17 January 2013
EMA/302364/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Komboglyze	SAXAGLIPTIN / METFORMIN HYDROCHLORIDE
Onglyza	SAXAGLIPTIN

Procedure No. EMEA/H/C/xxxx/WS/0295

Note

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

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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 9 July 2012 an application for a variation, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

This application concerns the following medicinal products:

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

The following variation was requested:

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

The WSA 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 Onglyza and Komboglyze to include combination of metformin, a suphonylurea and saxagliptin, i.e. triple oral 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 and to harmonize these for the two products. Furthermore, the WSA proposed this opportunity to bring the PI in line with the latest QRD template version 8.2.

The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Appointed Rapporteur for the WS procedure: Pieter de Graeff

1.2. Steps taken for the assessment

Submission date:	9 July 2012
Start of procedure:	22 July 2012
Rapporteur's preliminary assessment report circulated on:	14 September 2012
Rapporteur's updated assessment report circulated on:	12 October 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 October 2012
MAH's responses submitted to the CHMP on:	14 November 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 December 2012
CHMP opinion:	17 January 2013

Information on Paediatric requirements

Onglyza

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) [P/97/2011] on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP for saxagliptin (P/97/2011) was not yet completed as some measures were deferred.

Komboglyze

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).

2. Scientific discussion

2.1. Introduction

Saxagliptin is a selective, orally administered, xanthine-based inhibitor of dipeptidylpeptidase-4 (DPP-4). The recommended therapeutic dose of saxagliptin is 5 mg once daily. Like other DPP-4 inhibitors, saxagliptin lowers blood glucose by extending the half-life of glucagon-like peptide 1 (GLP-1), which is secreted in response to a meal. GLP-1 lowers blood glucose by augmenting the glucose-stimulated insulin release and limiting glucagon secretion to slow gastric emptying and to induce satiety. Therefore, saxagliptin predominately affects postprandial glycaemic excursions. The advantages of DPP-4 inhibitors over other established antidiabetic medications include the low risk of hypoglycaemia and lack of weight gain.

Onglyza (saxagliptin) and Komboglyze (saxagliptin/metformin) were approved throughout the European Union on 1 October 2009 and 24 November 2011, respectively.

The MAH proposed to extend the indication for the treatment of type 2 diabetes as triple combination (saxagliptin in combination with metformin and a sulphonylurea (SU)).

The clinical program to support the addition of the “in combination with metformin and a SU” indication was developed in accordance with the “Notes for Guidance on Clinical Investigations of Medicinal Products in the Treatment of Diabetes Mellitus” (CPMP/EWP/1080/00).

The present worksharing application for Onglyza and Komboglyze is supported by study D1680L00006, a 24-week, multicentre, randomised, parallel-group, double-blind, placebo-controlled Phase 3b study, which assessed the efficacy and safety of saxagliptin 5 mg as an adjunct to metformin plus SU in improving glycaemic control in adult subjects with T2DM. In study D1680L00006, saxagliptin and metformin were administered as separate tablets rather than as the FDC product.

2.2. Clinical Efficacy aspects

2.2.1. Methods – analysis of data submitted

The main study of this application is study D1680L00006.

Methods

Study design

Study D1680L00006 was a 24-week, multicenter, randomized, parallel-group, double-blind, placebo-controlled Phase 3b study to evaluate the efficacy and safety of saxagliptin compared with placebo as add-on therapy to a stable metformin dose plus a stable SU dose in subjects with T2DM who have inadequate glycaemic control (HbA1c ≥7% and ≤10%). Subjects were to be on a stable combined dose of metformin extended release (XR) or immediate release (IR) (at maximum tolerated dose [MTD], with minimum dose for enrolment being 1500 mg) plus SU (gliclazide, gliclazide modified release [MR], or glimepiride at MTD with minimum dose for enrolment being ≥50% of the maximum recommended dose) for at least 8 weeks prior to enrolment.

The protocol was amended following enrolment of the first subjects to widen the inclusion and exclusion criteria by allowing use of any SU (including glibenclamide) in combination with metformin for at least 8 weeks prior to enrolment. Following amendment, enrolled subjects were to be on a stable combined dose of metformin XR or IR (at MTD, with minimum dose for enrolment being 1500 mg) plus SU (at MTD, with minimum dose for enrolment being ≥50% of the maximum recommended dose) for at least 8 weeks prior to enrolment.

During the enrolment/screening and 24-week double-blind treatment periods, subjects continued their own (open-label) metformin plus SU at the doses ascertained during enrolment. Metformin and SU were not supplied as part of the investigational products and, thus, were not subject to the treatment compliance check that was performed for saxagliptin and placebo.

Subjects were randomized (1:1) to either saxagliptin 5 mg or matching placebo once daily by oral administration. The metformin and SU doses were to remain constant during the 24-week double-blind treatment period.

Study population

The population of Study D1680L00006 consisted of male and female subjects with T2DM, aged between 25 and 83 years of age (inclusive), with inadequate glycaemic control (defined as HbA1c levels ≥7.0% and ≤10.0%) and were on a stable combined dose of metformin plus SU for at least 8 weeks prior to enrolment.

Endpoints

The **primary efficacy endpoint** was the change in HbA1c level from baseline until Week 24.

Secondary endpoints assessed at week 24 were:

- Change in PPG (measured 2 hours after breakfast) from baseline to Week 24;
- Change from baseline in FPG;
- Proportion of subjects achieving a therapeutic glycaemic response (defined as HbA1c < 7%);

Other efficacy endpoints were the changes from baseline to week 24 for TC, LDL-C, HDL-C, and TG; Subject-reported endpoints using the EQ-5D questionnaire; Change in insulin, C-peptide, and glucagon from baseline to Week 24.

Statistical analysis

Sample size

To demonstrate a significant difference between saxagliptin and placebo—as add-on therapy to the combination of metformin plus SU—in the change in HbA1c from baseline to Week 24, a total of 240

subjects randomised and treated (120 subjects per treatment group) was needed to provide approximately 80% power at a 2-sided significance level of 0.05, assuming a true difference of 0.40% and a standard deviation (SD) of 1.1%.

Assuming a 4% drop-out rate of subjects who were randomised but did not return for a post-baseline assessment, a total of 250 subjects was required for randomisation. Assuming a 10% screening failure rate for subjects who were consented and enrolled but were not eligible for randomisation, a total of 275 subjects was planned for enrolment/screening.

Primary endpoint

The primary efficacy analysis was to compare the difference between saxagliptin 5 mg once daily as add-on therapy to metformin plus SU versus placebo as add-on therapy to metformin plus SU, in subjects with T2DM, as determined by the change in HbA1c levels from baseline to Week 24.

The primary analysis for efficacy variables was based on the Full Analysis set, which included subjects who took at least 1 dose of investigational product and had both baseline and post-baseline efficacy data. For this study, a sensitivity analysis was performed for the Per Protocol (PP) analysis set since the pre-defined criterion of >10% of subjects in either treatment group of the Full Analysis set having significant deviations from the protocol (as defined in the Statistical Analysis Plan [SAP]) was met.

The change from baseline to Week 24 in HbA1c was analysed using an analysis of covariance (ANCOVA) model with treatment group and country as fixed effects and baseline HbA1c value as a covariate. Missing Week 24 values were imputed using the last observation carried forward (LOCF) method. The model was used to derive a least squares estimate of the treatment difference in the mean change from baseline with corresponding 2-sided 95% confidence interval (CI) and 2-sided p-value. In addition, 2-sided 95% CIs for the mean change within each treatment group were calculated.

Sequential testing methodology

A fixed-sequence test method was adopted for the overall primary efficacy variable (HbA1c change from baseline to Week 24), and the 3 secondary efficacy variables to control the Type I error rate so as not to exceed the 5% level. The fixed-sequence test method was applied to these variables in the following sequential order:

Change from baseline to Week 24 in HbA1c (or the last post-baseline measurement prior to Week 24 if no Week 24 assessment was available).

Change from baseline to Week 24 in 2-hour PPG (or the last post-baseline measurement prior to Week 24 if no Week 24 assessment was available).

Change from baseline to Week 24 in FPG (or the last post-baseline measurement prior to Week 24 if no Week 24 assessment was available).

Proportion of subjects achieving a glycaemic response defined as HbA1c <7.0% was compared using a logistic regression model.

Statistical inference began with the overall primary efficacy variable. If the saxagliptin treatment group was statistically significantly superior in the change from baseline in HbA1c at Week 24 over the placebo group at the 5% level, then statistical inference continued with (2) in the sequence above—the first secondary efficacy variable (2-hour PPG); otherwise, statistical inference of the overall efficacy variables was stopped (any p value that follows cannot be considered as significant in this confirmatory analysis when the fixed-sequence procedure is used to control the overall Type I error rate, even if the p-value is <0.05).

Similar testing was followed with the prescribed sequential order (1) to (4) as the above steps with the same decision rule at each of the variable evaluations until all 3 secondary variables were analysed or testing was interrupted at any non-significant findings at the 5% level.

Analysis sets

The primary and secondary efficacy endpoint analyses were performed on the Full analysis set using LOCF to estimate any missing values at Week 24. The safety endpoints were analysed using the Safety analysis set. The decision to include or exclude subjects from each analysis set was performed in a blind data review prior to unblinding.

Randomised analysis set

All subjects randomised to double-blind treatment at Week 1 (Day 0) were included in the Randomised analysis set.

Full analysis set

The Full analysis set included all randomised subjects who received at least 1 dose of investigational product during the 24-week double-blind treatment period and who had a non missing baseline value and at least 1 post-baseline value for at least 1 efficacy parameter. The Full analysis set followed the principles of intention-to-treat in that all efficacy measures were summarised and analysed according to the treatment to which subjects were randomised, regardless of the treatment actually received.

Per Protocol analysis set

The PP analysis set was a subset of the Full analysis set including subjects with no reasons for exclusion. These exclusions for the PP analysis set were explicitly defined in the SAP and the subjects with exclusions were identified prior to database locking. A PP analysis on the primary variable was only to be performed if >10% of subjects in either treatment group of the Full analysis set have significant protocol violations or deviations. Otherwise, analysis of the primary variable was restricted to the Full analysis set.

2.2.2. Results

Disposition of subjects

Table 1 Disposition of subjects (Randomised analysis set)

	Number (%) of subjects	
	Saxa + Met + SU N=129	Pla + Met + SU N=128
Subjects randomised and treated	129	128
Subjects completing 24 weeks of treatment	113 (87.6)	113 (88.3)

Subjects discontinuing from the study	16 (12.4)	15 (11.7)
Reason for discontinuing from the study		
T2DM worsened	8 (6.2)	7 (5.5)
Subject decision	2 (1.6)	3 (2.3)
AE	1 (0.8)	3 (2.3)
Incorrect enrolment - subject did not meet inclusion/ exclusion criteria	2 (1.6)	1 (0.8)
Severe non-compliance to protocol	2 (1.6)	0
Developed calculated CrCl <60 mL/min or an increase in serum creatinine of ≥44.2 µmol/L (≥0.5 mg/dL) above baseline	1 (0.8)	1 (0.8)

AE Adverse event; CrCl Creatinine clearance; Met Metformin; Pla Placebo; Saxa Saxagliptin; SU Sulfonylurea; T2DM Type 2 diabetes mellitus

Disposition of subjects is shown in the table above.

The study was conducted at 35 study centres in: United Kingdom (12 sites), Canada (4 sites), Australia (7 sites), India (6 sites), Korea (4 sites), and Thailand (2 sites).

Of the 383 subjects who entered the enrolment/screening period, 126 subjects did not enter the randomised, double-blind treatment period due to subject decision (n=11), lost to follow-up (n=1), and eligibility criteria not fulfilled (n=114). Thus, a total of 257 subjects were randomised and treated.

In table 1 the following is indicated:

- A total of 257 subjects were assigned to randomised double-blind treatment with either saxagliptin + metformin + SU (n=129) or placebo + metformin + SU (n=128).
- The proportion of subjects who completed the 24-week, double-blind, randomised treatment period was similar in the 2 treatment groups (approximately 88%).
- The most common reason for discontinuation in both treatment groups was worsening of T2DM (6.2% [n=8] in the saxagliptin group and 5.5% [n=7] in the placebo group).
- One subject (0.8%) in each treatment group withdrew due to a calculated CrCl of <60 mL/min or an increase in serum creatinine of ≥44.2 µmol/L (≥0.5 mg/dL) above baseline.
- The proportion of subjects discontinuing study treatment due to an AE during double-blind treatment was in the saxagliptin group 0.8% [n=1] and in the placebo group 2.3% [n=3].

Protocol deviations

The number of subjects with important protocol deviations in each treatment group are summarised in the table below.

Table 2 Summary of significant protocol deviations and violations leading to exclusion from the PP analysis set (Full analysis set)

Parameter[a]	Number (%) of subjects	
	Saxa + Met + SU N=127	Pla + Met + SU N=128
Subjects with at least 1 significant protocol deviation	**19 (15.0)**	**16 (12.5)**
Randomised but did not satisfy entry criterion #3 (Section 5.3.1)	5 (3.9)	5 (3.9)
Poor treatment compliance (<80% or >120%)	2 (1.6)	1 (0.8)
Use of excluded concomitant medication	12 (9.4)	10 (7.8)

[a] Subjects may have more than 1 deviation.
Met Metformin; Pla Placebo; PP Per protocol; Saxa Saxagliptin; SU Sulfonylurea

In total, 19 (15.0%) and 16 (12.5%) subjects from the saxagliptin and placebo groups, respectively, were excluded from the PP analysis set. The majority of subjects were excluded for use of a prohibited concomitant medication (12 [9.4%] and 10 [7.8%] subjects in the saxagliptin and placebo groups, respectively), namely CYP3A4 inducers and/or CYP3A4/5 inhibitors. On further clarification requested from the applicant by CHMP during the procedure, an analysis provided showed the number of individuals with significant protocol deviations leading to exclusion from the PP population to be small when the erroneously counted CYP3A4 inhibitor/inducers/substrates are neglected. The FAS included all individuals with significant protocol deviations. Results of the FAS and PP analysis were similar, indicating that the treatment effect of saxagliptin was robust and consistent and therefore the remaining concern was resolved.

Subjects analysed (analysis sets)

The analysis sets and the number of subjects in each analysis set are summarised in the table below. The Randomised analysis set comprised 257 subjects, of whom 255 (99.2%) were included in the Full analysis set, 220 (85.6%) were included in the PP analysis set, and 257 (100%) were included in the Safety analysis set. The 2 treatment groups were balanced with regard to inclusion in the respective analysis sets.

Table 3 Analysis sets

	Number (%) of subjects		
Analysis set	**Saxa + Met + SU**	**Pla + Met + SU**	**Total**
Consented analysis set[a]	NA	NA	383
Randomised analysis set[b]	129 (100)	128 (100)	257 (100)
Full analysis set[c]	127 (98.4)	128 (100)	255 (99.2)
Per Protocol analysis set[d]	108 (83.7)	112 (87.5)	220 (85.6)
Safety analysis set[e]	129 (100)	128 (100)	257 (100)

The denominator of each % is the number of subjects in the Randomised analysis set.

[a] All subjects who gave informed consent and were enrolled.

[b] All subjects randomised to double-blind treatment at Week 1 (Day 0).

[c] All randomised subjects who received at least 1 dose of investigational product during the 24-week double-blind treatment period and who had a non-missing baseline value and at least 1 post-baseline value for at least 1 efficacy parameter.

[d] All subjects with no reasons for exclusion.

[e] All randomised subjects who received at least 1 dose of double-blind randomised investigational product.

Met Metformin; Pla Placebo; Saxa Saxagliptin; SU Sulfonylurea

Demographic and key-baseline characteristics

The demographic and key baseline characteristics of subjects in the Randomised analysis set are summarised in the table below.

The demographic and key baseline characteristics were generally balanced across the 2 treatment groups. The subjects ranged in age from 25 to 83 years with a mean (SD) age of 57.0 (10.54) years. A total of 196 subjects (76.3%) were <65 years of age. Of the 257 randomised and treated subjects, the majority of subjects in each treatment group were male (62.0% and 57.8% in the saxagliptin and placebo groups, respectively). Body weight ranged from 40 to 155 kg with a mean (SD) of 82.4 (19.86) kg and 80.3 (18.47) kg for the saxagliptin and placebo groups, respectively. The respective mean (SD) BMI was 29.4 (5.26) kg/m2 and 29.1 (4.93) kg/m2 for the saxagliptin and placebo groups.

Table 4 Demographics and key baseline characteristics (Randomised analysis set)

	Saxa + Met + SU N=129	Pla + Met + SU N=128	Total N=257
Age, year[a]			
n	129	128	257
Mean (SD)	57.2 (9.55)	56.8 (11.49)	57.0 (10.54)
Median	58.0	56.5	57.0
Range	33, 83	25, 83	25, 83
Age categorisation, n (%)[a]			
<65 years	101 (78.3)	95 (74.2)	196 (76.3)
≥65 years	28 (21.7)	33 (25.8)	61 (23.7)
Gender, n (%)			
Male	80 (62.0)	74 (57.8)	154 (59.9)
Female	49 (38.0)	54 (42.2)	103 (40.1)
Race, n (%)			
White	59 (45.7)	57 (44.5)	116 (45.1)
Asian	70 (54.3)	71 (55.5)	141 (54.9)
Ethnic group, n (%)			
Asian (other than Chinese and Japanese)	68 (52.7)	69 (53.9)	137 (53.3)
Chinese	1 (0.8)	1 (0.8)	2 (0.8)
Other	24 (18.6)	25 (19.5)	49 (19.1)
Not Applicable[b]	36 (27.9)	33 (25.8)	69 (26.8)
Country, n (%)			
Australia	25 (19.4)	25 (19.5)	50 (19.5)
Canada	10 (7.8)	10 (7.8)	20 (7.8)
India	35 (27.1)	34 (26.6)	69 (26.8)
Korea	25 (19.4)	24 (18.8)	49 (19.1)
Thailand	8 (6.2)	10 (7.8)	18 (7.0)
United Kingdom	26 (20.1)	25 (19.5)	51 (19.8)

Height, cm[a]			
n	129	128	257
Mean (SD)	166.9 (11.23)	165.6 (10.82)	166.2 (11.02)
Median	167.0	166.0	166.0
Range	144, 190	141, 189	141, 190
Weight, kg[a]			
n	129	128	257
Mean (SD)	82.4 (19.86)	80.3 (18.47)	81.4 (19.17)
Median	78.0	80.0	80.0
Range	51, 155	40, 130	40, 155
Waist circumference, cm[a]			
n	128	128	256
Mean (SD)	100.7 (15.51)	99.2 (13.40)	100.0 (14.48)
Median	99.0	98.5	99.0
Range	75, 150	72, 145	72, 150
BMI, kg/m^2			
n	129	128	257
Mean (SD)	29.4 (5.26)	29.1 (4.93)	29.2 (5.09)
Median	28.7	29.2	28.8
Range	21, 53	18, 45	18, 53

The denominator of each % is the number of subjects in the Randomised analysis set.
[a] At the time of screening.
[b] Entered, for example, when the subject did not consider himself or herself to belong to a specific ethnic group.
BMI Body Mass Index; Met Metformin; Pla Placebo; Saxa Saxagliptin; SD Standard deviation; SU Sulfonylurea

Mean dose of Metformin and SU in the randomized set

In the randomized set mean baseline dose of Metformin (1957.00 mg) and of SU [Glibenclamide (15.50 mg), Gliclazide (159.63 mg), Glimepiride (5.04 mg), and Glipizide (17.78 mg)] was sufficient.

Baseline diabetes characteristics

Baseline diabetes characteristics for the Randomised analysis set are summarised in the table below.

The baseline disease characteristics of HbA1c, PPG, and FPG were representative of subjects with uncontrolled T2DM who have inadequate glycaemic control when treated with combination therapy with metformin plus SU. The mean baseline values for these 3 parameters were slightly higher in the saxagliptin group compared with the placebo group.

For HbA1c, the mean (SD) value at baseline was 8.38% (0.856%) and 8.19% (0.832%) in the saxagliptin and placebo groups, respectively. Differences in these baseline disease characteristics were accounted for in the efficacy analysis by using baseline value as a covariate in the ANCOVA analysis.

Table 5 Baseline diabetes characteristics (Randomised analysis set)

	Saxa + Met + SU N=129	Pla + Met + SU N=128	Total N=257
HbA1c, %			
n	129	128	257
Mean (SD)	8.38 (0.856)	8.19 (0.832)	8.28 (0.848)
Median	8.30	8.10	8.20
Range	6.60, 10.50	6.60, 10.00	6.60, 10.50
PPG, mmol/L			
n	122	122	244
Mean (SD)	14.94 (4.263)	14.74 (3.869)	14.84 (4.064)
Median	14.75	14.50	14.70
Range	6.60, 26.80	6.10, 25.40	6.10, 26.80
PPG, mg/dL			
n	122	122	244
Mean (SD)	269.18 (76.814)	265.60 (69.713)	267.39 (73.220)
Median	265.77	261.26	264.86
Range	118.92, 482.88	109.91, 457.66	109.91, 482.88
FPG, mmol/L			
n	123	123	246
Mean (SD)	9.00 (2.626)	8.63 (2.130)	8.82 (2.393)
Median	8.60	8.60	8.60
Range	4.10, 20.20	4.00, 17.20	4.0, 20.2
FPG, mg/dL			
n	123	123	246
Mean (SD)	162.24 (47.322)	155.45 (38.370)	158.84 (43.125)
Median	154.95	154.95	154.95
Range	73.87, 363.96	72.07, 309.91	72.07, 363.96

Baseline is defined as the last assessment within 42 days before the first dose of study treatment.
FPG Fasting plasma glucose; HbA1c Glycosylated haemoglobin; Met Metformin; Pla Placebo; PPG Postprandial glucose; Saxa Saxagliptin; SD Standard deviation; SU Sulfonylurea

Primary efficacy endpoint: change in HbA1c from baseline to Week 24

The table below summarises the ANCOVA model results for the change in HbA1c from baseline to Week 24 of the double-blind treatment period for the Full analysis set (LOCF) (the primary analysis).

Table 6 Change in HbA1c from baseline to Week 24 (LOCF) (Full analysis set)

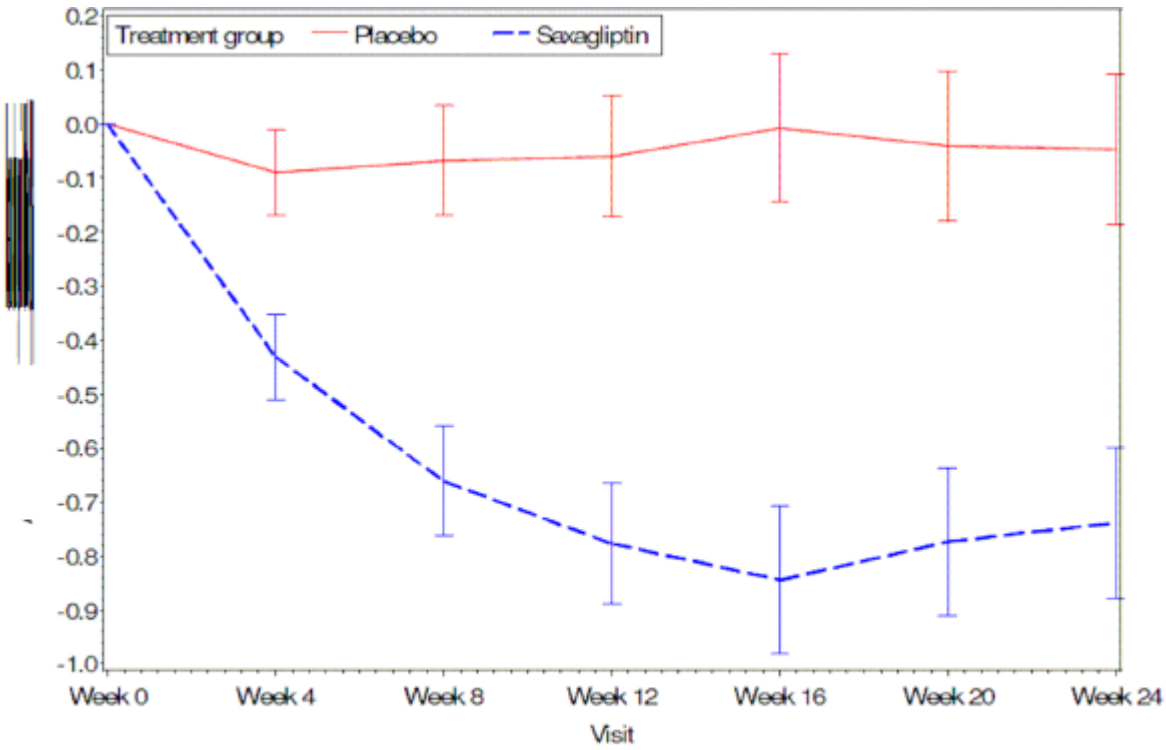
	Saxa + Met + SU N=127	Pla + Met + SU N=128
n	127	127
Units: %		
Baseline mean (SE)	8.37 (0.075)	8.17 (0.073)
Week 24 mean (SE)	7.63 (0.089)	8.12 (0.098)
Mean change from baseline (SE)	-0.74 (0.070)	-0.05 (0.072)
Adjusted change from baseline		
Mean (SE)	-0.74 (0.075)	-0.08 (0.074)
2-sided 95% CI	-0.89, -0.60	-0.23, 0.07
Difference versus Pla + Met + SU		
Mean (SE)[a]	-0.66 (0.099)	NA
2-sided 95% CI	-0.86, -0.47	NA
P-value	<0.0001*	NA

Baseline is defined as the last assessment within 42 days before the first dose of study treatment.
ANCOVA model: post - pre = pre + treatment + country
[a] Estimate = Adjusted mean change for Saxa + Met + SU – Adjusted mean change for Pla + Met + SU.
ANCOVA Analysis of covariance; CI Confidence interval; HbA1c Glycosylated haemoglobin; LOCF Last observation carried forward; Met Metformin; NA Not applicable; Pla Placebo; Saxa Saxagliptin; SE Standard error; SU Sulfonylurea
* Between-group comparison significant after controlling overall alpha of the study.

Mean baseline HbA1c values were slightly higher in the saxagliptin group compared with the placebo group. The adjusted mean change from baseline to Week 24 was -0.74% for the saxagliptin group and -0.08% for the placebo group. Based on the difference in adjusted mean changes from baseline, treatment with saxagliptin significantly decreased HbA1c compared with placebo in the Full analysis set. The difference in adjusted mean changes between the 2 groups (saxagliptin minus placebo) was -0.66% (2-sided 95% CI, -0.86% to -0.47%; p<0.0001).

Mean HbA1c values over time during the 24-week double-blind treatment period are summarised graphically for the Full analysis set (LOCF) in the figure below.

Figure 1 **Mean change in HbA1c from baseline (95% CI) during the double-blind treatment period (LOCF; Full analysis set)**



Treatment groups: Saxagliptin = saxagliptin + metformin + SU; Placebo = placebo + metformin + SU
CI Confidence interval; HbA1c Glycosylated haemoglobin; LOCF Last observation carried forward; SU Sulfonylurea

In contrast with placebo for saxagliptin a reduction from baseline was observed at weeks 4, 8, 12 and progressively greater to week 16. This reduction was maintained through week 24.

More than 10% of subjects in the Full analysis set were excluded from the PP analysis set. Therefore a sensitivity analysis of the change in HbA1c from baseline to Week 24 was performed using the PP analysis set (see table below).

The results from the Full analysis set (LOCF) were confirmed in the PP analysis. Adjusted mean changes from baseline to Week 24 (LOCF) in the PP analysis were -0.70% for the saxagliptin group and -0.09% for the placebo group. The difference in adjusted mean changes between the 2 groups (saxagliptin minus placebo) was -0.61% (2-sided 95% CI, -0.82% to -0.40%; p<0.0001).

Table 7 Change in HbA1c from baseline to Week 24 (LOCF) (Per Protocol analysis set)

	Saxa + Met + SU N=108	Pla + Met + SU N=112
n	108	112
Units: %		
Baseline mean (SE)	8.35 (0.079)	8.20 (0.079)
Week 24 mean (SE)	7.65 (0.096)	8.13 (0.105)
Mean change from baseline (SE)	-0.70 (0.079)	-0.07 (0.077)
Adjusted change from baseline		
Mean (SE)	-0.70 (0.083)	-0.09 (0.081)
2-sided 95% CI	-0.87, -0.54	-0.25, 0.07
Difference versus Pla + Met + SU		
Mean (SE)[a]	-0.61 (0.109)	NA
2-sided 95% CI	-0.82, -0.40	NA
P-value	<0.0001*	NA

Baseline is defined as the last assessment within 42 days before the first dose of study treatment.
ANCOVA model: post - pre = pre + treatment + country
[a] Estimate = Adjusted mean change for Saxa + Met + SU – Adjusted mean change for Pla + Met + SU.
ANCOVA Analysis of covariance; CI Confidence interval; HbA1c Glycosylated haemoglobin; LOCF Last observation carried forward; Met Metformin; NA Not applicable; Pla Placebo; Saxa Saxagliptin; SE Standard error; SU Sulfonylurea
* Between-group comparison significant after controlling overall alpha of the study.

Secondary endpoints

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

Treatment with saxagliptin + metformin + SU resulted in a significantly greater reduction in **2-hour PPG at Week 24** compared with placebo + metformin + SU. The difference in adjusted mean changes between the 2 groups (saxagliptin minus placebo) was -0.93 mmol/L (-16.74 mg/dL) (2-sided 95% CI, -1.77 to -0.09 mmol/L [-31.85 to -1.62 mg/dL]; p=0.0301) (see table below)

Table 8 Change in 2-hour PPG from baseline to Week 24 (LOCF) (Full analysis set)

	Saxa + Met + SU N=127	Pla + Met + SU N=128
n	115	113
Units: mmol/L		
Baseline mean (SE)	14.85 (0.392)	14.54 (0.351)
Week 24 mean (SE)	14.17 (0.362)	14.96 (0.359)
Mean change from baseline (SE)	-0.68 (0.368)	0.42 (0.338)
Adjusted change from baseline		
Mean (SE)	-0.65 (0.330)	0.28 (0.325)
2-sided 95% CI	-1.30, 0.00	-0.36, 0.92
Difference versus Pla + Met + SU		
Mean (SE)[a]	-0.93 (0.426)	NA
2-sided 95% CI	-1.77, -0.09	NA
P-value	0.0301*	NA
Units: mg/dL		
Baseline mean (SE)	267.64 (7.058)	261.98 (6.319)
Week 24 mean (SE)	255.32 (6.521)	269.49 (6.461)
Mean change from baseline (SE)	-12.31 (6.627)	7.51 (6.085)
Adjusted change from baseline		
Mean (SE)	-11.66 (5.949)	5.08 (5.847)
2-sided 95% CI	-23.38, 0.07	-6.45, 16.60
Difference versus Pla + Met + SU		
Mean (SE)[a]	-16.74 (7.667)	NA
2-sided 95% CI	-31.85, -1.62	NA

Baseline is defined as the last assessment within 42 days before the first dose of study treatment.
ANCOVA model: post - pre = pre + treatment + country
[a] Estimate = Adjusted mean change for Saxa + Met + SU – Adjusted mean change for Pla + Met + SU.
ANCOVA Analysis of covariance; CI Confidence interval; LOCF Last observation carried forward; Met Metformin; NA Not applicable; Pla Placebo; PPG Postprandial glucose; Saxa Saxagliptin; SE Standard error; SU Sulfonylurea
* Between-group comparison significant after controlling overall alpha of the study.

Similar results were obtained in the Full analysis set using observed values.

Saxagliptin + metformin + SU produced a numerically greater reduction compared with placebo + metformin + SU in **FPG at Week 24**. The difference in adjusted mean changes between the 2 groups (saxagliptin minus placebo) was -0.44 mmol/L (-7.90 mg/dL) (2-sided 95% CI, -0.94 to 0.06 mmol/L [-16.96 to 1.15 mg/dL]; p=0.0868).

The proportion of subjects achieving a **therapeutic glycaemic response, defined as HbA1c <7.0% at Week 24**, was higher in the saxagliptin group (30.7%) than in the placebo group (9.4%). The

adjusted odds ratio for the difference in proportions between the 2 groups (saxagliptin/placebo) was 9.006 (2-sided 95% CI, 3.852 to 21.05) (see table below).

Table 9 Proportion of subjects achieving therapeutic response (HbA1c <7.0%) at Week 24 (LOCF) (Full analysis set)

	Saxa + Met + SU N=127	Pla + Met + SU N=128
n	127	127
Number (%) achieving therapeutic response (HbA1c <7.0%)	39 (30.7)	12 (9.4)
Difference in proportion vs Pla + Met + SU		
Difference (%)[a]	21.3	NA
Odds ratio estimate (saxagliptin/placebo)[b]	9.006	
2-sided 95% CI for the odds ratio	3.852, 21.05	NA
P-value	<0.0001	NA

The denominator of each percentage is the number of subjects in the treatment group at Week 24 (LOCF).
[a] Proportion for Saxa + Met + SU – Proportion for Pla + Met + SU.
[b] Logistic regression model: Response (Yes/No) = HbA1c at baseline + group + country
CI Confidence interval; LOCF Last observation carried forward; Met Metformin; NA Not applicable; Pla Placebo; Saxa Saxagliptin; SU Sulfonylurea

Other efficacy endpoints

Saxagliptin + metformin + SU compared with placebo + metformin + SU had similar non–clinically relevant effects on mean changes from baseline to Week 24 in **fasting plasma lipids (TC, LDL, HDL-C, TG)** as well as on **fasting levels of insulin**, **C-peptide**, and **glucagon**.

The changes from baseline to Week 24 were similar in the saxagliptin and placebo groups in subject-reported **health status assessed with the EQ-5D**.

Summary of main study

The following tables summarise the efficacy results from the main studiy supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10 Summary of Efficacy for study D1680L00006

Title: A 24-week, multicentre, randomised, double-blind, placebo-controlled Phase IIIb study to evaluate the efficacy and safety of saxagliptin in combination with metformin and sulfonylurea in subjects with Type 2 diabetes who have inadequate glycaemic control with the combination of metformin and sulfonylurea			
Study identifier	Study code: D1680L00006 ClinicalTrials.gov identifier: NCT01128153		
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group; metformin plus sulfonylurea treatment failure subjects		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 2 weeks NA
Hypothesis	Superiority after 24 weeks		
Treatment groups	Saxa 5 mg + Met + SU		Saxagliptin 5 mg on a background therapy of open-label metformin (at pre-study dose, ≥1500 mg) plus SU (at pre-study dose, ≥50% of maximum recommended dose), 24 weeks, 129 randomized[a]
	Plac + Met + SU		Placebo on a background therapy of open-label metformin (at pre-study dose, ≥1500 mg) plus SU (at pre-study dose, ≥50% of maximum recommended dose), 24 weeks, 128 randomized[a]
Endpoints and definitions	Primary endpoint	HbA1c	Adjusted mean change from baseline to Week 24
	Secondary endpoint	2-hour PPG	Adjusted mean change from baseline to Week 24 in 2-hour PPG (2 hours after morning meal)
	Secondary endpoint	FPG	Adjusted mean change from baseline to Week 24
	Secondary endpoint	HbA1c <7.0%	Therapeutic glycemic response, defined as the proportion of subjects achieving HbA1c <7.0% at Week 24
Database lock	23 August 2011		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis dataset, consisting of all randomized subjects who took at least one dose of double-blind study medication during the 24 week double-blind period and who had a non-missing baseline value and at least 1 post-baseline value for at least 1 efficacy parameter		
Descriptive statistics and estimate variability	Treatment group	Saxa 5 mg + Met + Su	Plac + Met + SU
	Number of subjects (Full analysis dataset)	127	128
	HbA1c (%) (adjusted mean change)	-0.74	-0.08
	Standard error	0.075	0.074
	2-hour PPG (mg/dL) (adjusted mean change)	-11.66	5.08
	Standard error	5.949	5.847
	FPG (mg/dL) (adjusted mean change)	-5.28	2.62
	Standard error	3.751	3.599
	HbA1c <7.0% (percent)	30.7	9.4

Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Saxa 5 mg (+Met+SU) vs Plac (+Met+SU)
		Mean difference from Plac	-0.66
		95% CI	(-0.86, -0.47)
		P-value	<0.0001*
	Secondary endpoint: 2-hour PPG (mg/dL)	Comparison groups	Saxa 5 mg (+Met+SU) vs Plac (+Met+SU)
		Mean difference from Plac	-16.74
		95% CI	(-31.85, -1.62)
		P-value	0.0301*
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Saxa 5 mg (+Met+SU) vs Plac (+Met+SU)
		Mean difference from Plac	-7.90
		95% CI	(-16.96, 1.15)
		P-value	0.0868
	Secondary endpoint: HbA1c <7.0% (percent)	Comparison groups	Saxa 5 mg (+Met+SU) vs Plac (+Met+SU)
		Difference from Plac	21.3
		95% CI	NC
		Odds ratio (saxagliptin/placebo)	9.006
		95% CI	(3.852, 21.05)
		P-value	<0.0001**

Notes
Source: D1680L00006 CSR

The statistical analysis plan specified that the ANCOVA LOCF analysis was the primary presentation of the efficacy endpoints (eg, HbA1c, 2-hour PPG, and FPG).

[a] Subjects randomized and treated

* Statistically significant at prespecified level. For primary endpoint, between-group comparison significant at $\alpha = 0.05$ with 2-sided test. All secondary endpoints were evaluated in a hierarchical testing procedure at the 0.05 significance level.

**Not significant because findings for the preceding endpoint in hierarchical testing, FPG, were not significant.

CI Confidence interval; FPG Fasting plasma glucose; HbA1c Glycosylated hemoglobin; Met Metformin; NC Not calculated; Plac Placebo; PPG Postprandial glucose; Saxa Saxagliptin; SU Sulfonylurea

2.2.3. Discussion

Discussion on clinical efficacy

The design of the study was considered adequate to evaluate the value of saxagliptin when added to metformin plus SU in T2DM.

The primary efficacy analysis was to compare the difference between saxagliptin 5 mg once daily as add-on therapy to metformin plus SU versus placebo as add-on therapy to metformin plus SU, in subjects with T2DM, as determined by the change in HbA1c levels from baseline to Week 24.

The primary and secondary endpoints were agreed.

In general the inclusion and exclusion criteria seemed adequate and similar to those used in former studies in T2DM patients. 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. Two forms of Metformin have been used: Metformin XR and Metformin IR. The XR formulation is not approved in all EU Member States, as it was considered somewhat less effective than the IR formulation. However, the mean dose of >1800 mg was considered to be high enough by CHMP to overcome any concern with possible small differences due to formulation.

There were no significant differences between treatment groups in the percentages of patients who completed the study and the percentage of withdrawals. Also the reasons for withdrawal were not significantly different between the treatment groups. A relatively large group of subjects discontinued from study: 12.4% in the saxagliptin group. However nearly the same percentage discontinued in the placebo group: 11.7%. Reason for discontinuation due to worsening of T2DM (that is lack of efficacy) was 6.2 and 5.5% respectively.

The study was conducted at 35 study centres in: United Kingdom (12 sites), Canada (4 sites), Australia (7 sites), India (6 sites), Korea (4 sites), and Thailand (2 sites).

Considering the large number of sites (35) and the small number of subjects enrolled at most sites the CHMP was concerned about a possible centre effect. Consequently, the MAH has performed an analysis according to country in which the centres were located, which did not show any interaction and therefore resolved the issue.

There were no relevant differences between treatment groups in demographics and baseline disease characteristics.

45% of patients were white, 27% were from India, 20% from Australia, 20% from UK, 19% from Korea, 7% from Canada and 7% from Thailand.

The mean baseline dose of metformin and SU (Glibenclamide, Gliclazide, Glimepiride and Glipizide, respectively) in the randomized set was considered as sufficient by CHMP.

The baseline disease characteristics of HbA1c, PPG, and FPG were representative of subjects with uncontrolled T2DM who have inadequate glycaemic control when treated with combination therapy with metformin plus SU. Baseline disease characteristics can be considered typical for T2DM patients.

The mean baseline values for HbA1c, PPG, and FPG were slightly higher in the saxagliptin group compared with the placebo group. For HbA1c, the mean (SD) value at baseline was 8.38% (0.856%) and 8.19% (0.832%) in the saxagliptin and placebo groups, respectively. Differences in these baseline disease characteristics were accounted for in the efficacy analysis.

According to the data in table 5, the range of HbA1c was 6.60 – 10.50 %, whereas the eligibility criteria were defined as subjects with HbA1c ≥7% and ≤10% to be randomized to receive either saxagliptin 5 mg or matching placebo once daily by oral administration for 24 weeks. The applicant provided as explanation for this extended range that those values were obtained at visit 3, which was not used as enrolement criterion and this was considered by CHMP not to have a relevant effect on the results obtained.

Results from the FAS and PP analysis indicate that the addition of saxagliptin to metformin + SU was more effective than placebo in lowering HbA1c. The difference of -0.66% was clinically relevant.

Both primary and secondary parameters indicate that the addition of saxagliptin to T2DM patients treated with metformin + SU was effective. Saxagliptin + metformin + SU was superior to placebo + metformin + SU in lowering HbA1c from baseline to Week 24 (adjusted mean changes of -0.74% for

the saxagliptin group and -0.08% for the placebo group, with a difference versus placebo of -0.66% [2-sided 95% CI, -0.86% to -0.47%; p<0.0001] for saxagliptin). The proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c <7.0% at Week 24, was higher in the saxagliptin group (30.7%) than in the placebo group (9.4%).

A relatively large group of subjects discontinued from this 24 weeks study: 12.4% in the saxagliptin group was initially of concern for CHMP. However nearly the same percentage discontinued in the placebo group: 11.7%. Reason for discontinuation due to worsening of T2DM was 6.2 and 5.5% respectively, indicating possible lack of efficacy in these patients. The effect on FPG was not large enough for continuation but even in those subjects there was still a considerable placebo-corrected mean reduction in HbA1c, which was found to be satisfactory by CHMP.

Conclusions on clinical efficacy

Saxagliptin 5 mg added to a stable dose of metformin plus SU was superior to placebo added to a stable dose of metformin plus SU in lowering HbA1c and 2-hour PPG from baseline to Week 24.

In contrast with placebo for saxagliptin a reduction in HbA1c from baseline was observed at weeks 4, 8, 12 and progressively greater to week 16. This reduction was maintained through week 24.

The adjusted mean changes were -0.74% for the saxagliptin group and -0.08% for the placebo group, with a difference versus placebo of -0.66% [2-sided 95% CI, -0.86% to -0.47%; p<0.0001] for saxagliptin).

2.3. Clinical Safety aspects

The main study of this application is study D1680L00006.

2.3.1. Methods – analysis of data submitted

Patient exposure

Duration of exposure is given in the table below.

Mean (SD) exposure to investigational product was similar in both treatment groups (158.9 [31.41] days in the saxagliptin group and 160.1 [29.73] days in the placebo group), with median exposures of 168 days in both treatment groups. Please also refer to Disposition of subjects as given in table 1.

Table 11 Duration of exposure to investigational product (Safety analysis set)

Exposure (days)	Saxa + Met + SU (N=129)	Pla + Met + SU (N=128)
1 to 11	1 (0.8)	0
12 to 25	1 (0.8)	1 (0.8)
26 to 53	2 (1.6)	4 (3.1)
54 to 81	3 (2.3)	1 (0.8)
82 to 109	3 (2.3)	2 (1.6)
110 to 137	3 (2.3)	4 (3.1)
138 to 165	8 (6.2)	7 (5.5)
≥166	108 (83.7)	109 (85.2)
Summary statistics		
Mean (SD)	158.9 (31.41)	160.1 (29.73)
Median	168.0	168.0
Range	11 to 180	22 to 181

Duration of treatment is the last dosing date – first dosing date + 1.
Met Metformin; Pla Placebo; Saxa Saxagliptin; SD Standard deviation; SU Sulfonylurea

2.3.2. Results

Adverse events

Number of Subjects with at least 1 adverse event is given in the table below.

The proportion of subjects with AEs during the 24-week double-blind treatment period was lower in the saxagliptin group than the placebo group: 62.8% (n=81) in the saxagliptin group and 71.7% (n=91) in the placebo group. The proportion of subjects with treatment-related AEs (as assessed by the investigator to have a reasonable possibility that the event may have been caused by the investigational product) was higher in the saxagliptin group than the placebo group (16.3% and 10.2% in the saxagliptin and placebo groups, respectively). There were no deaths during the study. SAEs were reported in a total of 10 subjects, 3 (2.3%) subjects in the saxagliptin group and 7 (5.5%) in the placebo group. One (0.8%) subject in the saxagliptin group and 3 (2.3%) subjects in the placebo group discontinued treatment due to AEs; of these AEs, 1 in the placebo group was an SAE.

Table 12 Number (%) of subjects with at least 1 adverse event in any category (Safety analysis set)

	Number (%) of subjects[a]	
	Saxa + Met + SU (N=129)	**Pla + Met + SU (N=128)**
At least 1 AE	81 (62.8)	91 (71.7)
At least 1 treatment-related AE[b]	21 (16.3)	13 (10.2)
Deaths	0	0
At least 1 SAE	3 (2.3)	7 (5.5)
At least 1 treatment-related SAE[b]	1 (0.8)	0
At least 1 AE leading to discontinuation of IP	1 (0.8)	3 (2.3)
At least 1 SAE leading to discontinuation of IP	0	1 (0.8)

Includes events with onset after first dose of investigational product, and events with onset during screening that worsened during double-blind treatment, through last visit (Visit 9/End-of-Study).
Events of hypoglycaemia are included in all categories.
[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
[b] Treatment-related as assessed by the investigator to have a reasonable possibility that the event may have been caused by the investigational product.
AE Adverse event; IP Investigational product; Met Metformin; Pla Placebo; Saxa Saxagliptin; SAE Serious adverse event; SU Sulfonylurea

Number (%) of subjects with at least 1 adverse event by system organ class (see table below).

Please note that hypoglycaemic events based on a predefined list of PTs are discussed separately and are not included in the following AE summaries.

Table 13 Number (%) of subjects with at least 1 adverse event by system organ class (Safety analysis set)

System Organ Class	Number (%) of subjects[a]	
	Saxa + Met + SU (N=129)	Pla + Met + SU (N=128)
Total subjects with an AE	77 (59.7)	89 (69.5)
Infections and infestations	34 (26.4)	44 (34.4)
Gastrointestinal disorders	24 (18.6)	23 (18.0)
Nervous system disorders	16 (12.4)	7 (5.5)
Musculoskeletal and connective tissue disorders	13 (10.1)	15 (11.7)
Metabolism and nutrition disorders	12 (9.3)	14 (10.9)
Respiratory, thoracic and mediastinal disorders	10 (7.8)	10 (7.8)
Skin and subcutaneous tissue disorders	7 (5.4)	12 (9.4)
Vascular disorders	7 (5.4)	3 (2.3)
Eye disorders	6 (4.7)	4 (3.1)
General disorders and administration site conditions	5 (3.9)	5 (3.9)
Investigations	5 (3.9)	5 (3.9)
Psychiatric disorders	4 (3.1)	6 (4.7)
Injury, poisoning and procedural complications	3 (2.3)	9 (7.0)
Blood and lymphatic system disorders	3 (2.3)	6 (4.7)
Renal and urinary disorders	2 (1.6)	4 (3.1)
Ear and labyrinth disorders	2 (1.6)	0
Endocrine disorders	2 (1.6)	0
Cardiac disorders	1 (0.8)	3 (2.3)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.8)	2 (1.6)
Hepatobiliary disorders	1 (0.8)	1 (0.8)
Reproductive system and breast disorders	1 (0.8)	0

Includes events with onset after first dose of investigational product, and events with onset during screening that worsened during double-blind treatment, through last visit (Visit 9/End-of-Study).
Hypoglycaemia events based on a predefined list of PTs are excluded from this table.
[a] Number (%) of subjects with AEs, sorted by SOC in decreasing order of frequency for saxagliptin group.
AE Adverse event; Met Metformin; Pla Placebo; PT Preferred Term; Saxa Saxagliptin; SOC System Organ Class; SU Sulfonylurea

Adverse events occurring in ≥2% of subjects in either treatment group are given in the table below.

The proportion of subjects with AEs (excluding hypoglycaemic events) was 59.7% in the saxagliptin group and 69.5% in the placebo group. The SOCs with the highest number of subjects with AEs (≥10% in the saxagliptin group) were infections and infestations (34 [26.4%] subjects in saxagliptin group and 44 [34.4%] in the placebo group), gastrointestinal disorders (24 [18.6%] subjects in the saxagliptin group and 23 [18.0%] in the placebo group), nervous system disorders (16 [12.4%] subjects in saxagliptin group and 7 [5.5%] in the placebo group), and musculoskeletal and connective tissue disorders (13 [10.1%] subjects in saxagliptin group and 15 [11.7%] in the placebo group). Another

SOC with an incidence of ≥5% in the saxagliptin group and greater than placebo was vascular disorders (5.4% vs 2.3% in the placebo group). At the PT level, the most common AEs (≥5%) in the saxagliptin group were nasopharyngitis (6.2%), diarrhoea (5.4%), and hypertension (5.4%); the most common AEs in the placebo group were nasopharyngitis (9.4%), urinary tract infection (6.3%), and dyslipidaemia (5.5%). AEs with an incidence of ≥2% in the saxagliptin group and at least 1% greater than in the placebo group were diarrhoea (5.4% vs 3.9% in the placebo group), hypertension (5.4% vs 1.6%), cough (3.1% vs 0.8%), flatulence (3.1% vs 0), and peripheral neuropathy (2.3% vs 0).

Table 14 Summary of adverse events occurring in ≥2% of subjects in either treatment group (Safety analysis set)

Preferred Term	Number (%) of subjects[a]	
	Saxa + Met + SU (N=129)	Pla + Met + SU (N=128)
Total subjects with an AE	77 (59.7)	89 (69.5)
Nasopharyngitis	8 (6.2)	12 (9.4)
Diarrhoea	7 (5.4)	5 (3.9)
Hypertension	7 (5.4)	2 (1.6)
Upper respiratory tract infection	6 (4.7)	6 (4.7)
Dyslipidaemia	5 (3.9)	7 (5.5)
Urinary tract infection	4 (3.1)	8 (6.3)
Hyperglycaemia	4 (3.1)	4 (3.1)
Headache	4 (3.1)	3 (2.3)
Cough	4 (3.1)	1 (0.8)
Flatulence	4 (3.1)	0
Gastritis	3 (2.3)	3 (2.3)
Dizziness	3 (2.3)	2 (1.6)
Neuropathy peripheral	3 (2.3)	0
Nausea	2 (1.6)	4 (3.1)
Pain in extremity	2 (1.6)	4 (3.1)
Arthralgia	2 (1.6)	3 (2.3)
Rash	2 (1.6)	3 (2.3)
Anaemia	1 (0.8)	5 (3.9)
Back pain	1 (0.8)	4 (3.1)
Constipation	1 (0.8)	3 (2.3)
Oral candidiasis	0	3 (2.3)
Pharyngitis	0	3 (2.3)
Insomnia	0	3 (2.3)

Includes events with onset after first dose of investigational product, and events with onset during screening that worsened during double-blind treatment, through last visit (Visit 9/End-of-Study).
Hypoglycaemia events based on a predefined list of PTs are excluded from this table.
[a] Number (%) of subjects with AEs, sorted by PT in decreasing order of frequency for the saxagliptin group.
AE Adverse event; Met Metformin; Pla Placebo; PT Preferred Term; Saxa Saxagliptin; SU Sulfonylurea

Most AEs in both treatment groups were mild or moderate in intensity. Four (3.1%) subjects in each group had AEs that were severe in intensity. In the saxagliptin group, severe AEs included an SAE of hepatitis in 1 (0.8%) subject that was assessed by the investigator to be possibly related to study treatment (see Section 8.3.2 and Section 8.3.4.2), an SAE of lower respiratory tract infection in 1 (0.8%) subject that was not considered by the investigator to be possibly related to study treatment (see Section 8.3.2), and AEs of bursitis and carotid artery occlusion reported in 1 (0.8%) subject each, neither of which was considered by the investigator to be possibly related to study treatment. In the placebo group, severe AEs included influenza-like illness, and SAEs of cartilage injury, renal colic, and asthma reported in 1 (0.8%) subject each (also see Section 8.3.2), none of which were considered by the investigator to be possibly related to study treatment.

Serious adverse event / deaths / other significant events

Deaths

No AEs with fatal outcome were reported.

Serious adverse events

Subjects who had serious adverse events are tabulated in the table below.

A total of 10 subjects experienced SAEs during the double-blind treatment period, 3 (2.3%) subjects in the saxagliptin group and 7 (5.5%) in the placebo group. In the saxagliptin group, the SAEs included lower respiratory tract infection, laryngeal cancer, and hepatitis in 1 subject each. Of these, hepatitis was considered by the investigator to be possibly related to study treatment. The subject, although asymptomatic, was diagnosed with hepatitis, pancreatitis, and calculus cholecystitis after the subject's end-of-study laboratory evaluations revealed elevated transaminases and total bilirubin.

In the placebo group, SAEs included influenza, osteomyelitis, squamous cell carcinoma, cartilage injury, renal colic, and asthma in 1 subject each, and arthritis and musculoskeletal stiffness in 1 subject. None of the SAEs in the placebo group were considered by the investigator to be possibly related to treatment.

Table 15 Number (%) of subjects who had serious adverse events (Safety analysis set)

System Organ Class Preferred Term	Number (%) of subjects[a] Saxa + Met + SU (N=129)	 Pla + Met + SU (N=128)
Total subjects with an SAE	3 (2.3)	7 (5.5)
INFECTIONS AND INFESTATIONS	1 (0.8)	2 (1.6)
Lower respiratory tract infection	1 (0.8)	0
Influenza	0	1 (0.8)
Osteomyelitis	0	1 (0.8)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.8)	1 (0.8)
Laryngeal cancer	1 (0.8)	0
Squamous cell carcinoma	0	1 (0.8)
HEPATOBILIARY DISORDERS	1 (0.8)	0
Hepatitis	1 (0.8)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (0.8)
Cartilage injury	0	1 (0.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (0.8)
Arthritis	0	1 (0.8)
Musculoskeletal stiffness	0	1 (0.8)
RENAL AND URINARY DISORDERS	0	1 (0.8)
Renal colic	0	1 (0.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (0.8)
Asthma	0	1 (0.8)

Includes SAEs with onset after first dose of investigational product, and events with onset during screening that worsened during double-blind treatment, through 30 days after last dose.

Events of hypoglycaemia, based on a predefined list of PTs, were included in the counts of SAEs.

[a] Number (%) of subjects with SAEs, sorted by SOC followed by PT in decreasing order of frequency for the saxagliptin group. A subject can have one or more PTs reported under a given SOC.

Met Metformin; Pla Placebo; PT Preferred term; SAE Serious adverse event; Saxa Saxagliptin; SOC System Organ Class; SU Sulfonylurea

Discontinuation due to adverse events

A summary of subjects who experienced AEs that led to discontinuation from study treatment is given in the table below.

A total of 4 subjects discontinued due to AEs during the double-blind treatment period, 1 (0.8%) in the saxagliptin group (headache) and 3 (2.3%) in the placebo group (abdominal distension, diabetes mellitus inadequate control, and asthma). Of these AEs, the events of headache in the saxagliptin group and abdominal distension in the placebo group were considered by the investigator to be possibly related to study treatment, and the event of asthma in the placebo group was an SAE.

Table 16 Number (%) of subjects who had an adverse event leading to discontinuation (Safety analysis set)

System Organ Class Preferred Term	Number (%) of subjects[a] Saxa + Met + SU (N=129)	 Pla + Met + SU (N=128)
Total subjects with an AE leading to discontinuation	1 (0.8)	3 (2.3)
NERVOUS SYSTEM DISORDERS	1 (0.8)	0
Headache	1 (0.8)	0
GASTROINTESTINAL DISORDERS	0	1 (0.8)
Abdominal distension	0	1 (0.8)
METABOLISM AND NUTRITIONAL DISORDERS	0	1 (0.8)
Diabetes mellitus inadequate control	0	1 (0.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (0.8)
Asthma	0	1 (0.8)

Includes events with onset after first dose of investigational product, and events with onset during screening that worsened during double-blind treatment.
Events of hypoglycaemia, based on a predefined list of PTs, were included in the counts of AEs leading to discontinuation.
[a] Number (%) of subjects with an AE leading to discontinuation, sorted by SOC followed by PT in decreasing order of frequency for the saxagliptin group.
Met Metformin; Pla Placebo; PT Preferred term; SAE Serious adverse event; Saxa Saxagliptin; SOC System Organ Class; SU Sulfonylurea

Adverse events of special interest

Hypoglycaemic adverse events

Subjects self-monitored their fasting blood glucose levels (at least every other day) and recorded in their subject diary their fasting glucose values, any symptoms suggestive of hypoglycaemia, and fingerstick glucose values obtained at the time of a symptomatic event. A hypoglycaemic event could be an episode with symptoms and confirmed low glucose, an episode with low glucose, or an episode with symptoms when glucose was not measured.

Hypoglycaemic AEs were classified into 3 categories: major, minor, and suggestive events based on CHMP criteria. A hypoglycaemic AE was classified as a major event if it was a symptomatic episode requiring external assistance due to severe impairment in consciousness or behaviour, with a plasma glucose level <3.0 mmol/L (54 mg/dL), and resulted in prompt recovery after glucose or glucagon administration. A hypoglycaemic AE was classified as a minor event if it was symptomatic associated with a blood glucose level <3.0 mmol/L (54 mg/dL) and no need for assistance, or an asymptomatic plasma glucose measurement <3.0 mmol/L (54 mg/dL). Events suggestive of hypoglycaemia were events with symptoms that the subject experiences as hypoglycaemia, where plasma glucose measurements were not available.

A total of 13 (10.1%) subjects experienced 19 AEs of hypoglycaemia in the saxagliptin group and 8 (6.3%) subjects experienced 16 AEs of hypoglycaemia in the placebo group during the double-blind treatment period. No subject in either treatment group experienced an SAE of hypoglycaemia. No subject in either treatment group had a major hypoglycaemic event during the double-blind treatment period. Of the 19 AEs of hypoglycaemia in the saxagliptin group, 4 were minor events and 15 were suggestive events. Of the 16 AEs of hypoglycaemia in the placebo group, 5 were minor events and 11 were suggestive events. Confirmed hypoglycaemia events were defined as symptomatic hypoglycaemia with a fingerstick glucose value of ≤2.8 mmol/L [50 mg/dL]). Two (1.6%) subjects in the saxagliptin group and none in the placebo group had confirmed hypoglycaemia events. One saxagliptin subject and 2 placebo subjects had their dose of SU down-titrated during the double-blind treatment period due to hypoglycaemic events.

Hepatic disorders One (0.8%) subject in the saxagliptin group had an AE of hepatitis. Following repeat laboratory testing, the subject was diagnosed with asymptomatic hepatitis, pancreatitis, and calculus cholecystitis. The subject received no further study treatment as he had completed the study.

No subjects in the placebo group experienced hepatic disorders during the double-blind treatment period.

No subject in either treatment group had a **lymphopaenic AE, thrombocytopaenic AE, localised oedema** during the double-blind treatment period.

There were no AEs of **selected skin disorders** in the saxagliptin group; 1 (0.8%) subject in the placebo group had an AE of skin ulcer.

Infection-related AEs were observed more frequently in the placebo group compared to the saxagliptin group. AEs in the SOC infections and infestations were reported in 34 (26.4%) subjects in the saxagliptin group and in 44 (34.4%) subjects in the placebo group. The most common infections (occurring in .2% of subjects in either treatment group) were nasopharyngitis (6.2% in the saxagliptin group and 9.4% in the placebo group), upper respiratory tract infection (4.7% in each group), urinary tract infection (3.1% and 6.3%), and pharyngitis (0 and 2.3%). Based on the SOC infections and infestations, SAEs were reported for 1 (0.8%) subject in the saxagliptin group (lower respiratory tract infection) and for 2 (1.6%) subjects in the placebo group (influenza and osteomyelitis in 1 subject each). No infection-related AEs led to discontinuation of investigational product.

One (0.8%) subject in each treatment group had an AE of **hypersensitivity** (urticaria) during the double-blind treatment period

There were no AEs of **fracture** in the saxagliptin group; 1 subject (0.8%) in the placebo group had an AE of rib fracture.

One (0.8%) subject in the saxagliptin group had an AE of **pancreatitis**. No subjects in the placebo group experienced pancreatitis during the double-blind treatment period.

One (0.8%) subject in the saxagliptin group and no subjects in the placebo group had AEs indicative of an **acute cardiovascular event**, that was considered to be severe and not related to study treatment.

Laboratory findings

There were no clinically relevant changes from baseline noted in mean haematology values in either treatment group.

There were no trends observed for either treatment group based on individual shifts from baseline for any clinical chemistry parameter, including renal function as assessed by CrCl and albumin:creatinine ratio.

Laboratory abnormalities related to liver function were present in 1 saxagliptin treated and two placebo treated subjects.

Vital signs

There were no apparent treatment-related effects on vital signs noted in either treatment group.

ECG abnormalities

One subject in the saxagliptin group had a clinically important ECG finding (T-wave inversion) during the double-blind treatment period that was not present at baseline; this event was adjudicated and the final adjudication confirmed that there were non-specific ST–T-wave ECG changes compatible with lanoxin therapy and no clinical evidence of myocardial Infarction.

2.3.3. Discussion

Discussion on clinical safety

The safety profile of saxagliptin was comparable to that of placebo. There were no unexpected adverse events. The proportion of subjects experiencing any AE was lower in the saxagliptin group compared with the placebo group (62.8% and 71.7% in the saxagliptin and placebo groups, respectively; 59.7% and 69.5%, respectively, when hypoglycaemic events were excluded).

There were no deaths during the study.

No significant differences in SAEs were observed.

The incidence of AEs, SAEs, and AEs leading to discontinuation was similar between the 2 treatment groups.

Although the dose of SU was sufficiently high it is notable that the incidence of hypoglycaemic events in the saxagliptin triple therapy group, while higher than in the control group, remained low.

Analysis of adverse events of special interest did not reveal unexpected adverse events. The incidence of hypoglycaemic AEs was low in both treatment groups but was higher in the saxagliptin group compared with the placebo group (10.1% and 6.3%, respectively); only 2 subjects (saxagliptin group) had confirmed hypoglycaemia (symptomatic with fingerstick plasma glucose ≤2.8 mmol/L [50 mg/dL]).

There were no apparent treatment-related effects on vital signs noted in either treatment group.

Conclusions on the clinical safety

The safety and tolerability profile of saxagliptin + metformin + SU was similar to that of placebo + metformin + SU. The proportion of subjects experiencing any AE was 62.8% in the saxagliptin group and 71.7% in the placebo group. Most common affected SOCs were infections and infestations (saxagliptin 26.4%, placebo 34.4%), gastrointestinal disorders (saxagliptin 18.6%, placebo 18.0%), nervous system disorders (saxagliptin 12.4%, placebo 5.5%), and musculoskeletal and connective tissue disorders (saxagliptin 10.1%, placebo 11.7%). Nasopharyngitis (6.2%, diarrhoea (5.4 %) and hypertension (5.4%) were the most common AEs in the saxagliptin group, whereas nasopharyngitis (9.4%), urinary tract infection (6.3%) and dyslipidemia (5.5%) were the most common AEs in the placebo group.

The incidence of hypoglycaemic AEs was low in both treatment groups but was higher in the saxagliptin group compared with the placebo group (10.1% and 6.3%, respectively); only 2 subjects (saxagliptin group) had confirmed hypoglycaemia (symptomatic with fingerstick plasma glucose ≤2.8 mmol/L [50 mg/dL]).

An AE of an acute cardiovascular event (carotid artery occlusion) was reported in 1 saxagliptin-treated subject. The event was judged to not be a cardiovascular event upon adjudication.

One subject in the saxagliptin group had a clinically important ECG finding (T-wave inversion) during the double-blind treatment period compatible with digoxin therapy There were no other clinically relevant changes in clinical laboratory values, vital signs, or ECGs. No indications of renal or other system impairments were reported throughout the study.

Saxagliptin 5 mg administered as add-on therapy to metformin plus SU in subjects with T2DM was well tolerated with a safety profile comparable to placebo as add-on to metformin plus SU.

2.4. Risk management plan

Based on the current Risk Management Plans (version 2 for Onglyza, version 3 for Komboglyze) the risk management systems were considered acceptable by CHMP. Only minor updates are required to the RMP.

The MAH has agreed to include the minor updates required by CHMP to the RMP in the next RMP updates that will be submitted within three months following CHMP opinion of the current procedure, with the format and content of the updated RMP in line with the requirements of the new pharmacovigilance legislation, for which reference is made to GVP module V.

For further details of the PRAC advice see Attachment 5.

Table 17 and 18. Summaries of the risk management plans

Onglyza

Safety issues	**Agreed pharmacovigilance activities**	**Agreed risk minimisation activities**
Hypersensitivity reactions	Routine PV with targeted questionnaire for spontaneous reports. Epidemiology program for further risk evaluation for hospitalization or ER visits with severe	Product labeling (SmPC) is sufficient to address safety concern. Hypersensitivity reactions, including severe hypersensitivity are listed in the SmPC:

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
	hypersensitivity reactions. Hypersensitivity reactions are secondary safety objective in CV outcomes study.	Section 4.3 Contradindication; Section 4.4 Special warnings and precautions for use; Section 4.8 Undesirable effects
Pancreatitis	Routine PV with targeted questionnaire for spontaneous reports Supplemental case report forms for clinical studies Pancreatitis is a safety objective in a large cardiovascular outcomes trial (Study CV181088 /D1680C00003; SAVOR) for Onglyza. In addition, a planned adjudication of the reports of pancreatitis in a blinded fashion is currently under the monitoring plan.	SmPC is sufficient to address safety concern. Pancreatitis is listed in SmPC under Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects
Infections	Routine PV with targeted questionnaires for spontaneous reports Supplemental case report forms for clinical studies Epidemiology program for further risk evaluation for hospitalized infections	Product labeling (SmPC) is sufficient to address safety concern. Specific events of infections are listed in the adverse reaction table in Section 4.8 Undesirable effects of the SmPC
Gastrointestinal-related AEs	Routine PV	Product labeling (SmPC) is sufficient to address safety concern. Specific GI-related AEs are listed in the adverse reaction table in Section 4.8 Undesirable effects of the SmPC
Important potential risks		
Skin lesions (ulcer erosion and necrosis)	Routine PV with targeted questionnaires for spontaneous reports Supplemental case report forms for clinical studies Skin reactions are a secondary safety objective in CV outcomes study	Product labeling is sufficient to address safety concern. Skin lesions are described in the product labeling (SmPC): Section 4.4 Special warnings and precautions for use Section 5.3 Preclinical safety data
Lymphopenia	Routine PV with targeted questionnaires for spontaneous reports Supplemental case report forms for clinical studies Lymphopenia is a secondary objective in CV outcomes study	Product labeling is sufficient to address safety concern. Effect on lymphocyte counts is described in the product labeling (SmPC): Section 4.8 Undesirable effects

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
	Epidemiology program for evaluation of risk factors for lymphopenia	
Thrombocytopenia	Routine PV with targeted questionnaires for spontaneous reports Supplemental case report forms for clinical studies Thrombocytopenia is a secondary objective in CV outcomes study	None
Hypoglycemia	Routine PV Supplemental case report forms for clinical studies	Product labeling is sufficient to address safety concern. Hypoglycemia is described in the product labeling (SmPC): Section 4.4 Special warnings and precautions for use; Section 4.8 Undesirable effects
Opportunistic infections	Routine PV with targeted questionnaires for spontaneous reports	None
Bone fracture	Routine PV with targeted questionnaires for spontaneous reports Bone fracture is a secondary safety objective in CV outcomes study	None
Severe cutaneous adverse reaction	Routine PV with targeted questionnaires for spontaneous reports Epidemiology program for further risk evaluation for hospitalization or ER visits with severe skin reactions. Skin reactions are a secondary safety objective in CV outcomes study.	None
Important missing / limited information		
Patient ≥ 75 years of age	Routine PV	Product labeling is sufficient to address safety concern. Specific information for the elderly population is described in the product labeling (SmPC): Section 4.2 Posology and method of administration; Section 4.4 Special warnings and precautions for use; Section 5.2 Pharmacokinetic

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		properties
Paediatric population	Routine PV A paediatric plan has been approved by EMA and FDA and the studies initiated in 2011	Safety not established in this population. Refer to this document under Section 1.3.1 describing the ongoing-planned paediatric studies Specific information for the paediatric population is described in the SmPC : Section 4.2 Posology and method of administration
Patient with severe hepatic impairment	Routine PV Epidemiology program for further risk evaluation of hospitalization for acute liver failure Liver abnormalities is a secondary safety objective in CV outcomes trial	Specific information regarding the use of saxagliptin in patients with severe hepatic impairment is provided in the SmPC in Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use
Patients with cardiovascular disease (defined as significant cardiovascular history within 6 months) and patients with compromised cardiac function (CHF) III and IV	Routine PV CV outcomes trial is being conducted to evaluate the effect of saxagliptin on the incidence of CV death, myocardial infarction, or ischaemic stroke in patients with Type 2 diabetes Ongoing CV adjudication in clinical trial program Epidemiology program for further risk evaluation of major adverse cardiovascular events	Safety not established in this population. No experience in clinical studies with saxagliptin in patients with cardiac failure (NYHA class III IV) is described in the SmPC: Section 4.4 Special warnings and precautions for use
Patient with immunocompromised conditions	Routine PV Descriptive analyses will be performed for events in patients with a history of immunocompromised status, in addition, analyses to explore possible differences in hazard ratios by patient characteristics, are planned for the 6 Epidemiology studies presented in Annex 5.	None
Pregnancy/breast-feeding	Routine PV Pregnancy outcome follow up.	Specific information regarding the use of saxagliptin in pregnant patients and breast-feeding patients is described in the SmPC: Section 4.6 Fertility, pregnancy and lactation Effects on fertility were observed in preclinical animal studies is

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		described in the SmPC: Section 5.3Preclinical safety data
Malignancy/neoplasm	Routine PV Cancer associated with saxagliptin use will be evaluated in the CV outcomes trial	None

Komboglyze

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Lactic acidosis	Routine PV	Product labeling is sufficient to address safety concern. Lactic acidosis is listed in the product labeling (SmPC): Section 4.2 Posology and method of administration; 4.4 Special warnings and precautions for use; 4.5 Interaction with other medicinal products and other forms of interaction; Section 4.8 Undesirable effects; 4.9 Overdose
Hypersensitivity reactions	Routine PV	Product labeling is sufficient to address safety concern. Specific hypersensitivity reactions are listed in the product labeling (SmPC): Section 4.3 Contradindication; Section 4.4 Special warnings and precautions for use; Section 4.8 Undesirable effects
Pancreatitis	Routine PV Pancreatitis is a safety objective in a large cardiovascular outcomes trial (Study CV181088 /D1680C00003; SAVOR) for Onglyza. In addition, a planned adjudication of the reports of pancreatitis in a blinded fashion is currently under the monitoring plan.	Product labeling is sufficient to address safety concern. Pancreatitis is listed in the product labeling (SmPC): Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects
Hepatitis	Routine PV	Product labeling is sufficient to address safety concern. Hepatitis is listed in the product labeling (SmPC): Section 4.8 Undesirable effects
Infections	Routine PV	Product labeling is sufficient to address safety concern. Specific infections are listed in the product labeling (SmPC): Section 4.8 Undesirable effects
Gastrointestinal-related AEs	Routine PV	Product labeling is sufficient to

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		address safety concern. Specific GI-related AEs are listed in the product labeling (SmPC): Section 4.8 Undesirable effects
Vitamin B12 deficiency	Routine PV	Product labeling is sufficient to address safety concern. Vitamin B12 deficiency is listed in the product labeling (SmPC): Section 4.8 Undesirable effects
Important Potential Risks:		
Skin lesions (ulcer, erosion, and necrosis)	Routine PV	Product labeling is sufficient to address safety concern. Skin lesions are described in the product labeling (SmPC): Section 4.4 Special warnings and precautions for use Section 5.3 Preclinical safety data
Lymphopenia	Routine PV	Product labeling is sufficient to address safety concern. Effect on lymphocyte counts is described in the product labeling (SmPC): Section 4.8 Undesirable effects
Thrombocytopenia	Routine PV	None
Hypoglycemia	Routine PV	Product labeling is sufficient to address safety concern. Hypoglycemia is described in the product labeling (SmPC): Section 4.8 Undesirable effects
Bone fracture	Routine PV	None
Severe cutaneous adverse reactions	Routine PV	None
Opportunistic infections	Routine PV	None
Important Missing/Limited Information		
Safety in patient ≥ 75 years of age	Routine PV	Product labeling is sufficient to address safety concern. Specific information for the elderly population is described in the product labeling (SmPC): Section 4.2 Posology and method of administration; Section 4.4 Special warnings and precautions for use; Section 5.2 Pharmacokinetic properties
Safety in paediatric population < 18 years of age	Routine PV A paediatric plan (eg, PIP) has been approved by EMA and FDA and the studies will be initiated in 2011.	Safety not established in this population. Refer to section 1.3.1 describing the ongoing-planned paediatric studies. Specific information for the paediatric population is described in the product labeling (SmPC): Section 4.2 Posology and method

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		of administration
Safety in pregnancy/breast feeding	Routine PV	Product labeling is sufficient to address safety concern. Specific information (warnings and precautions) regarding the use of saxagliptin metformin FDC in pregnancy and nursing women is described in the product labeling (SmPC): Section 4.6 Fertility, pregnancy and lactation
Safety in patients with cardiovascular disease (defined as significant cardiovascular history within 6 months) and patients with compromised cardiac function (CHF NYHA class III and IV)	Routine PV A large cardiovascular outcomes trial (CV181088/D1680C00003 [SAVOR]) for Onglyza is being conducted to evaluate the effect of saxagliptin on the incidence of CV death, myocardial infarction, or ischaemic stroke in patients with Type 2 diabetes Ongoing CV adjudication in saxagliptin clinical trial program Saxagliptin epidemiology program for further risk evaluation of major adverse cardiovascular events.	Product labeling is sufficient to address safety concern. Specific information for this population is described in the product labeling (SmPC): Section 4.3 Contraindication
Safety in immunocompromised patient	Routine PV	Product labeling is sufficient to address safety concern. Warning and precaution information for the immunocompromised patients is described in the product labeling (SmPC): Section 4.4 Special warnings and precautions for use
Malignancy/neoplasm	Routine PV Assessment in cardiovascular outcomes study (CV181088/D1680C00003 [SAVOR])	None

The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product.

2.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed (changes highlighted as “strike-through” and “underlined”):

Onglyza

4.1 Therapeutic indications

~~Add-on combination therapy~~
Onglyza is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control:

as dual oral therapy in combination with

- ~~in combination with~~ metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control.
- ~~in combination with~~ a sulphonylurea, when the sulphonylurea alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate.
- ~~in combination with~~ a thiazolidinedione, when the thiazolidinedione alone with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a thiazolidinedione is considered appropriate.

as triple oral therapy in combination with

- metformin plus a sulphonylurea when this regimen alone, with diet and exercise, does not provide adequate glycaemic control

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

4.2 Posology and method of administration

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~~. Onglyza tablets must not be split or cut. When Onglyza is used in combination with insulin or a sulphonylurea, a lower dose of the insulin or sulphonylurea may be required to reduce the risk of hypoglycaemia (see section 4.4).

The safety and efficacy of saxagliptin as triple oral therapy in combination with metformin and a thiazolidinedione~~, or with metformin and a sulphonylurea,~~ has not been established.

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4.7 Effects on ability to drive and use machines

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In addition, patients should be alerted to the risk of hypoglycaemia when Onglyza is used in combination with other antidiabetic medicinal products known to cause

hypoglycaemia (e.g. insulin, sulphonylureas).

4.8 Undesirable effects

. . .

Description of selected adverse reactions

. . .

As add-on to metformin plus a sulphonylurea: dizziness (common), fatigue (common) and flatulence (common).

Hypoglycaemia
Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required.

When used as add-on combination therapy with metformin plus sulphonylurea, the overall incidence of reported hypoglycemia was 10.2 % for Onglyza 5 mg and 6.3% for placebo.

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.

~~When used as add-on combination therapy with metformin plus sulphonylurea, the overall incidence of reported hypoglycemia was 10.2 % for Onglyza 5 mg and 6.3% for placebo.~~

5.1 Pharmacodynamic properties

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Saxagliptin add-on combination therapy with metformin and sulphonylurea
A total of 257 patients with type 2 diabetes participated in a 24-week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin (5 mg once daily) in combination with metformin plus sulphonylurea (SU) in patients with inadequate glycemic control (HbA1c ≥7% and ≤10%). Saxagliptin (n=127) provided significant improvements in HbA1c and PPG compared with the placebo (n=128). The HbA1c change for saxagliptin compared to placebo was -0.7% at Week 24.

. . .

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 D1680L00006: add-on to metformin plus SU (n=257)	8.4	-0.7	-0.7(-0.9,-0.5)[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)	8.7	-0.7	-0.4 (-0.6, -0.2)[3]
Overall population (n=300)			

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.

Komboglyze

4.1 Therapeutic indications

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Komboglyze is also indicated in combination with a sulphonylurea (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 the maximally tolerated dose of both metformin and the sulphonylurea does not provide adequate glycaemic control.

4.3 Posology and method of administration

Posology
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For patients inadequately controlled on dual combination therapy of a sulphonylurea and metformin, or for patients switching from triple combination therapy of saxagliptin, metformin and a sulphonylurea taken 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 a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia (see section 4.4).

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4.4 Special warnings and precautions for use

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

4.7 Effects on ability to drive and use machines

. . . In addition, patients should be alerted to the risk of hypoglycaemia when Komboglyze is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. insulin, sulphonylureas).

4.8 Undesirable effects

. . .

Description of selected adverse reactions

. . .

As add-on to metformin and a sulphonylurea: dizziness (common), fatigue (common) and flatulence (common).

. . .

When used as add-on to metformin plus a sulphonylurea, the overall incidence of reported hypoglycemia was 10.2 % for saxagliptin 5 mg and 6.3% for placebo.

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5.1 Pharmacodynamic properties

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Saxagliptin add-on combination therapy with metformin and sulphonylurea

A total of 257 patients with type 2 diabetes participated in a 24-week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin (5 mg once daily) in combination with metformin plus sulphonylurea (SU) in patients with inadequate glycemic control (HbA1c ≥7% and ≤10%). Saxagliptin (n=127) provided significant improvements in HbA1c and PPG compared with the placebo (n=128). The HbA1c change for saxagliptin compared to placebo was -0.7% at Week 24.

Table 4 Key efficacy results in placebo-controlled, combination therapy studies of saxaglipin and metformin

	Mean baseline HbA1c (%)	Mean change[1] from baseline HbA1c (%)	Placebo-corrected mean change in HbA1c (%) (95% CI)
ADD-ON/INITIAL COMBINATION WITH METFORMIN STUDIES			
24-weeks			
Saxa 5 mg daily add-on to metformin; Study CV181014 (n=186)	8.1	-0.7	-0.8 (-1.0, -0.6)[2]
Saxa 5 mg daily initial combination with metformin; Study CV181039[3]:			
Overall population (n=306)	9.4	-2.5	-0.5 (-0.7, -0.4)[4]
Baseline HbA1c ≥ 10% stratum (n=107)	10.8	-3.3	-0.6 (-0.9, -0.3)[5]
12-weeks			
Saxa 2.5 mg twice daily add-on to metformin; Study CV181080 (n=74)	7.9	-0.6	-0.3 (-0.6,-0.1)[6]
ADD-ON/COMBINATION STUDIES WITH ADDITIONAL THERAPIES			
Add on to insulin (+/- metformin)			
Saxa 5 mg daily, Study CV181057: Overall population (n=300)	8.7	-0.7	-0.4 (-0.6, -0.2)[2]
24-weeks			
Saxa 5 mg daily add on to metformin plus sulphonylurea; Study D1680L00006 (n=257)	8.4	-0.7	−0.7 (−0.9, −0.5)[2]

n=Randomized patients

[1] Adjusted mean change from baseline adjusted for baseline value (ANCOVA).

[2] p< 0.0001 compared to placebo.

[3] Metformin was uptitrated from 500 to 2000 mg per day as tolerated.

[4] Mean HbA1c change is the difference between the saxagliptin 5 mg + metformin and metformin alone groups (p< 0.0001).

[5] Mean HbA1c change is the difference between the saxagliptin 5 mg + metformin and metformin alone groups.

[6] p-value = 0.0063 (between group comparisons significant at α = 0.05)

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were reviewed and accepted by the CHMP.

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

Benefits

Beneficial effects

A study was performed to evaluate the efficacy and safety of saxagliptin compared with placebo as add-on therapy to a stable metformin dose plus a stable SU dose in subjects with T2DM who have inadequate glycaemic control (HbA1c ≥7% and ≤10%). Study D1680L00006 was a 24-week, multicenter, randomized, parallel-group, double-blind, placebo-controlled Phase 3b study in 257 subjects.

Saxagliptin 5 mg added to a stable dose of metformin plus SU was superior to placebo in lowering HbA1c and 2-hour PPG from baseline to Week 24. In contrast with placebo for saxagliptin a reduction in HbA1c from baseline was observed at weeks 4, 8, 12 and progressively greater to week 16. This reduction was maintained through week 24.

The adjusted mean changes were -0.74% for the saxagliptin group and -0.08% for the placebo group, with a difference versus placebo of -0.66% [2-sided 95% CI, -0.86% to -0.47%; p<0.0001] for saxagliptin).

Secondary endpoints were in line with these results.

Uncertainty in the knowledge about the beneficial effects

Uncertainties about a possible centre effect were addressed by the MAH with an analysis according to country in which the centres were located, which did not show any interaction.

Risks

Unfavourable effects

In general saxagliptin was well tolerated and there were no new unexpected adverse events.

The proportion of subjects experiencing any treatment-related AE was higher in the saxagliptin group compared with the placebo group (16.3% and 10.2% in the saxagliptin and placebo groups, respectively; 11.6% and 7.0%, respectively, when hypoglycaemic events were excluded).

There were no deaths during the study.

SAEs were reported in a total of 10 subjects: 3 (2.3%) subjects in the saxagliptin group. Of these, only 1 SAE (hepatitis) was considered to be possibly related to saxagliptin. One (0.8%) subject in the saxagliptin group discontinued due to an AE and 3 (2.3%) subjects in the placebo group discontinued due to an AE.

The incidence of hypoglycaemic AEs was low in both treatment groups but was higher in the saxagliptin group compared with the placebo group (10.1% and 6.3%, respectively); two subjects (saxagliptin group) had confirmed hypoglycaemia (symptomatic with fingerstick plasma glucose ≤2.8 mmol/L [50 mg/dL]).

Uncertainty in the knowledge about the unfavourable effects

A relatively large number of subjects discontinued from this 24 weeks study. However, discontinuation was balanced between the saxagliptin group (12.4%) and the placebo group (11.7%).

Benefit-risk balance

Importance of favourable and unfavourable effects

The effect on HbA1c of saxagliptin when added to stable doses of metformin and SU is an important benefit. The difference with placebo in change from baseline (-0.66%) is clinically relevant.

The incidence of hypoglycaemia was low in both groups, which is a benefit.

In general saxagliptin was well tolerated and there were no new unexpected adverse events.

Benefit-risk balance

Discussion on the benefit-risk balance

The effect of adding saxagliptin to ongoing metformin and SU on HbA1c is demonstrated. Treatment was associated with a small increase in hypoglycaemic events which can be expected. In a former study (CV181040), submitted with the MAA, adding saxagliptin to SU resulted in percentages hypoglycaemia of 14.6 in the saxagliptin group and 10.1% in the placebo group. Results in the current study are somewhat lower.

Saxagliptin was well tolerated.

Conclusion

The overall B/R of saxagliptin as add-on therapy to a stable metformin dose plus a stable SU dose in subjects with T2DM who have inadequate glycaemic control is positive.

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) requested		Type
C.I.6.a	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 Onglyza and Komboglyze to include combination of metformin, a suphonylurea and saxagliptin, i.e. triple oral therapy. The Package Leaflet and Labelling are updated accordingly.

Furthermore, the PI is being brought in line with the latest QRD template version 8.2.

Furthermore, in the SmPC and the Package Leaflet minor typographical errors were corrected and these were harmonized for the two products.

The requested variation worksharing procedure proposed amendments to the Summary of Product

Characteristics, Annex II, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.