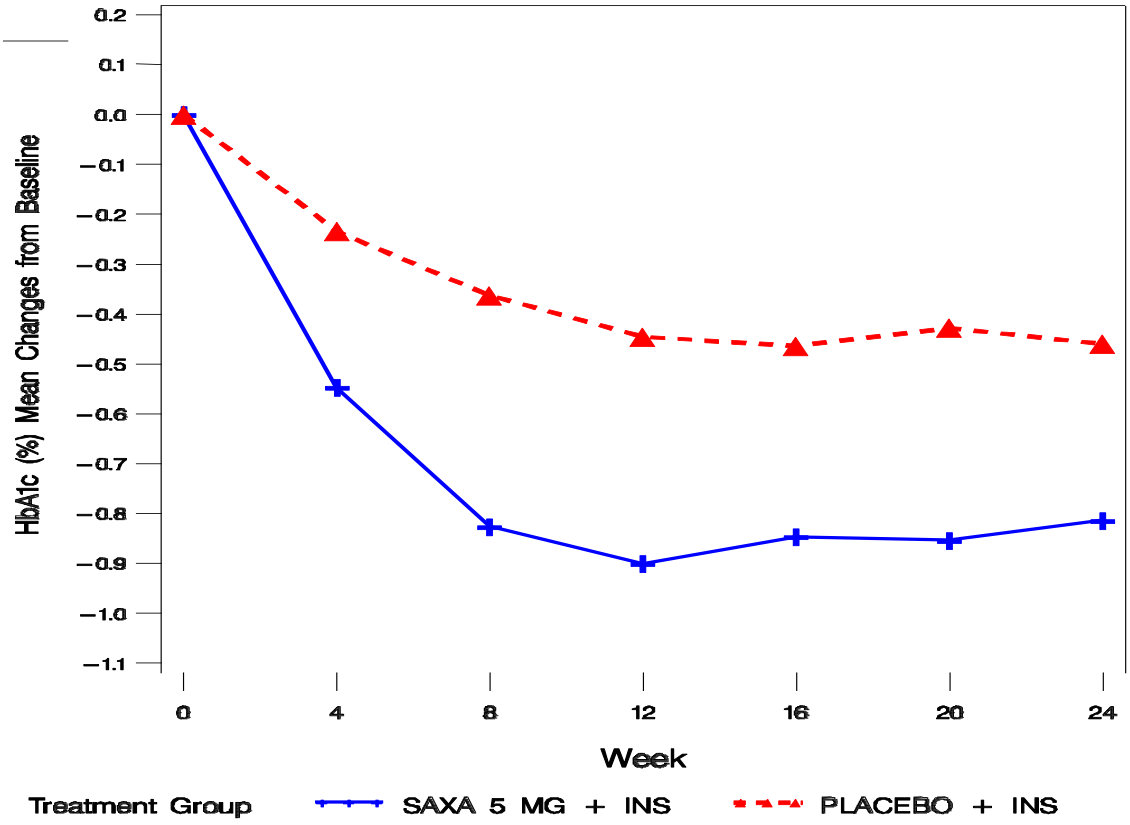


Figure 4: HbA1c mean change from baseline (LOCF) over time during ST treatment period – subjects who took metformin at baseline, Study 057

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 5). 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 Week24, 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/m^2 for saxagliptin treated subjects and 31.76 kg/m^2 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

and0.05 kg/m^2 (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/m^2 (95% CI [-0.07, 0.30]).

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 HbA1C of 0.32%, likely attributable to dietary and exercise factors, some of which may have extended beyond randomisation.

Despite the addition of saxagliptin, mean total insulin dose increased from baseline to week 24. However, the mean increase in the saxagliptin group (1.7 units) was lower than in the placebo group (5.0 units).

A small increase in body weight was seen in both groups (0.39 kg versus 0.18 kg in the saxagliptin versus placebo group, respectively).

Efficacy results from the long term extension period of study 057 are listed in a subsequent section.

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)	

	Saxa 5mg + INS	Placebo + INS
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
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)	

	Saxa 5mg + INS	Placebo + INS
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 year 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, versus -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 as part of variation II/011 for Onglyza. In response, the MAH submitted further details on the number of 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.

Long term efficacy (ST+LT treatment period)

During the LT treatment period of study 57, all subjects who had not yet been rescued were moved to the flexible insulin regimen, while continuing the same study medication. The efficacy analyses in the ST+LT treatment period of study 57 were generated based on randomised subjects regardless of insulin dose. In reporting the ST findings, the efficacy analyses included only results prior to rescue, which could have led to minor differences between Week 24 results in the ST versus the ST+LT treatment periods.

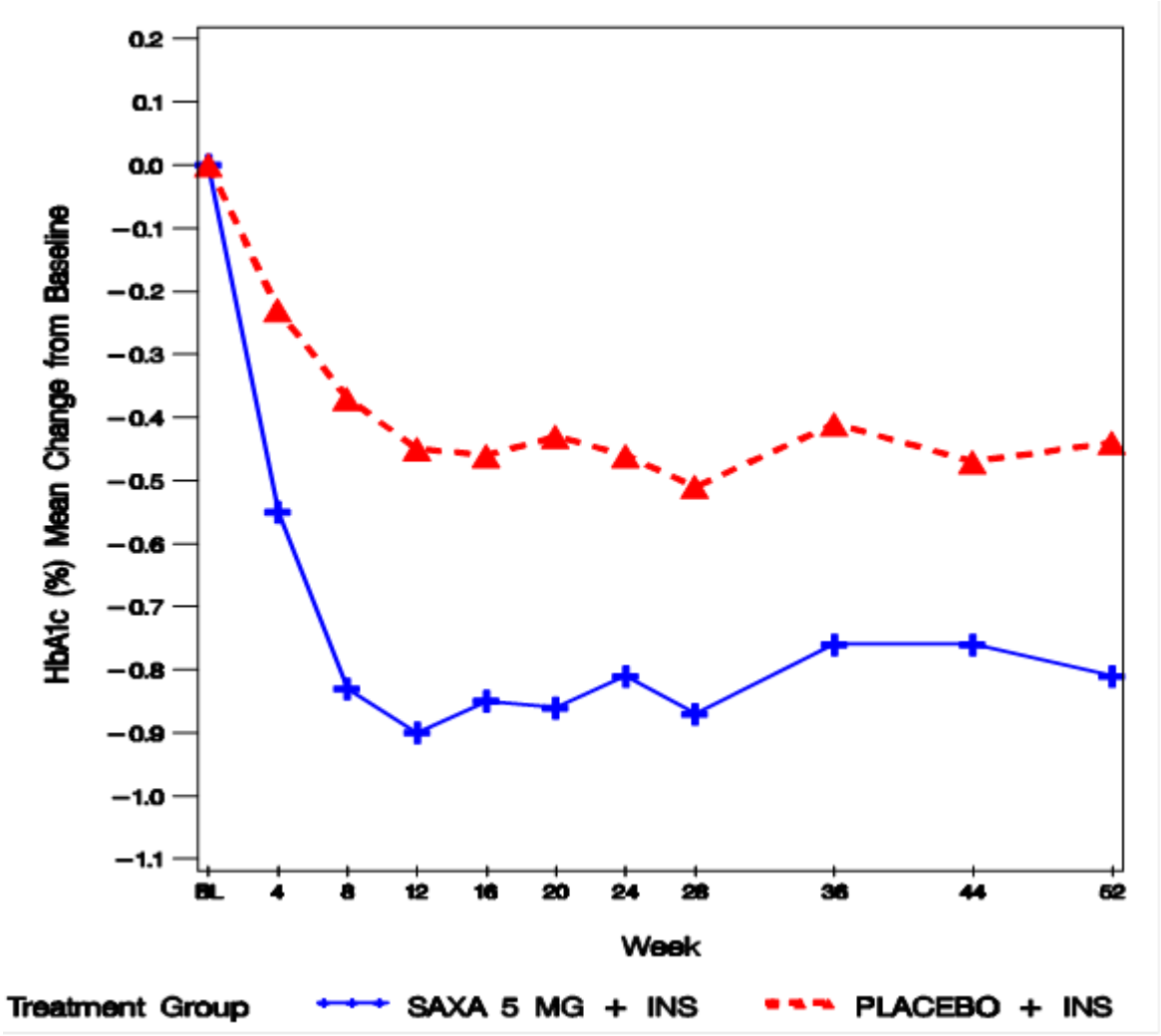
The effect of saxagliptin treatment on HbA1c was analyzed using the repeated measures analysis (mixed model), LOCF, and observed values methodologies. The difference in the adjusted mean change from baseline versus placebo was -0.37% (95% CI [-0.54, -0.20]) at Week 24 and -0.37% (95% CI [-0.55, -0.19]) at Week 52. The adjusted mean change from baseline to Week 52 was -0.75% (95% CI [-0.85, -0.64]) for the saxagliptin treatment group and -0.38% (95% CI [-0.53, -0.23]) for the placebo group.

The results from the LOCF analysis were similar to those from the repeated measures analysis.

The results from **subgroup analyses by metformin use** in the ST+LT period were similar to those seen at Week 24, i.e. treatment with saxagliptin 5 mg in combination with insulin and metformin resulted in HbA1c reductions from baseline at Week 52 (repeated measures analysis) that were similar to treatment with saxagliptin plus insulin without metformin.

Figure 5 presents the mean reductions from baseline HbA1c (repeated measures analysis) during the ST+LT treatment period in the subgroup with metformin use.

Figure 5: HbA1c (%) mean change from baseline (repeated measures analysis) over time during the ST+LT treatment period – Subjects who took metformin at baseline



At Week 52, the percentages of subjects who had achieved a therapeutic glycaemic response (HbA1c <7%) were 21.3% for the saxagliptin treatment group and 8.7% for the placebo group (difference: 12.6%). 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: 23.8%; placebo: 8.7%) or were not receiving metformin (saxagliptin: 16.0%; placebo: 8.7%).

The effect of saxagliptin treatment on MTDDI (mean total daily insulin dose) was analyzed using the repeated measures analysis (mixed model) and LOCF methodologies. Both methodologies indicated increases from baseline in MTDDI were seen in both treatment groups through Week 52, with numerically smaller increases in the saxagliptin group.

For subgroups according to metformin use, increases were seen in MTDDI. However, the magnitude was not similar between subgroups with metformin and without metformin use at baseline. Among subjects with metformin use at baseline, the increase in the saxagliptin group was 5.2 units and in the placebo group 7.58 units (difference in change from baseline saxagliptin versus placebo: -2.38 units (95% CI [-5.06, 0.30])). Among subjects with no metformin use at baseline, the increase in the

saxagliptin group was 6.78 units and in the placebo group 4.71 units (difference in change from baseline saxagliptin versus placebo: +2.06 units (95% CI [-1.94, 6.06])).

The effect of saxagliptin treatment on body weight was analyzed using the repeated measures analysis (mixed model) and LOCF methodologies. The results from the LOCF analyses for both endpoints were similar to those from the repeated measures analysis in that numerical increases from baseline in body weight were seen in both treatment groups through Week 52.

2.2.2. Discussion on clinical efficacy

The addition of saxagliptin to patients treated with insulin resulted in a modest, but statistically significant decrease of HbA1c. The maximum decrease in HbA1c 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, a difference in placebo-corrected response between Asian and European patients or Asian and White patients has also 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.

The placebo group already had a reduction in HbA1c of 0.32%, questioning whether subjects were truly diet/exercise failures or not. The possible main reasons are a "study effect", i.e. patients being more aware of their lifestyle and glucose control, and increase in insulin dose. Nevertheless, the study demonstrated that saxagliptin plus insulin produced a statistically significant reduction in HbA1c compared to placebo plus insulin after 24 weeks of double-blind treatment, with a treatment difference of 0.41% compared to the reduction with placebo alone.

Long-term data are consistent with a sustained treatment effect of saxagliptin on HbA1c, up to 52 weeks of treatment.

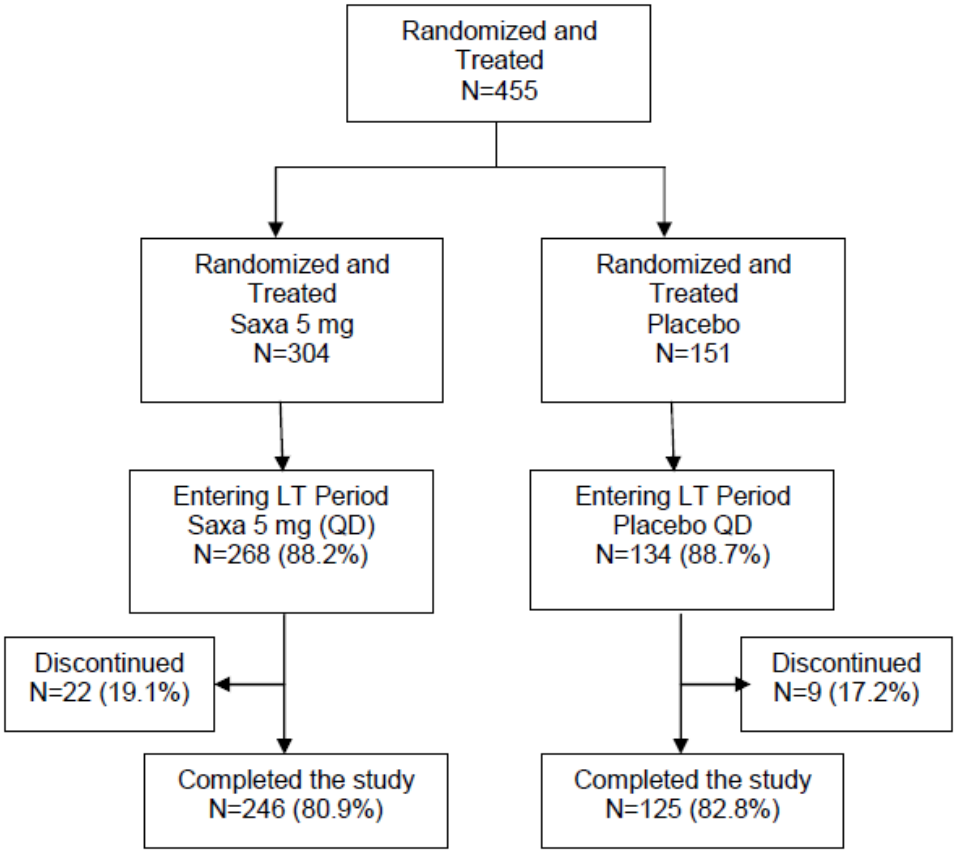
2.3. Clinical safety aspects

2.3.1. Methods – analysis of data submitted

Patient exposure

In study 057, a total of 455 subjects (saxagliptin: 304; placebo: 151) received double-blind study medication during the 52-week ST+LT period. The mean duration of exposure to study medication was 46.5 weeks in the saxagliptin group and 46.7 in the placebo group. A total of 402 (88.4%) of these 455 subjects completed 24 weeks of treatment and entered the 28-week LT treatment period and 371 (81.5%) completed the 52-week ST+LT treatment period.

See also



Note: The denominator of each % is the number of randomized and treated subjects.
LT = long term; QD = once daily; SAXA = saxagliptin

Figure 2 and Table 1.

2.3.2. Results

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 proportion of subjects who experienced at least 1 AE during the ST+LT treatment period in the saxagliptin-treated subjects was 66.4% and 71.5% in the placebo-treated subjects.

Table 7 presents AEs (excluding events of hypoglycaemia) that occurred in ≥ 2% of subjects. In the saxagliptin group the 4 most common events were urinary tract infection, nasopharyngitis, upper respiratory tract infection, and headache whereas in the placebo group the 4 most common events were influenza, urinary tract infection, upper respiratory tract infection, and nasopharyngitis.

Table 7: Most Common Adverse Events (Incidence >=2%) - Summary by System Organ Class and Preferred Term During ST + LT Treatment Period, study 057

System Organ Class (SOC) (%) Preferred Term (PT) (%)	SAXA 5MG + INS N=304	PLACEBO + INS N=151
TOTAL SUBJECTS WITH AN EVENT	187(61.5)	104 (68.9)
INFECTIONS AND INFESTATIONS	108 (35.5)	62 (41.1)
urinary tract infection	24 (7.9)	12 (7.9)
nasopharyngitis	19 (6.3)	10 (6.6)
upper respiratory tract infection	19 (6.3)	11 (7.3)
bronchitis	16 (5.3)	5 (3.3)
pharyngitis	11 (3.6)	8 (5.3)
influenza	10 (3.3)	14 (9.3)
cystitis	8 (2.6)	3 (2.0)
gastroenteritis	7 (2.3)	2 (1.3)
GASTROINTESTINAL DISORDERS	57 (18.8)	25 (16.6)
diarrhoea	14 (4.6)	7 (4.6)
constipation	12 (3.9)	5 (3.3)
abdominal pain	8 (2.6)	2 (1.3)
gastritis	8 (2.6)	2 (1.3)
nausea	5 (1.6)	5 (3.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	50 (16.4)	30 (19.9)
arthralgia	13 (4.3)	5 (3.3)
back pain	10 (3.3)	6 (4.0)
osteoarthritis	7 (2.3)	0
pain in extremity	7 (2.3)	10 (6.6)
musculoskeletal pain	3 (1.0)	6 (4.0)
NERVOUS SYSTEM DISORDERS	45 (14.8)	22 (14.6)
headache	18 (5.9)	6 (4.0)
dizziness	8 (2.6)	3 (2.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	30 (9.9)	11(7.3)
oedema peripheral	9 (3.0)	5 (3.3)
INVESTIGATIONS	21 (6.9)	9 (6.0)
blood creatine phosphokinase increased	7 (2.3)	1 (0.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	21 (6.9)	13 (8.6)
cough	7 (2.3)	6 (4.0)
VASCULAR DISORDERS	19 (6.3)	11 (7.3)
hypertension	9 (3.0)	8 (5.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	10 (3.3)	6 (4.0)
anaemia	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.

Several related AEs occurring in ≤2 subjects were not included in the SmPC as justified by the MAH and agreed by CHMP.

With respect to the adverse events listed in Table 8, some of the adverse events were reported with higher frequencies in the saxagliptin group relative to the placebo group, most of which are included in section 4.8 of the SmPC, but not all of them (in particular the events "bronchitis" and "arthralgia"). During this procedure, the MAH clarified the methodology applied for inclusion of AEs in the SmPC,

using pooled data and a cut off difference used for inclusion of AEs in section 4.8 and this was considered to be acceptable by the CHMP.

Serious adverse events and deaths

One death, as a result of myocardial infarction, was reported during the 24-week ST period in a patient taking saxagliptin. 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.

Another death occurred during the LT period in a patient taking saxagliptin but not metformin. The investigator reported an SAE of intestinal gangrene that was very severe / grade IV in intensity and judged by investigator as not being related to study medication.

Other serious adverse events (SAEs) during the ST+LT treatment period of Study 57 were reported for a similar proportion of subjects in the saxagliptin (25/304 subjects, 8.2%) and placebo (13/151 subjects, 8.6%) groups. Sixteen subjects in the saxagliptin group and also taking metformin had SAEs (7.7% of saxagliptin subjects taking metformin); 10 subjects in the placebo group and also taking metformin had SAEs (9.5% of placebo subjects taking metformin).

Adverse events leading to discontinuation

Twelve subjects (9 [3.0%] in the saxagliptin group and 3 [2.0%] in the placebo group) discontinued study medication due to AEs during the ST+LT treatment period. Six subjects in the saxagliptin group and also taking metformin had AEs leading to discontinuation (2.9% of saxagliptin subjects taking metformin); 2 subjects in the placebo group and also taking metformin had SAEs (1.9% of placebo subjects taking metformin).

Most AEs leading to discontinuation of treatment were reported to be of mild or moderate intensity. Severe or very severe AEs led to discontinuation in 4 subjects in the saxagliptin group and 1 subject in the placebo group.

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+LT treatment period was 7.6% in the saxagliptin group and 6.6% in the placebo group. During the ST+LT treatment period, 23 subjects in the saxagliptin group (15/209 [7.2%] subjects taking metformin and 8/95 [8.4%] not taking metformin) and 10 subjects in the placebo group (5/105 [4.8%] subjects taking metformin and 5/46 [10.9%] subjects not taking metformin) had confirmed events of hypoglycaemia. Most of these confirmed hypoglycaemic events with associated symptoms were mild or moderate in intensity. Five severe confirmed hypoglycaemic events were reported: 2 (0.7%) subjects in the saxagliptin group with 4 severe events and 3 (2.0%) subjects in the placebo group with 3 severe events. There were no reports of very severe confirmed hypoglycaemic events with associated symptoms.

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. Overall, during the ST+LT treatment period, a total of 69 (22.7%) subjects in the saxagliptin group and 40 (26.5%) subjects in the placebo group experienced a hypoglycaemic AE. These included hypoglycaemia in

19.4% and 24.5% of subjects, and blood glucose decreased in 4.3% and 7.3% of subjects, respectively. Most hypoglycaemic events were of mild or moderate intensity.

The proportion of subjects who had AEs included in the SOC **Skin and Subcutaneous Tissue Disorders** was similar in the saxagliptin (4.9%) and placebo (5.3%) groups. The most common of these AEs were allergic dermatitis, skin ulcer, and urticaria each in 2 (0.7%) subjects in the saxagliptin group and dermatitis and rash each in 2 (1.3%) subjects in the placebo group.Skin-related AEs matching the predefined PTs were reported for 3 (1.0%) subjects in the saxagliptin group (all taking metformin) and 1 (0.7%, taking metformin) subject in the placebo group. All of these AEs were mild or moderate in intensity, none were SAEs, and none led to discontinuation.

A similar proportion of subjects had AEs prior to rescue in the SOC **Infections and Infestations** (saxagliptin: 35.5%; placebo: 41.1%). These AEs most common AEs in this SOC included urinary tract infection, upper respiratory tract infection, nasopharyngitis and influenza; the incidence of these events was balanced across the treatment groups.

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.

Six subjects (4 [1.3%] in the saxagliptin group and 2 [1.3%] in the placebo group had cardiovascular AEs that were confirmed by an adjudication committee: in the saxagliptin group there were two SAEs of acute myocardial infarction, one intestinal gangrene, and one case of acute coronary syndrome. In the placebo group there was a SAE of thalamic infarction and a SAE of transient ischaemic attack.

SAEs in 3 other saxagliptin subjects (myocardial ischemia and cardiac failure, cardiac failure in, and hypertension and angina were not confirmed by the adjudication committee.

None of these AEs were considered by the investigator to be related to study medication.

Three (1.0%) subjects in the saxagliptin group and 1 (0.7%) subject in the placebo group had **hypersensitivity AEs**. Two of these hypersensitivity AEs occurred during the short-term study period, both in the saxagliptin group (reported term of allergy symptoms, and urticaria). In the LT period there were two cases of urticarial, one in the saxagliptin group and one in the placebo group.

No subject in the saxagliptin group and 1 (0.7%) subject in the placebo group had an AE matching the pre-specified preferred terms for **pancreatitis**.

Six subjects, 3 (1.7%) subjects in the saxagliptin group and 3 (2.0%) subjects in the placebo group had **fracture** AEs. These included foot fracture in the 2(0.7%) subjects in the saxagliptin group, ankle fracture in 1 (0.3%) subject in the saxagliptin group, and 1 (0.7%) subject each with hand fracture, humerus fracture, and lower limb fracture in the placebo group. Ankle fracture in the saxagliptin group was an SAE, but 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 57 (18.8%) subjects and placebo group 25 (16.6%) subjects. Gastrointestinal-related AEs by PT reported by ≥2% of subjects in either treatment group during the ST period were constipation (3.9% versus 3.3% in the saxagliptin and placebo groups, respectively), diarrhoea (4.6% versus 4.6%, respectively), abdominal pain (2.6% versus 1.3%, respectively), gastritis (2.6% versus 1.3%, respectively), and nausea (1.6% versus 3.3%, respectively).

Overall, 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.

Laboratory findings

There were no marked abnormalities reported for decreased or increased platelets. For saxagliptin-treated subjects, marked abnormalities were reported in 2 (0.7%) subjects each for decreased hemoglobin and decreased hematocrit, and for 1 (0.3%) subject for decreased neutrophils. For placebo-treated subjects, marked abnormalities were reported in 2 (1.3%) subjects for decreased hematocrit and 1 (0.7%) subject for decreased leukocytes.

Marked abnormalities of decreased lymphocytes were noted for 3 (1.0%) subjects in the saxagliptin group and 2 (1.3%) subjects in the placebo group. Two additional placebo-treated subjects had baseline (Day -1) lymphocyte counts that were considered to be marked laboratory abnormalities. Of these marked laboratory abnormalities, 1 in the saxagliptin group was reported as an AE of lymphopenia.

Increased eosinophils were noted for 9 (3.0%) subjects in the saxagliptin group and 7 (4.7%) subjects in the placebo group.

Alkaline phosphatase levels elevated >1.5 × ULN were noted for 10 (3.3%) subjects in the saxagliptin group and 5 (3.3%) subjects in the placebo group. Additionally, there were 2 (0.7%) subjects in the saxagliptin group and 1 (0.7%) subject in the placebo with alkaline phosphatase levels >3 × baseline and >ULN. Markedly abnormal elevated ALT (>3 × ULN) was reported for 5 (1.7%) subjects in the saxagliptin group and 3 (2.0%) in the placebo group. Of these, 3 saxagliptin-treated subjects and 1 placebo-treated subject had marked elevations of ALT during the ST treatment period. One (0.7%) subject in the placebo group had markedly abnormal elevated total bilirubin (>1.5 × ULN). However, no subject had ALT >3 × ULN and a total bilirubin >1.5 × ULN or ALT >3 × ULN and a total bilirubin

>2 mg/dL (34.2 µmol/L) (see CV181057 ST+LT CSR Table 8.7.2).

Marked abnormalities of elevated AST (> 3 x ULN) were noted for 2 (0.7%) subjects in the saxagliptin group and no subject in the placebo group.

Six (2.0%) subjects in the saxagliptin group and 2 (1.4%) subjects in the placebo group had marked abnormalities of elevated CK >5 × ULN. 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.

Sixteen subjects (8 [2.7%] in the saxagliptin group and 8 [5.4%] in the placebo group) had marked abnormalities of elevated potassium (≥1.2 × baseline and ≥6.0 mEq/L [6.0 mmol/L]). In most cases, these elevations represented a single high value and potassium levels had returned to within normal limits by the last recorded value.

Decreased potassium levels were reported as marked abnormalities (<0.8 × baseline and ≤3.2 mEq/L [3.2 mmol/L]) for 3 (1.0%) subjects in the saxagliptin group and 1 (0.7%) in the placebo group. In all

4 subjects, these decreases represented just 1 or 2 low values and potassium levels had returned to within normal limits by the last recorded value.

The most frequent urinary marked abnormality was urinary WBCs (measured quantitatively),which was present in 35/115 (30.4%) subjects in the saxagliptin group and 10/53 (18.9%) subjects in the placebo group. Marked abnormalities of haematuria (measured via dipstick) were seen in14/297 (4.7%) subjects in the saxagliptin group and 2/146 (1.4%) subjects in the placebo group. Few subjects had marked abnormalities of urinary protein (8/297 [2.7%] saxagliptin subjects and3/146 [2.1%] placebo subject) or urinary RBCs (8/53 [15.1%]saxagliptin subjects and 1/31 [3.2%] placebo subject. Based on further clarification provided by the MAH, the urine microscopy numerical differences in Study CV181057 represents probably a chance variation and this was agreed by CHMP.

Vital signs

Of the 227 subjects who had normal ECG tracings at baseline, 15/153 (9.8%) who received saxagliptin and 11/74 (14.9%) who received placebo had abnormal tracings at Week 52. A varying spectrum of ECG abnormalities was noted over all treatment groups.

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.

In the Short-term study report, the MAH presented the ECG findings for all patients who had an abnormal ECG during lead-in or short term treatment period. The MAH had then been requested to present the data for patients who turned form normal ECG at baseline to abnormal at week 24and none of the abnormal ECG tracings was found to be of clinical relevance.

2.3.3. Discussion

In general saxagliptin was well tolerated. There were no unexpected or new adverse events.

The proportion of subjects who experienced at least 1 AE during the ST+LT treatment period in the saxagliptin-treated subjects was 66.4% and 71.5% in the placebo-treated subjects.

In the saxagliptin group the 4 most common events were urinary tract infection, nasopharyngitis, upper respiratory tract infection, and headache whereas in the placebo group the 4 most common events were influenza, urinary tract infection, upper respiratory tract infection, and nasopharyngitis.

One death, as a result of myocardial infarction, was reported during the 24-week ST period in a patient taking saxagliptin. Another death, due to intestinal gangrene, occurred during the LT period in a patient taking saxagliptin but not metformin. Both deaths were considered not related to study medication. Cardiovascular events will be monitored closely and the data presented in Periodic Safety Update Reports.

Several related AEs occurring in ≤2 subjects, were not included in the SmPC. However, the MAH had given a thorough rationale for why these AEs had not been included and that was accepted by CHMP.

Patients on saxagliptin had no more hypoglycaemia than placebo treated patients.

With respect to vital signs, the MAH had been requested during the procedure to present the data for patients who turned from normal ECG at baseline to abnormal at week 24. None of the abnormal ECG tracings was found to be of clinical relevance and therefore this was satisfactory for the CHMP.

2.4. Risk management plan

The MAH provided the following justification for not submitting an update of the current RMP as part of this type II variation: The Saxagliptin and Metformin HCl Fixed Dose Combination EU Risk Management Plan version 2 (dated 21 September 2011) was updated to include long-term exposure data from study CV181057 as well as data on identified and potential risks. Thus, version 2 of the EU RMP appropriately summarizes important identified and potential risks for the saxagliptin and metformin fixed dose combination in the context of the approved indications as well as the change in indication proposed with this type II variation (use in combination with insulin in adults with type 2 diabetes mellitus). The Saxagliptin and Metformin HCl Fixed Dose Combination EU Risk Management Plan version 2 (dated 21 September 2011) was provided in the context of the recent MAA submission; reference is therefore made to the documents provided in eCTD sequence 0005 (dated 19 October 2011).

This justification was considered acceptable by CHMP.

2.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

SmPC:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Komboglyze is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets.

Komboglyze is also indicated in combination with insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control.

4.2 Posology and method of administration

Posology

. . .

For patients switching from separate tablets of saxagliptin and metformin
Patients switching from separate tablets of saxagliptin and metformin should receive the doses of saxagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy of insulin and metformin, or, for patients controlled on triple combination therapy of insulin, and metformin plus saxagliptin as separate tablets.
The dose of Komboglyze should provide saxagliptin 2.5 mg twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Komboglyze is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia (see section 4.4).

4.4 Special warnings and precautions for use

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

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

. . .

Use with medicinal products known to cause hypoglycaemia
Insulin is known to cause hypoglycaemia. Therefore, a lower dose of insulin may be required to reduce the risk of hypoglycaemia when used in combination with Komboglyze.

4.8 Undesirable effects

. . .

Hypoglycaemia
. . .
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

. . .

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.

The Package Leaflet has been updated accordingly. In addition minor editorial corrections have been made throughout the Product Information (attachment 1).

3. Overall conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

The efficacy and safety of the addition of saxagliptin to insulin or insulin plus metformin 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. After this short term period, patients entered a long-term phase of 28 weeks.

The addition of saxagliptin to patients treated with insulin or insulin plus metformin resulted in a statistically significant decrease of HbA1c. The maximum was reached at week 12 and was maintained through 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).

Placebo-corrected mean reductions from baseline HbA1c were -0.20% [95% CI -0.62% to 0.21%] for EU subjects and -0.46% [95% CI -0.65% to -0.26%] for non-EU subjects. Analysis of data did not reveal a treatment-by-region interaction. There was no difference in effect between Whites and Asian people. Mean difference from control was -0.44% and -0.46% respectively.

Long-term data are consistent with a sustained treatment effect of saxagliptin on HbA1c, up to 52 weeks of treatment.

Uncertainty in the knowledge about the beneficial effects

In both groups a relatively large percentage of patients discontinued because of lack of glycaemic control (22.7% vs 32.8 in the saxagliptin and placebo group, respectively).

There was a relatively large reduction in HbA1c of 0.32% in the placebo group. The possible main reasons are a "study effect", i.e. patients being more aware of their lifestyle and glucose control, and increase in insulin dose. Nevertheless, the study demonstrated that saxagliptin plus insulin produced a statistically significant reduction in HbA1c compared to placebo plus insulin after 24 weeks of double-blind treatment, with a treatment difference of 0.41%.

Considering the large number of sites and the small number of subjects enrolled at most sites, a centre effect could not be excluded. However, an analysis of centre effects was not considered to provide additional meaningful information due to the large number of sites and the small number of subjects enrolled at most sites and the MAH's approach was considered acceptable by CHMP.

Risks

Unfavourable effects

In general saxagliptin (in insulin-treated patients with or without metformin) was well tolerated. There were no unexpected or new adverse events.

The proportion of subjects who experienced at least 1 AE during the ST+LT treatment period in the saxagliptin-treated subjects was 66.4% and 71.5% in the placebo-treated subjects.

In the saxagliptin group the 4 most common events were urinary tract infection, nasopharyngitis, upper respiratory tract infection, and headache whereas in the placebo group the 4 most common events were influenza, urinary tract infection, upper respiratory tract infection, and nasopharyngitis.

Patients on saxagliptin had no more hypoglycaemia than placebo treated patients.

Uncertainty in the knowledge about the unfavourable effects

During the short-term treatment period, 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.

Another death, due to intestinal gangrene, occurred during the long-term treatment period. This event was also not considered related to study drug.

There were 3 (1.0%) subjects who reported skin or neuropathic ulcers in the saxagliptin treatment group. These ulcers were mild in intensity, did not lead to discontinuation, and resolved during saxagliptin therapy.

Balance

Importance of favourable and unfavourable effects

The addition of saxagliptin (in insulin-treated patients with or without metformin) 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). However, in this heavily treated population with advanced diabetes, the total effect was considered sufficient and clinically relevant by CHMP.

Saxagliptin (in insulin-treated patients with or without metformin) was in general well tolerated, with no unexpected findings, and no more side effects than the placebo treated patients. Although three cardiac adverse events were serious, there was no established relation with saxagliptin. Cardiovascular adverse events will be closely monitored and reported in PSURs. There were no abnormal ECG tracings of clinical importance.

Benefit-risk balance

The effect of adding saxagliptin (in insulin-treated patients with or without metformin) on HbA1c was modest, however considered still clinically relevant for the patient group involved. Treatment was not associated with an increase in events of hypoglycaemia, and there was slightly less of a need to increase the daily insulin dose over time in the saxagliptin group. Saxagliptin was well tolerated. Cardiovascular adverse events will be closely monitored and reported in PSURs.

Conclusions

The benefit risk balance for Komboglyze in the combined use with insulin is considered positive by CHMP.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

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

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to extend the indication for combination of Komboglyze with insulin (i.e., triple combination therapy). The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to include minor editorial corrections in the PI.