EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CHMP/432717/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Invented name Onglyza

Procedure No. EMEA/H/C/001039/II/0018

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

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List of abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the curve
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
CSR	Clinical study report
CTD	Common Technical Document
CV	Cardiovascular
DAE	AE leading to the discontinuation of study treatment
DPP4	Dipeptidyl peptidase 4
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
HbA1c	Glycosylated haemoglobin
ICH	International Conference on Harmonisation
IR	Immediate release
LOCF	Last observation carried forward
LT	Long-term
MAA	Marketing Authorization Application
PK	Pharmacokinetic(s)
PPG	Postprandial glucose
QAM	Once daily in the morning
QD	Once daily
QPM	Once daily in the evening
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy (CTD Module 2.7.3)
SCS	Summary of Clinical Safety (CTD Module 2.7.4)
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
ST	Short-term
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione
US	United States

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 3 December 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Onglyza	Saxagliptin	See Annex A

The following variation was requested:

Variation 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 MAH proposed the update of sections 4.1, 4.2 and 5.1 of the SmPC in order to extend the indication to include monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. The Package Leaflet was proposed to be updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0.

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

Rapporteur: Pieter de Graeff

1.2. Steps taken for the assessment

Submission date:	3 December 2012
Start of procedure:	25 January 2013
Rapporteur's preliminary assessment report circulated on:	25 March 2013
Co-Rapporteur's preliminary assessment report circulated on:	19 March 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2013
MAH's responses submitted to the CHMP on:	22 May 2013
Rapporteurs' Joint Assessment report on the MAH's responses circulated on:	10 June 2013
CHMP opinion:	27 June 2013

Information on Paediatric requirements

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

- Treatment of type 2 diabetes mellitus

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

2. Scientific discussion

2.1. Introduction

Saxagliptin, a DPP-4 inhibitor, is approved through a centralized procedure (initially in 2009) in the European Union (EU) in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control:

as dual oral therapy in combination with

- metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control.
- 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.
- 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.

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

In the EU, the generally recommended dose for saxagliptin is 5 mg QD. For patients with moderate or severe renal impairment, the recommended dose is 2.5 mg QD.

The current type II variation seeks approval for the use of saxagliptin, as monotherapy in adult patients aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control in patients inadequately controlled by diet and exercise alone, and for whom metformin is inappropriate due to contraindications or intolerance.

The proposed recommended dose is 5 mg once daily (QD).

This extended indication is documented by the following documentation:

- New information from 2 Phase 3 monotherapy studies (D1680C00005 and D1680C00008) performed in Asians;
- Previously submitted studies that already have been assessed in previous applications (2 monotherapy (studies CV181011 and CV181038) and several additional studies);
- New analyses from data pooled across all Phase 3 monotherapy studies that have been conducted.

Saxagliptin belongs to the class of dipeptidylpeptidase 4 (DPP-4) - inhibitors developed to treat T2DM. The DPP-4 inhibitors act by enhancing the body`s own ability to control blood glucose by increasing the active levels of incretin hormones. The incretins improve glycaemic control in a glucose dependent manner through different pathways, including triggering pancreatic insulin synthesis and secretion and suppression of pancreatic glucagon secretion.

The clinical program to support the addition of the monotherapy 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, May 2000, and its update: "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" (CPMP/EWP/1080/00 Rev. 1).

2.2. Clinical Efficacy aspects

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

Tabular overview of clinical studies

Table 1 briefly describes the studies that contribute to the evaluation of saxagliptin as a monotherapy. These include 4 Phase 3 monotherapy studies and several additional studies. These studies were previously submitted and assessed, except for the 2 Phase 3 monotherapy studies (D1680C00005 and D1680C00008) in Asians.

Table 1 Summary of studies contributing to the evaluation of saxagliptin monotherapy

Study Number	Study objectives (HbA1c criteria at screening/ randomization)	Randomized and treated subjects (All/Saxa)	Duration short-term (total)	Saxagliptin (mg) dosage
Phase 3 monotherapy studies				
CV181011	Safety and efficacy (HbA1c 7%-10% at screening)	401/306*	24 weeks (206 weeks)	2.5, 5, or 10 QD AM
CV181038	Safety and efficacy (HbA1c 7%-10% at screening)	365/291	24 weeks (76 weeks)	2.5, 5, or 2.5/5 QD AM, or 5 QD PM
D1680C00005 (CV181063)	Safety and efficacy (HbA1c 7%-10% at randomization)	568/284	24 weeks	5 QD AM
D1680C00008 (CV181082)	Safety and efficacy (HbA1c 7%-10% at randomization)	213/107	24 weeks	5 QD AM
Supportive studies				
CV181008	Dose-finding safety and efficacy (HbA1c 6.8%-9.7% at screening)	423/315	12 weeks or 6 weeks	2.5, 5, 10, 20, or 40 QD or 100 QD
CV181039	Safety and efficacy (HbA1c 8%-12% at screening)	1306/978	24 weeks (76 weeks)	5 QD + metformin IR or 10 QD +metformin IR or 10 mg QD (Metformin titratable from 500 to 2000 mg)
D1680C00007 (CV181062)	Effect of saxagliptin compared with placebo in adult subjects with T2DM and renal impairment (moderate, severe, and end-stage) (HbA1c 7%-11% at screening)	170 / 85	12 weeks (52 weeks)	2.5 mg QD + background medication
D1680C00001 (CV181054)	Safety and efficacy of saxagliptin in combination with metformin compared with SU in combination with metformin (HbA1c 6.5%-10% at screening)	858 / 428	52 weeks (104 weeks)	5 mg + metformin IR QD (Glipizide 5-10 mg + metformin IR; metformin at pre-study dose, 1500-3000 mg)
D1680C00002 (CV181056)	Safety and efficacy of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin (HbA1c 6.5%-10% at screening)	801 / 403	18 weeks	5 mg + metformin IR QD (Sitagliptin 100 mg + metformin; metformin at pre-study dose, 1500-3000 mg)

* An additional 66 subjects received open-label saxagliptin in Study CV181011.

AM In the morning; HbA1c Glycosylated hemoglobin; IR Immediate release; PM In the evening; QD Once daily; Saxa Saxagliptin; SU Sulfonylurea; T2DM Type 2 diabetes mellitus.

2.2.1.1. Dose response studies

The proposed recommended dose for saxagliptin monotherapy is 5 mg once daily in adult patients with T2DM who are inadequately controlled by diet and exercise alone, and for whom metformin is inappropriate due to contraindications or intolerance. Saxagliptin 5 mg is also the approved dose for combination therapy. In previously submitted Phase 1 and Phase 2 studies, administration of saxagliptin 5 mg was associated with greater inhibition of plasma DPP4 activity at the trough of the dosing interval compared to 2.5 mg. Based on the dose finding study, CV181008, which examined a range of doses of saxagliptin (2.5 to 100 mg), the efficacy of saxagliptin 5 mg was further characterized in Phase 3 studies. All doses examined in CV181008 resulted in a statistically and clinically relevant reduction in A1C, although 5 mg led to the numerically largest reduction. The phase 3 studies as well as post-marketing experience provided evidence to support the use of saxagliptin 5 mg, both as a combination therapy and as monotherapy.

The saxagliptin 2.5 mg dose was also observed to be effective and is proposed for patients with moderate or severe renal impairment, consistent with evidence of increased exposure with renal impairment and the current dosing recommendations for saxagliptin combination therapy.

The dose finding study suggested no dose-effect relationship, and doses of 2.5, 5 and 10 mg were chosen for the Phase 3 studies. The applicant has not given further reasons for not including the 2.5 mg in the new monotherapy studies. Considering the lack of difference in clinical efficacy and safety seen for saxagliptin 2.5 mg and 5 mg seen in the previous assessed monotherapy studies, it was considered unfortunate not having included a 2.5 mg treatment group in the new monotherapy studies.

2.2.1.2. Main studies

The focus of this submission is on 4 Phase 3 monotherapy studies (CV181011, CV181038, D1680C00005, and D1680C00008), of which the latter two are newly completed in Asian patients and not assessed previously. Study CV181011 and Study CV181038 were reviewed in the original saxagliptin registration dossier.

2.2.2. Methods – analysis of data submitted

Design

All main studies were randomized, double-blind, placebo-controlled trials. An overview of the 4 Phase 3 study designs is provided in Figure 1. The primary assessment point of efficacy was at 24 weeks. Following screening, subjects entered a 2-4 week dietary and exercise placebo lead-in period; subjects demonstrating lead-in period compliance were eligible for randomization into the short-term period.

Study CV181011. The primary efficacy objective for the ST treatment period of this study was to compare, after 24-weeks oral administration of double-blind treatment, the change from baseline in HbA1c achieved with each dose of saxagliptin versus placebo in treatment-naïve subjects with T2DM who have inadequate glycaemic control defined.

Study CV181038. The primary efficacy objective for the ST treatment period of this study was to compare, after 24-weeks oral administration of double-blind treatment, the change from baseline in HbA1c achieved with saxagliptin 2.5 mg QAM, 5 mg QAM, and 2.5 mg titrated to 5 mg QAM (2.5/5 mg QAM) versus placebo in treatment-naïve subjects with T2DM who have inadequate glycaemic control defined. No titration of study medication was permitted during the study. Open-label metformin (500 mg titratable to 2000 mg) was administered as rescue medication if subjects met pre-defined rescue criteria.

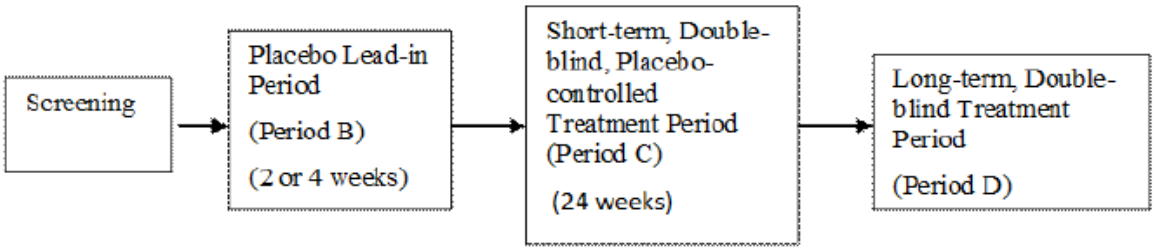
The two new Phase 3 studies (D1680C00005 and D1680C00008) were conducted subsequently to confirm the previous positive findings for saxagliptin 5 mg as monotherapy. These studies were regional studies with similar study designs as applied in study CV181011, and CV181038 to evaluate saxagliptin as monotherapy in Asian populations (China, India, The Philippines, and South Korea).

Study D1680C00005. Recruited treatment-naïve subjects in the Asian Pacific region.

Study D1680C00008. Recruited treatment naïve subjects in an Indian population.

Double-blind extension period. After completion of the 24-week short-term (ST) treatment period in studies CV181011 and CV181038, eligible subjects were to continue into a long-term (LT) extension period (182 weeks in CV181011 and 52 weeks in CV181038) to assess the durability of efficacy and LT safety.

Figure 1 Design overview of Phase 3 monotherapy studies



Study participants

Inclusion criteria

The inclusion criteria for all 4 Phase 3 monotherapy studies selected adult patients with T2DM who were treatment-naïve and who were generally at an early stage of disease (HbA1c criteria for randomization of 7% to 10%). The study population included those who might otherwise seek first-line treatment with metformin; ***these studies did not specifically include or exclude subjects who were metformin contraindicated or metformin intolerant.***

Outcomes/endpoints

Primary efficacy endpoint: Change from baseline in Hb1Ac at Week 24.

Secondary efficacy endpoints:

- FPG,
- proportion of patients achieving therapeutic glycaemic response,
- PPG area under the curve (AUC).

These secondary endpoints were subject to sequential testing to evaluate statistical significance in 2 or more of the individual Phase 3 studies depending on the endpoint. Although 120- minute PPG was not subject to the sequential testing methodology, results for 120-minute PPG are also presented, since they are clinically relevant and easier to interpret than PPG AUC results.

These primary and secondary endpoints are well established, typical of current studies of glycaemic control, and consistent with EMA "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" (CPMP/EWP/1080/00 Rev. 1).

Statistical methods

Statistical methodologies for efficacy analyses

All efficacy analyses were performed on data collected prior to rescue medication (consistent with efficacy analyses provided in the CSRs) so as to focus exclusively on the efficacy of saxagliptin monotherapy. The primary analysis in all 4 Phase 3 monotherapy studies was based on an ANCOVA model which utilized LOCF to impute missing data. Recent guidance from regulatory and academic sources is increasingly critical of the LOCF technique for imputation and a repeated measures analysis has been increasingly applied to studies of saxagliptin. Consequently, this submission also includes the repeated measures analyses conducted previously on the primary Hb1Ac endpoint on all 4 individual studies, as well as repeated measures analyses on pooled data for both the primary endpoint and the secondary endpoint FPG.

Pooled analyses: These have been conducted to further characterize the efficacy of saxagliptin monotherapy across studies and subgroups, to provide more precise estimates of treatment effects. This was a retrospective pooling. Since all studies involved in the 4 and 5-study pools had already been unblinded and reported, no type I error control for the pooled analyses was possible and no claims of type I error control have been made for these pooled analyses. All p-values generated from the poolings should be interpreted as nominal. The pooling was undertaken to provide a comprehensive summarisation of available monotherapy data and to improve the precision of estimation of treatment effects. Individual study results are also reported in the submission documents. These studies did utilise multiplicity correction to control Type I error.

The results of the pooled analysis should be interpreted as a summary of the data from the individual studies and be used as supportive evidence. The proof of efficacy must come from the individual studies.

Study CV181011 and Study CV181038 were assessed in the original saxagliptin registration dossier.

Study D1680C00005 and study D1680C00008 have not been submitted previously. Their design is similar to the 2 previously submitted studies and considered adequate. Primary and secondary endpoints are agreed. In- and exclusion criteria are acceptable.

During the procedure, the CHMP requested supplementary information how the data was pooled and whether raw or pre-processed data have been pooled. The applicant responded that pre-processed data have been pooled in all cases. The derived data sets from each study were pooled with modifications to variable names and formats as necessary to allow for proper integration. Data prior to initiation of rescue therapy up to 24-weeks were included for the 4-study pool and up to 12-weeks were included for the 5-study pool. The 2.5 mg, 5 mg, and control treatments were included from each of the studies. In order to best characterize the efficacy response while still being inclusive for the safety analyses, the 2.5 mg to 5 mg titration arm and the 5 mg QPM (once daily in the evening) arm in study CV181038 were excluded from the efficacy analysis but included in the safety analysis as part of the 2.5 mg and 5 mg arms, respectively. This was satisfactory to the CHMP as the pooled studies were designed generally in the same way, including the same type of patients, and using the same control treatment, and endpoints. Thus the pre-processing likely also have yielded the same results.

During the procedure, the CHMP had concerns with a possible centre effect: Considering the large number of sites and the small number of subjects enrolled at most sites a centre effect could not be excluded. Hence, an analysis of centre effects in D1680C00005 and D1680C00008 was requested (see below).

2.2.3. Results

Disposition of subjects

Within each of the 4 Phase 3 studies, the percentage of subjects completing the 24-week treatment period was similar across treatment groups (Fewer patients completed the 24-week randomized treatment period in studies CV181011 and CV181038 than in studies D1680C00005 and D1680C00008, primarily because rescued subjects were handled differently in these studies. However, because all efficacy analyses are based on data prior to rescue, the difference in completion rates does not impact the interpretation of the efficacy results. (Table 2)

Table 2 Disposition of subjects in the Phase 3 monotherapy studies at Week 24

Study Treatment Group	No. subjects randomized and treated	Subjects completing the 24-week period, n (%)[a]	Rescued n (%)
Study CV181011[b]			
Placebo	95	55 (57.9)	25 (26.3)
Saxa 2.5 mg	102	73 (71.6)	14 (13.7)
Saxa 5 mg	106	68 (64.2)	21 (19.8)
Study CV181038[b]			
Placebo	74	53 (71.6)	11 (14.9)
Saxa 2.5 mg QAM	74	55 (74.3)	8 (10.8)
Saxa 5 mg QAM	74	57 (77.0)	10 (13.5)
Study D1680C00005[c]			
Placebo	284	248 (87.3)	27(9.5)
Saxa 5 mg	284	262 (92.3)	14(4.9)
Study D1680C00008[c]			
Placebo	106	100 (94.3)	8 (7.5)
Saxa 5 mg	107	101 (94.4)	4 (3.7)
Pooled monotherapy[d]			
Placebo	559	456 (81.4)	73 (13.0)
Saxa 2.5 mg	176	128 (72.7)	22 (12.5)
Saxa 5 mg	571	488 (85.3)	50 (8.7)

Source: Table 5.1 of ST CSR CV181011, and Table 4 of ST CSR CV181011 Addendum; Tables 5.1A and 5.1B of ST CSR CV181038; Table 9 and Appendix 2.1B of CSR D1680C00005; Table 9 and Appendix 2.1B of CSR D1680C00008, Table 1.1 of Appendix 2.7.3.6.1.

Overall, within the studies, there were no differences between treatment groups in percentages of patients completing the 24-week period. As could be expected, more patients in the placebo groups needed rescue therapy.

Baseline data

In the 4 pooled Phase 3 monotherapy studies (Table 3), the mean age was 52.13 years, 11.6 % of subjects were ≥65 years of age, 53 % were male, 31.6 % were White, 64.9 % were Asians, and the mean weight was 76.82 kg. Across all 4 studies, the mean duration of T2DM at baseline was 1.5 years, the mean baseline Hb1Ac was 8.1%, and the mean baseline FPG was 9.1 mmol/L.

Demographic and baseline characteristics were generally balanced across the randomized treatment groups in the individual Phase 3 studies (Table 3). However, White subjects were primarily enrolled in Study CV181011 (85.0%) and Study CV181038 (69.6%), while Asian subjects were exclusively (100%) enrolled in Study D1680C00005 and Study D1680C00008. Studies CV181011 and CV181038 had greater baseline weight and body mass index (BMI), more patients ≥65 years of age, and a longer mean duration of T2DM, perhaps reflecting differences in racial composition or study conduct, thus providing a diverse overall population.

Table 3 Selected demographic and baseline disease characteristics for overall populations included in the Phase 3 monotherapy studies

	CV181011 (N=401)	CV181038 (N=365)	D1680C00005 (N=568)	D1680C00008 (N=213)	Pooled (N=1306)a
Mean age (yr) (SD)	53.46 (11.29)	54.98 (10.31)	51.40 (10.18)	48.68 (9.17)	52.13 (10.49)
Age ≥65 (%)	15.7	17.5	9.5	3.8	11.6
Male (%)	50.9	46.0	55.5	56.3	53.0
Race (%):					
White	85.0	69.6	0	0	31.6
Black /African American	5.5	6.6	0	0	2.3
Asian	4.5	23.3	100.0	100.0	64.9
Other	5.0	0.5	0	0	1.1
Mean weight (kg) (SD)	89.78 (17.86)	84.89 (17.70)	69.23 (11.88)	69.62 (12.10)	76.82 (17.22)
Mean baseline BMI (kg/m^2) (SD)	31.71 (4.59)	30.54 (4.95)	25.92 (3.56)	26.80 (4.28)	28.24 (4.89)
Mean duration of T2DM (yr) (SD)	2.6 (3.2)	1.7 (3.2)	1.0 (2.1)	0.9 (1.3)	1.5 (2.4)
Previous T2DM treatment	None	None	None	None	None
Mean baseline HbA1c (%) (SD)	7.9 (1.0)	7.9 (0.9)	8.1 (0.8)	8.3 (0.8)	8.1 (0.9)
Mean baseline FPG (mmol/L) (SD)	9.7 (2.4)	9.0 (2.4)	9.1 (2.3)	8.4 (2.1)	9.1 (2.3)
Mean baseline FPG (mg/dL) (SD)	175.0 (43.5)	162.0 (42.7)	164.2 (41.1)	150.7 (37.0)	163.6 (41.2)

Source: Tables 5.3.1 and 5.3.2 in ST CSR CV181011 and Table 5.3.2 in ST + LT CSR CV181011 Addendum; Tables 5.3.1 and 5.3.2 in ST CSR CV181038 and Table 5.3.2 in ST + LT CSR CV181038 Addendum, Tables 13 and 15 in CSR D1680C00005, and Tables 12 and 13 in CSR D1680C00008; Tables 2.1 and 3.1 in Appendix 2.7.3.6.1.

Note: The demographic and baseline disease characteristics of patients in the Phase 2b/3 monotherapy pool used to assess efficacy at Week 12 is presented in Tables 2.2 and 3.2 of Appendix 2.7.3.6.1.

[a] Since some treatment groups from the individual studies were not included in the pool, the number of subjects (N=1306) in the pool does not equal the sum of the number of subjects in each individual study.

Data Set: Randomized Subjects

BMI Body mass index; CSR Clinical Study Report; FPG Fasting plasma glucose; HbA1c Glycosylated hemoglobin; LT Long-term; NA Not available; SD Standard deviation; ST Short-term; T2DM Type 2 diabetes mellitus; yr Years

Study D1680C00005 and study D1680C00008 were performed in Asians. There is a growing body of evidence that the pathophysiology of type 2 diabetes differs between Whites and Asians. In general, Asian patients are characterized by a relatively lower BMI, higher amounts of visceral fat with a given BMI or waist circumference and a predominant insulin secretory defect (Kim et al. Diabetologia, January 2013). In the present application, BMI was considerably lower in the studies in Asians (25.9 and 26.8 kg/m2) as compared to the studies in White individuals (31.7 and 30.5 kg/m2). Therefore, the CHMP had concerns about different results in Asians compared with a white population, and the appropriateness of pooling of Asians and Whites. This was addressed to the applicant as a request for supplementary information during the procedure to which satisfactory information was received (see section 2.2.2 Methods – analysis of data submitted).

This submission seeks approval for the use of saxagliptin as monotherapy when metformin is inappropriate due to contraindications or intolerance. Contraindications may include cardiac and/or renal failure. Intolerance is usually due to gastrointestinal side effects.

All four main studies were performed in individuals without any contraindication or intolerance for metformin. Although results in these individuals may not be fully applicable to the intended population, there appears no reason to believe that this would influence efficacy, however.

Within each individual study, there were no relevant differences between treatment groups in demographics and baseline disease characteristics (Table 3).

Numbers analysed

Outcomes and estimation

Change from baseline in HbA1c at Week 24

The results of the main analysis (LOCF) of the primary endpoint across each of the 4 Phase 3 monotherapy studies demonstrated a statistically significant and clinically meaningful effect of saxagliptin 5 mg in lowering HbA1c at Week 24, compared to placebo (Table 4). Figures demonstrate the difference from placebo in adjusted mean change from baseline in HbA1c for the saxagliptin 5 mg dose in study D1680C00005 (Figure 2), and D1680C00008 (Figure 3).

The mean (95% confidence interval [CI]) of the pooled data was –0.51% (-0.62%, -0.39%).

Table 4 Mean change from baseline in HbA1c (%) at Week 24 (LOCF) – Individual and pooled Phase 3 monotherapy studies

Study	Saxagliptin 2.5 mg			Saxagliptin 5 mg			Placebo	
	n/N	Adj. mean change from baseline (SE)	Difference from placebo in adjusted mean change from baseline [95% CI]	n/N	Adj. mean change from baseline (SE)	Difference from placebo in adjusted mean change from baseline [95% CI]	n/N	Adj. mean change from baseline (SE)
CV181011	100/102	-0.43(0.10)	-0.62 [-0.90, -0.33]**+	103/106	-0.46 (0.10)	-0.64 [-0.93, -0.36]**+	92/95	0.19 (0.13)
CV181038	67/74	-0.71 (0.10)	-0.45[-0.74, -0.16]*+	69/74	-0.66 (0.10)	-0.40 [-0.69, -0.12]*+	68/74	-0.26 (0.10)
D1680C00005	NA	NA	NA	277/280	-0.84 (0.07)	-0.50 [-0.65, -0.34]**+	274/280	-0.34 (0.07)
D1680C00008	NA	NA	NA	104/106	-0.51 (0.10)	-0.46 [-0.73, -0.18]*+	105/105	-0.05 (0.10)
Pooled[a]	167/176	-0.66 (0.08)[b]	-0.54 [-0.73, -0.35]**b	553/571	-0.64 (0.04)[c]	-0.51 [-0.62, -0.39]**c	539/559	-0.13 (0.05)[d]

Figure 2 Study D1680C00005.Mean HbA1c values (LOCF) during the randomized treatment period (Full analysis set)

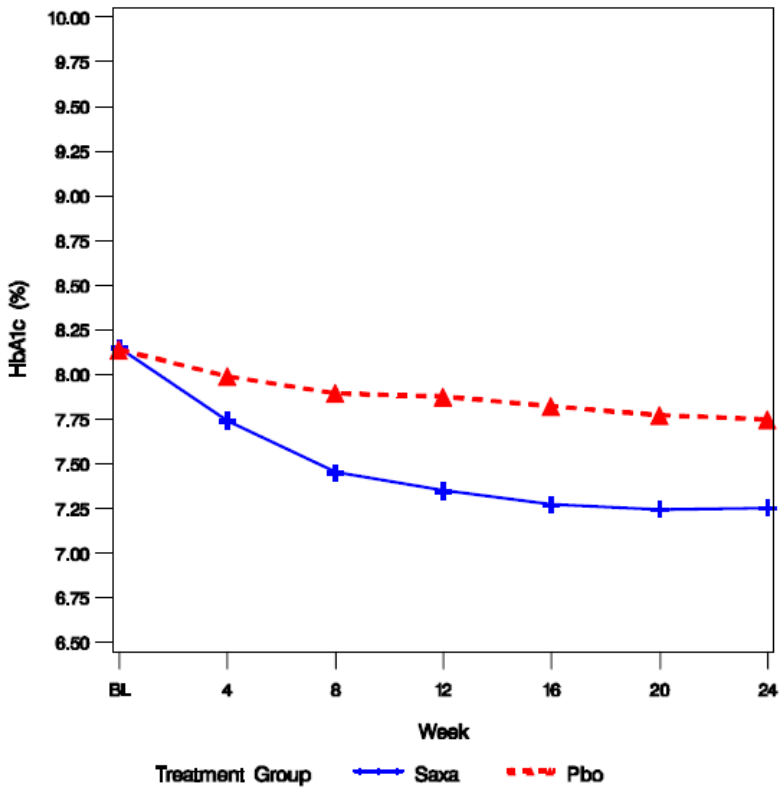
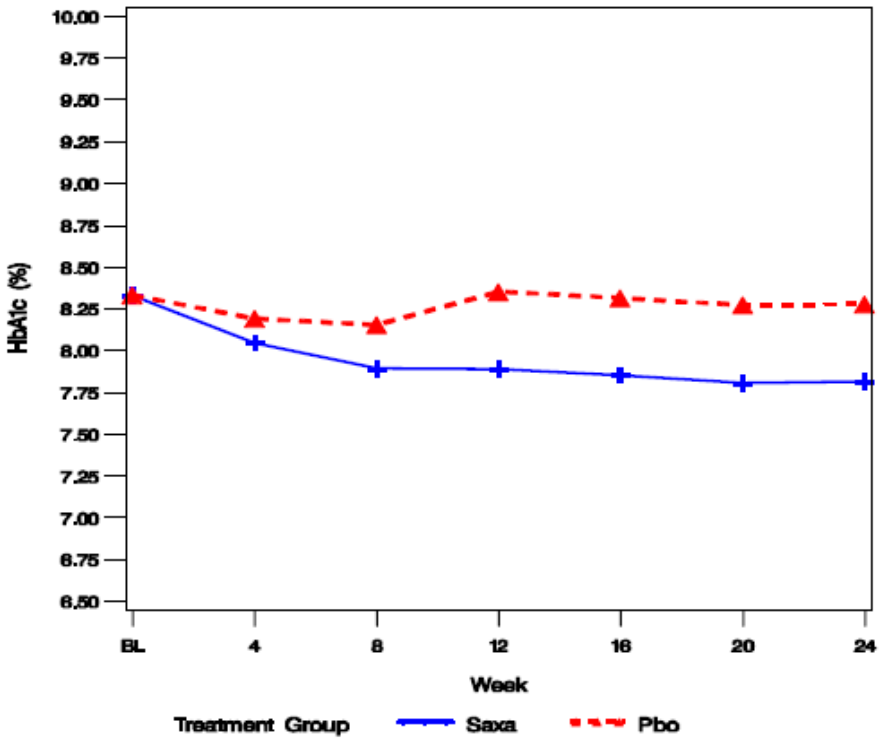


Figure 3 Study D1680C00008. Mean HbA1c values (LOCF) during the randomised treatment period (Full analysis set)



The primary analyses for the individual 4 Phase 3 monotherapy studies, as well as the pooled analyses in **Table** 4 were based on an ANCOVA model that utilized LOCF to impute missing data. Repeated measures

analyses of the primary endpoint (change from baseline in HbA1c at Week 24) were also performed for both the individual studies and the pooled analyses. The findings were consistent with the primary analyses. The 95% CI for the difference from placebo was less than zero (i.e. favourable) for all 4 studies at 5 mg and for the 2 studies at 2.5 mg, as well as for the pooled analyses at each dose. For the pooled analysis, the mean (95% CI) difference from placebo was -0.39% (-0.55, -0.22) for saxagliptin 2.5 mg and -0.45% (-0.55, -0.35) for saxagliptin 5 mg.

The efficacy of saxagliptin monotherapy was apparent across all subgroups (race, gender, age, baseline HbA1c) examined with the pooled data at 5 mg. For all these subgroups there was a clinically meaningful effect of saxagliptin. Also for all subgroups, the 95% CI for the difference from placebo was less than zero for the pooled data for the primary HbA1c endpoint from all 4 Phase 3 studies with saxagliptin 5 mg and from both studies with the saxagliptin 2.5 mg dose. Of particular interest are the findings for race, because of the imbalance between White and Asian subjects across the 4 Phase 3 monotherapy studies. In the pooled data at saxagliptin 5 mg there appeared to be small differences between the races; the adjusted mean change from baseline in HbA1c (95% CI) difference from placebo was –0.40% (-0.63, -0.16) for Whites (n=138) and –0.51% (-0.64, -0.38) for Asians (n=402).

Secondary endpoints

The findings from secondary endpoints are consistent with the efficacy of saxagliptin 5 mg established by the primary endpoint analyses. Statistically significant reductions from baseline in FPG at Week 24 compared with placebo were observed for the saxagliptin 5 mg treatment group in 3 of the 4 Phase 3 monotherapy studies (Table 5). In Study D1680C00008, treatment with saxagliptin 5 mg resulted in a numerically greater decrease from baseline in FPG compared to placebo, but this difference was not statistically significant. The pooled saxagliptin 5 mg group demonstrated a clinically meaningful change from baseline in FPG compared to placebo with a mean (95% CI) of –12.9 mg/dL (-17.49, 8.38) [-0.72 mmol/L (-0.97, -0.47)]. The saxagliptin 2.5 mg treatment groups also exhibited statistically significant reductions from baseline in FPG compared to placebo in the 2 studies (CV181011 and CV181038) with this dose. The pooled saxagliptin 2.5 mg group demonstrated a clinically meaningful change from baseline in FPG compared to placebo with a mean (95% CI) of -17.3 mg/dL (-24.77, -9.77) [-0.96 mmol/L (-1.37, -0.54)].

Table 5 Mean changes from baseline in FPG at Week 24 (LOCF) – Individual and pooled Phase 3 monotherapy studies

Study	Saxagliptin 2.5 mg			Saxagliptin 5 mg			Placebo	
	n/N	Adj. mean change from baseline (SE)	Difference from placebo in adjusted mean change from baseline [95% CI]	n/N	Adj. mean change from baseline (SE)	Difference from placebo in adjusted mean change from baseline [95% CI]	n/N	Adj. mean change from baseline (SE)
FPG mg/dL								
CV181011	101/102	-14.5 (3.82)	-20.6 [-31.47, -9.72]**+	105/106	-8.7 (3.74)	-14.7 [-25.50, -3.97]*+	92/95	6.1 (4.00)
CV181038	70/74	-11.4 (4.50)	-14.7 [-27.2, -2.3]*+	71/74	-10.7 (4.46)	-14.0 [-26.4, -1.6]*+	71/74	3.3 (4.46)
D1680C00005	NA	NA	NA	280/280	-16.1 (2.59)	-13.1 [-19.12, -7.13]**+	279/280	-3.0 (2.54)
D1680C00008	NA	NA	NA	106/106	-10.4 (3.83)	-10.2 [-20.91, 0.53]	104/105	-0.2 (3.86)
Pooled[a]	171/176	-16.6 (3.24)[b]	-17.3 [-24.77, -9.77]**b	562/571	-12.2 (1.74)[c]	-12.9 [-17.49, -8.38]**c	546/559	0.7 (1.77)[d]
FPG mmol/L								
CV181011	101/102	-0.81 (0.21)	-1.14 [-1.75, -0.54]**+	105/106	-0.48 (0.21)	-0.82 [-1.42, -0.22]*+	92/95	0.34 (0.22)
CV181038	70/74	-0.63 (0.25)	-0.82 [-1.51, -0.13]*+	71/74	-0.59 (0.25)	-0.78 [-1.47, -0.09]*+	71/74	0.18 (0.25)
D1680C00005	NA	NA	NA	280/280	-0.90 (0.14)	-0.73 [-1.06, -0.39]**+	279/280	-0.17 (0.14)
D1680C00008	NA	NA	NA	106/106	-0.66 (0.21)	-0.90 [-1.50, -0.30]	104/105	0.24 (0.22)
Pooled[a]	171/176	-0.92 (0.18)[b]	-0.96 [-1.37, -0.54]**b	562/571	-0.68 (0.10)[c]	-0.72 [-0.97, -0.47]**c	546/559	0.04 (0.10)[d]

In 2 of the 4 Phase 3 studies (CV181011 and D1680C00005), a statistically significantly greater proportion of subjects achieved a therapeutic glycaemic response (HbA1c <7%) in the saxagliptin 5 mg treatment group at Week 24 compared to placebo, and in 2 of the studies (CV181038 and D1680C00008)

the proportion of subjects achieving a therapeutic glycaemic response was numerically larger for the saxagliptin 5 mg treatment group, but the difference from placebo was not statistically significant (p>0.05) (Table 6). The pooled saxagliptin 5 mg treatment group demonstrated clinically meaningful greater differences in the proportion of subjects achieving therapeutic glycaemic response at Week 24 compared to placebo with a proportion (95% CI) of 14.0% (8.4%, 19.5%). The proportion of subjects achieving therapeutic glycaemic response in the saxagliptin 2.5 mg treatment group was not statistically significant (p >0.05) at Week 24, though numerically greater, when compared to placebo in the 2 studies where the saxagliptin 2.5 mg dose was evaluated. The pooled saxagliptin 2.5 mg treatment group demonstrated a clinically meaningful difference in the proportion of subjects achieving therapeutic glycaemic response compared to placebo with a proportion (95% CI) of 9.5% (1.6%, 17.9%).

Table 6 Percentage of subjects achieving therapeutic glycaemic response (HbA1c <7%) at Week 24 (LOCF) – Individual and pooled Phase 3 monotherapy studies

Study	Saxagliptin 2.5 mg		Saxagliptin 5 mg		Placebo
	Number (%) of subjects achieving therapeutic glycemic response (HbA1c <7%)	Difference (%) in proportions vs placebo [95% CI]	Number (%) of subjects achieving therapeutic glycemic response (HbA1c <7%)	Difference (%) in proportions vs placebo [95% CI]	Number (%) of subjects achieving therapeutic glycemic response (HbA1c <7%)
CV181011	35/100 (35.0)	11.1% [-3.1%, 24.9%]	39/103 (37.9)	14.0% [-0.1%, 27.6%][*+]	22/92 (23.9)
CV181038	24/67 (35.8)	0.5% [-15.9%, 16.7%]	31/69 (44.9)	9.6% [-7.1%, 25.8%]	24/68 (35.3)
D1680C00005	NA	NA	127/277 (45.8)	17.0% [8.9%, 24.9%][**+]	79/274 (28.8)
D1680C00008	NA	NA	23/104 (22.1)	8.8% [-1.7%, 19.3%]	14/105 (13.3)
Pooled[a]	59/167 (35.3)[b]	9.5% [1.6%, 17.9%][b]	220/553 (39.8)[c]	14.0% [8.4%, 19.5%][**c]	139/539 (25.8)[d]

In 2 of the Phase 3 monotherapy studies (CV181011 and D1680C00005) where PPG was measured, reductions from baseline in PPG AUC were statistically significant for the saxagliptin 5 mg treatment groups at Week 24 compared to placebo. In CV181038, the reductions from baseline in PPG AUC were numerically greater for the saxagliptin 5 mg treatment group compared to placebo (p=0.0043), but the sequential testing prohibited conclusions of statistical significance for this endpoint. The pooled saxagliptin 5 mg treatment group demonstrated clinically meaningful changes from baseline in PPG AUC at Week 24 compared to placebo with a mean (95% CI) of -4666 mg*min/dL (-6389, -2943) [-259.0 mmol*min/L (-354.67, -163.38)]. The saxagliptin 2.5 mg treatment group demonstrated reductions from baseline in PPG AUC at Week 24 compared to placebo in CV181011 (p=0.0003) and CV181038 (p=0.0059), but the sequential testing procedure prohibited conclusions of statistical significance in both studies. The pooled saxagliptin 2.5 mg treatment group demonstrated a clinically meaningful change from baseline in PPG AUC at Week 24 compared to placebo with a mean (95% CI) of -5148 mg*min/dL (-7288,-3007) [-285.7 mmol*min/L (-404.56, -166.93)].

Reductions in 120 minute PPG were not subjected to pre-specified multiplicity adjustment of testing for statistical significance, but are clinically relevant and support the clinical benefit of saxagliptin. The mean (95% CI) difference from placebo in change from baseline in 120 minute PPG for the pooled data from the 3 studies that measured 120 minute PPG was -29.6 mg/dL (-41.3, -17.9) [-1.64 mmol/L (-2.29, -0.99)] at saxagliptin 5 mg and –33.0 mg/dL (-47.4, -18.5) [-1.83 mmol/L (-2.63, -1.03)] at 2.5 mg.

In all of the main studies, saxagliptin monotherapy was associated with a modest, but significant effect on HbA1c considered to be of clinical relevance. For the pooled analyses, the treatment effect was –0.51% (-0.62%, -0.39%). There were differences between the races; the adjusted mean change from baseline in HbA1c (95% CI) difference from placebo was –0.40% (-0.63, -0.16) for Whites (n=138) and –0.51% (-0.64, -0.38) for Asians (n=402). The placebo response differs between studies, suggesting a difference in study population: during placebo treatment HbA1c increased by 0.01% in the Asians whereas it decreased by 0.4% in Whites.

The changes in HbA1c were accompanied by changes in the percentage of subjects achieving therapeutic glycaemic response (HbA1c <7%) and fasting and postprandial glucose values.

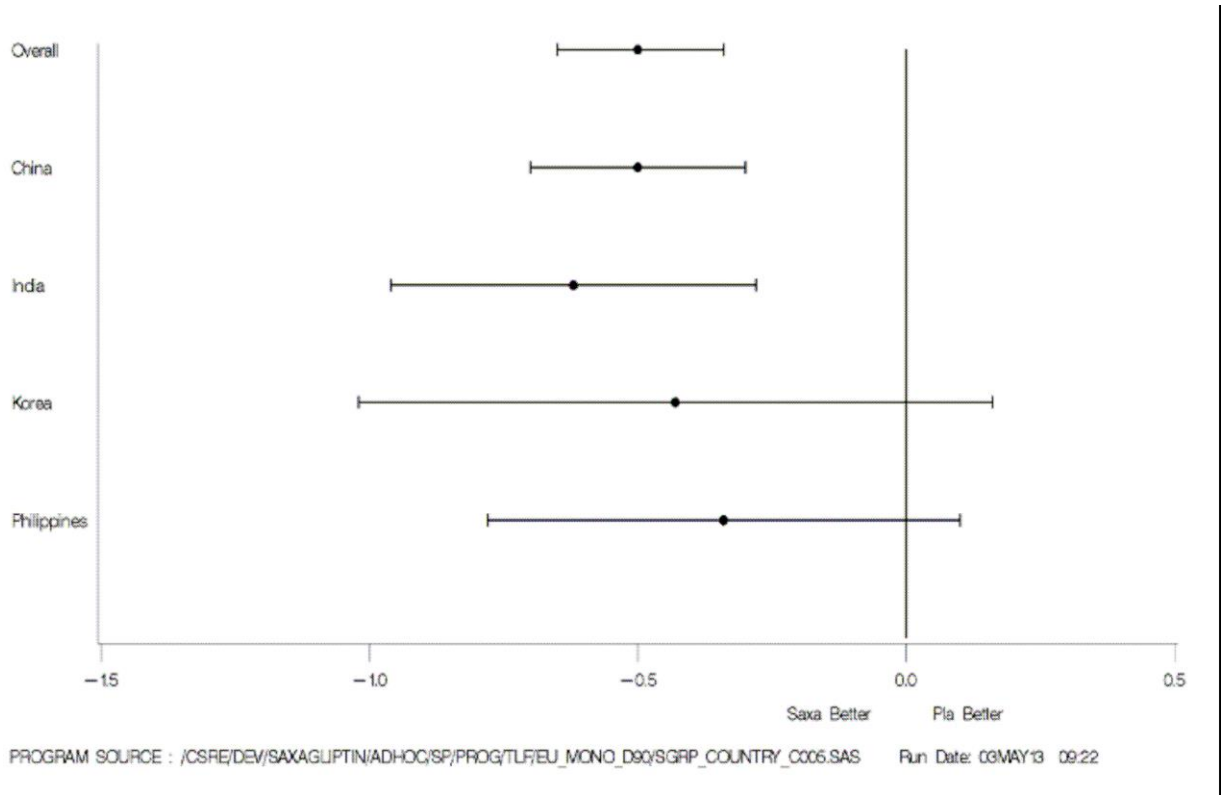
Analysis of Centre Effect

During the procedure, the CHMP had concerns with a possible centre effect: Considering the large number of sites and the small number of subjects enrolled at most sites a centre effect could not be excluded. Hence, an analysis of centre effects in D1680C00005 and D1680C00008 was requested during the procedure.

The applicant responded that the number of patients varied from centre to centre for studies D1680C00005 and D1680C00008. In both studies, a substantial proportion of centres had very few subjects randomised, which made the investigation of centre effects difficult since information had to be combined across centres.

Study D1680C00005 was conducted in China, India, Korea and the Philippines in a total of 39 centres. Thirteen of 39 centres had less than 10 subjects randomised per centre. Subgroup analyses were performed for changes from baseline to Week 24 in glycosylated haemoglobin (HbA1c) at the country level (ie, all centres combined within a country), and results are provided in Appendix 1 to the Statistical Report, included in the D1680C00005 Clinical Study Report (CSR), as well as in Table 1 and Figure 4, below. Treatment-by-country interactions were assessed by adding a treatment-by-country interaction term to the primary ANCOVA model in Study D1680C00005 (including terms for treatment and country, with baseline HbA1c as a covariate). The test for interaction of treatment-by-country had a p-value of 0.78, which showed no evidence of inconsistent treatment effects across countries.

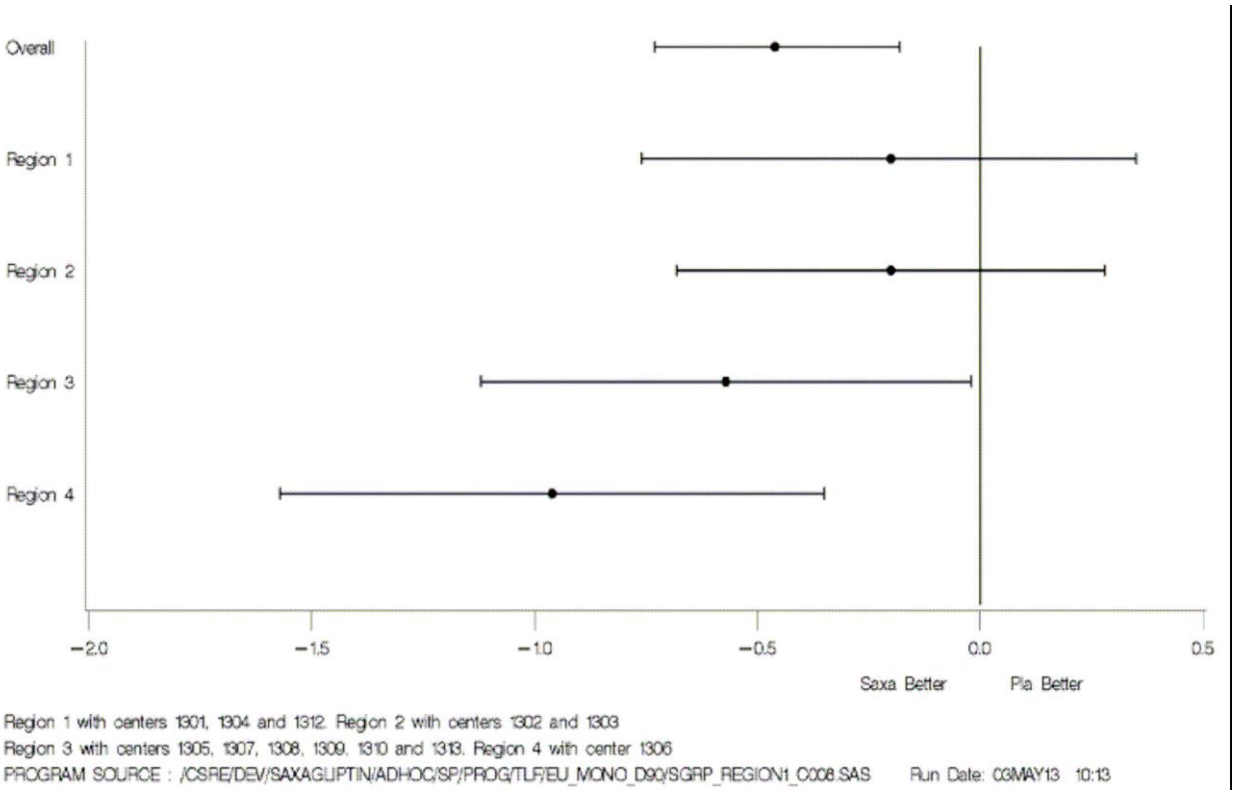
Figure 4. Study D1680C00005: Difference from placebo in HbA1c adjusted mean change from baseline at Week 24 (LOCF) by country, difference from control (5mg – placebo) with 95% CI



CI Confidence interval; HbA1c Glycosylated haemoglobin; LOCF Last observation carried forward; Saxa Saxagliptin

Study D1680C00008 was conducted only in India and comprised a total of 12 centres and 213 subjects randomised (211 subjects were included in the Full Analysis set, and 209 subjects were included in the analysis of HbA1c). Half of the centres had less than 10 subjects per centre. Subgroup analyses were performed for changes from baseline to Week 24 in HbA1c at the grouped region level. After considering the geographic location of each centre, all centres were grouped into 4 regions as follows: region 1 (Central States) consisted of centres 1301, 1304 and 1312; region 2 (Northern States) consisted of centres 1302 and 1303; region 3 (Southern States) consisted of centres 1305, 1307, 1308, 1309, 1310, and 1313; and region 4 (Centre 1306 in Bangalore) consisted of only centre 1306, since this centre had a sufficient number of randomised subjects (42 in total). The analysis of the primary endpoint was conducted with an ANCOVA model including terms for treatment, the grouped region, and treatment-by-grouped region interactions, with baseline HbA1c as a covariate. The test for interaction of treatment-by-grouped region had a p-value of 0.20. Overall, there were relatively consistent treatment effects across the 4 regions (see Figure 5).

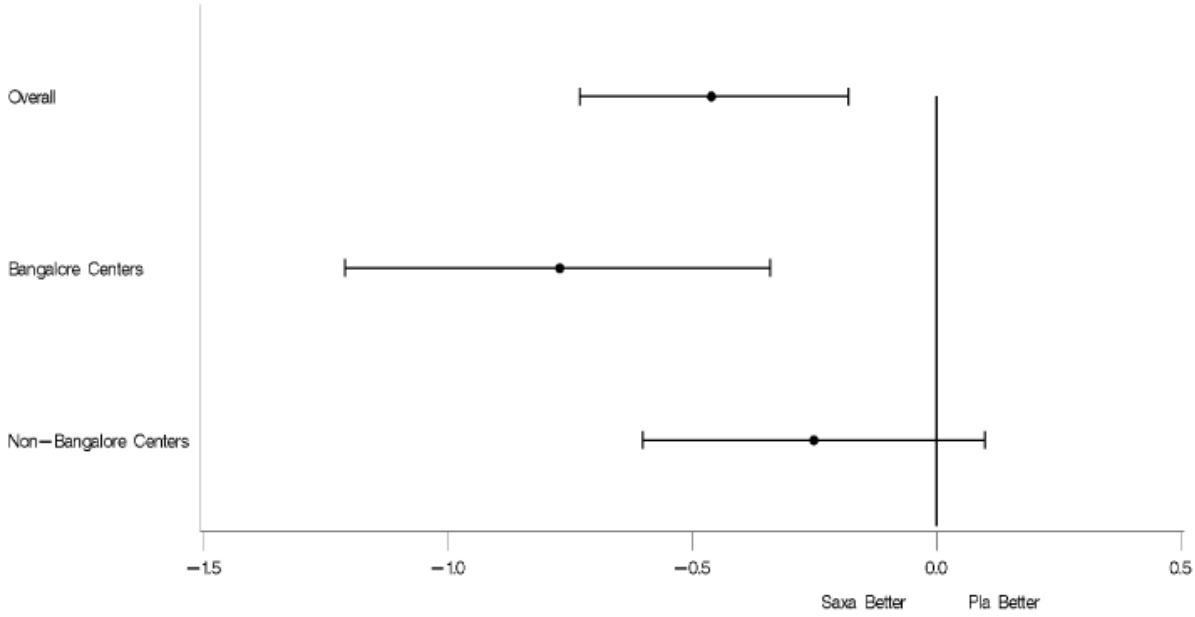
Figure 5. Study D1680C00008: Difference from placebo in HbA1c adjusted mean change from baseline at Week 24 (LOCF) by grouped region, difference from control (5 mg – placebo) with 95% CI



CI Confidence interval; HbA1c Glycosylated haemoglobin; LOCF Last observation carried forward; Saxa Saxagliptin

An exploratory analysis revealed a potential difference in effect among the Bangalore centres. Since 4 centres in Bangalore (1306, 1308, 1309, and 1313) contributed 85 randomised subjects to the total 213 randomised patients in the study, an alternative grouping strategy was performed to attempt to examine the effects of Bangalore centres vs. non-Bangalore centres. The same ANCOVA model as described above was fit substituting the 2-level region variable (Bangalore centres vs. other centres). The treatment-by-grouped interaction had a p-value of 0.07, but showed the same trend in favour of saxagliptin for both regions (Figure 6).

Figure 6. Study D1680C00008: Difference from placebo in HbA1c adjusted mean change from baseline at Week 24 (LOCF) by region (Bangalore centres vs non-Bangalore centres), difference from control (5mg – placebo) with 95% CI



CI: Confidence interval; HbA1c Glycosylated haemoglobin; LOCF Last observation carried forward; Saxa: Saxagliptin

In conclusion, saxagliptin demonstrated consistent treatment effects across regions, whether grouped by region or grouped by centre in both studies.

A third of the centres in study D1680C00005 had less than 10 subjects, and half the centres in study DC1680C00008, making it hard analysing centre effects without grouping them by region.

In study D1680C00005, the centres were grouped by country. The subsequent analysis did not reveal evidence of a treatment-by-country interaction effect. The point estimates for the different countries (ranging from -0.34 to -0.62, HbA1c change from baseline at week 24 difference between saxagliptin and placebo) were relatively close together, especially given the fact that even when grouped by country, the number of subjects is still rather low.

In study D1680C00008, the centres were grouped by region. The subsequent analysis did not reveal statistical evidence of a region-by-region interaction effect. However, the point estimates for the different regions (ranging from -0.20 to -0.96) were quite different. A subsequent exploratory analysis with an alternative grouping method, suggested a difference between Bangalore and non-Bangalore centres (-0.77 and -0.25, respectively). There was no statistically significant region-by-centre interaction. With so many centres involved, an outlier is not unexpected. As no differences were observed in study D1680C00005, it is considered a finding by chance. The CHMP considered therefore the issue as resolved

Summary of main studies

The following tables (Table 7, Table 8, Table 9, Table 10) summarise the efficacy results from the main studies 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 7 Summary of Efficacy for Study CV181011

Title: A multicentre, randomised, double-blind, placebo-controlled, Phase 3 trial to evaluate the efficacy and safety of saxagliptin (BMS-477118) as monotherapy in subjects with Type 2 Diabetes who have inadequate glycaemic control with diet and exercise					
Study identifier	Study code: CV181011 ClinicalTrials.gov identifier: NCT00121641				
Design	Multicentre, randomised, 4-arm, parallel group, double-blind, placebo-controlled; treatment naive subjects				
	Duration of main phase:	24 weeks			
	Duration of Run-in phase:	2 weeks			
	Duration of Extension phase:	182 weeks			
Hypothesis	Superiority after 24 weeks				
Treatment groups	Saxagliptin 2.5 mg	Saxagliptin 2.5 mg, 24 weeks, 102 randomised[a]			
	Saxagliptin 5 mg	Saxagliptin 5 mg, 24 weeks, 106 randomised[a]			
	Saxagliptin 10 mg	Saxagliptin 10 mg, 24 weeks, 98 randomised[a]			
	Placebo	Placebo, 24 weeks, 95 randomised[a]			
Endpoints and definitions	Primary endpoint	HbA1c	Adjusted mean change from baseline to Week 24		
	Secondary endpoint	FPG	Adjusted mean change from baseline to Week 24		
	Secondary endpoint	HbA1c <7.0%	Therapeutic glycaemic response, defined as the proportion of subjects achieving HbA1c <7.0% at Week 24		
	Secondary endpoint	PPG AUC	Adjusted mean change from baseline to Week 24 in AUC from 0 to 180 minutes for the PPG response to an OGTT		
Database lock	16 October 2006 (ST CSR) 04 April 2010 (ST + LT CSR)				
Results and Analysis					
Analysis description	**Primary Analysis (24-week ST phase)**				
Analysis population and time point description	Randomised subjects dataset, consisting of all randomised subjects who took at least one dose of double-blind study medication during the short-term (24 week) double-blind period				
Descriptive statistics and estimate variability	Treatment group	Saxagliptin 2.5 mg	Saxagliptin 5 mg	Saxagliptin 10 mg	Placebo
	Number of subjects (randomised subjects dataset)	102	106	98	95
	HbA1c (%) (adjusted mean change)	-0.43	-0.46	-0.54	0.19
	Standard error	0.10	0.10	0.10	0.10
	FPG (mg/dL) (adjusted mean change)	-14.53	-8.67	-16.75	6.06
	Standard error	3.82	3.74	3.89	4.00
	HbA1c <7.0% (percent)	35.0	37.9	41.1	23.9

	PPG AUC (mg•min/dL) (adjusted mean change)	-6868	-6896	-8084	-647
	Standard error	1167.7	1130.2	1176.2	1236.9
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Saxagliptin 2.5, 5, and 10 mg vs. Placebo		
		Mean difference from Placebo	-0.62, -0.64, -0.73		
		95% CI	(-0.90, -0.33), (-0.93, -0.36), (-1.02, -0.44)		
		P-value	<0.0001*, <0.0001*, <0.0001*		
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Saxagliptin 2.5, 5, and 10 mg vs. Placebo		
		Mean difference from Placebo	-20.60, -14.73, -22.81		
		95% CI	(-31.47, -9.72), (-25.50, -3.97), (-33.79, -11.84)		
		P-value	0.0002*, 0.0074*, <0.0001*		
	Secondary endpoint: HbA1c <7.0% (percent)	Comparison groups	Saxagliptin 2.5, 5, and 10 mg vs. Placebo		
		Difference from Placebo	11.1, 14.0, 17.1		
		95% CI	(-3.1, 24.9), (-0.1, 27.6), (2.8, 31.0)		
		P-value	0.1141, 0.0443*, 0.0133*		
	Secondary endpoint: PPG AUC (mg•min/dL)	Comparison groups	Saxagliptin 2.5, 5, and 10 mg vs. Placebo		
		Mean difference from Placebo	-6221, -6249, -7437		
		95% CI	(-9570, -2872), (-9546, -2952), (-10798, -4076)		
		P-value	0.0003[b], 0.0002*, <0.0001*		
Analysis description	**Secondary analysis (206-week ST + LT phase)[c]**				
Analysis population and time point description	Randomised subjects dataset, consisting of all randomised subjects who took at least one dose of double-blind study medication during the short-term (24 week) double-blind period. To be included in an analysis at any specific time point, the subject had to have a post-baseline measurement for the time point.				
Descriptive statistics and estimate variability	Treatment group	Saxagliptin 2.5 mg	Saxagliptin 5 mg	Saxagliptin 10 mg	Placebo
	Number of subjects (randomised subjects dataset)	102	106	98	95
	Rescue/ discontinuation (percent)[d]	85.9	79.2	88.4	90.8
	HbA1c (%) (adjusted mean change)	-0.29	-0.31	0.05	0.17
	Standard error	0.182	0.157	0.178	0.182
	FPG (mg/dL) (adjusted mean change)	-0.5	-0.8	6.9	1.6
	Standard error	6.98	5.88	6.64	6.88

	HbA1c <7.0% (percent)	22.0	27.2	24.2	20.7
	PPG AUC (mg•min/dL) (adjusted mean change)	-3469	-4417	1017	1590
	Standard error	1724.1	1548.2	1688.9	1722.2
Notes	Source: CV181011 ST CSR; CV181011 ST + LT CSR The evaluation period for the LT efficacy analyses included the ST + LT period; therefore, subjects who had an efficacy evaluation during the ST period contributed data for the analyses of both the ST and ST + LT periods of the study. The statistical analysis plan specified that the ANCOVA LOCF analysis was the primary presentation of the efficacy endpoints (e.g., HbA1c, FPG, and PPG AUC) and a repeated measures analysis was performed as a sensitivity analysis. This was the approach taken in the ST CSR. However, in light of the large and increasing amount of missing data over time in the LT extension period, the repeated measures analysis represented a more comprehensive approach to address the challenge of handling the missing data than the LOCF analysis. Hence, the repeated measures analysis was presented as the primary analysis of LT efficacy data in the ST + LT CSR (for HbA1c, FPG, and PPG AUC; LOCF was used for HbA1c <7.0%). Note: Since subjects in the control group were switched to metformin 500 mg at Week 24, no formal comparisons between treatment groups were planned for the long-term treatment period. [a] Subjects randomised and treated [b] The differences in mean reductions were nominally statistically significant for the saxagliptin 2.5 mg treatment group; however, the placement of this endpoint in the sequential testing procedure prohibited interpretation of statistical significance. [c] The final assessment of the efficacy endpoints HbA1c, FPG, and HbA1c <7% during the ST + LT phase occurred at Week 128. The final assessment of the efficacy endpoint PPG during the ST + LT phase occurred at Week 102. [d] Subjects discontinued due to lack of efficacy or rescued through Week 206 * Statistically significant at pre-specified level. For primary endpoint, between-group comparisons significant at α = 0.019, applying Dunnett's adjustment. All secondary endpoints were tested (sequentially) at the 0.05 significance level and only for groups where the primary endpoint showed statistical significance. AUC Area under the curve; CI Confidence interval; FPG Fasting plasma glucose; HbA1c Glycosylated haemoglobin; LT Long-term; NC Not calculated; OGTT Oral glucose tolerance test; PPG Postprandial glucose; ST Short-term;				

Table 8 Summary of Efficacy for Study CV181038

Title: A multicentre, randomised, double-blind, placebo-controlled, Phase 3 trial to evaluate the efficacy and safety of saxagliptin (BMS-477118) as monotherapy with titration in subjects with type 2 diabetes who have inadequate glycaemic control with diet and exercise		
Study identifier	Study code: CV181038 ClinicalTrials.gov identifier: NCT00316082	
Design	Multicentre, randomised, 5-arm, parallel-group, double-blind, placebo-controlled; treatment-naive subjects	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 2 weeks 52 weeks
Hypothesis	Superiority after 24 weeks	
Treatment groups	Saxagliptin 2.5 mg (QAM)	Saxagliptin 2.5 mg, QAM, 24 weeks, 74 randomised
	Saxagliptin 5 mg (QAM)	Saxagliptin 5 mg, QAM, 24 weeks, 74 randomised

	Saxagliptin 2.5/5 mg (QAM)		Saxagliptin titration from 2.5 to 5 mg, QAM, 24 weeks, 71 randomised
	Saxagliptin 5 mg (QPM)		Saxagliptin 5 mg, QPM, 24 weeks, 72 randomised
	Placebo		Placebo, QAM, 24 weeks, 74 randomised
Endpoints and definitions	Primary endpoint	HbA1c	Adjusted mean change from baseline to Week 24
	Secondary endpoint	FPG	Adjusted mean change from baseline to Week 24
	Secondary endpoint	HbA1c <7.0%	Therapeutic glycaemic response, defined as the proportion of subjects achieving HbA1c <7.0% at Week 24
	Secondary endpoint	PPG AUC	Adjusted mean change from baseline to Week 24 in AUC from 0 to 180 minutes for the PPG response to an OGTT
Database lock	17 January 2008 (ST CSR) 12 February 2009 (ST + LT CSR)		

Results and Analysis

Analysis description	**Primary Analysis (24-week ST phase)**				
Analysis population and time point description	Randomised subjects dataset, consisting of all randomised subjects who took at least one dose of double-blind study medication during the short-term (24 week) double-blind period				
Descriptive statistics and estimate variability	Treatment group	Saxagliptin 2.5 mg (QAM)	Saxagliptin 5 mg (QAM)	Saxagliptin 2.5/5 mg (QAM)	Saxagliptin 5 mg (QPM)[a]	Placebo
	Number of subjects (randomised subjects dataset)	74	74	71	72	74
	HbA1c (%) (adjusted mean change)	-0.71	-0.66	-0.63	-0.61	-0.26
	Standard error	(0.10)	(0.10)	(0.10)	(0.10)	(0.10)
	FPG (mg/dL) (adjusted mean change)	-11.4	-10.7	-12.5	-7.9	3.3
	Standard error	4.50	4.46	4.48	4.46	4.46
	HbA1c <7.0% (percent)	35.8	44.9	43.5	38.6	35.3
	PPG AUC (mg•min/dL) (adjusted mean change)	-8014	-8218	-7781	-6048	-3088
	Standard error	1246.9	1249.1	1261.0	1318.2	1259.7

Effect estimate per comparison	Primary endpoint: HbA1c (%)[a]	Comparison groups	Saxagliptin 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs. Placebo
		Mean difference from Placebo	-0.45, -0.40, -0.37, -0.35
		95% CI	(0.74, -0.16), (-0.69, -0.12), (-0.65, -0.08), (-0.63, -0.07)
		P-value	0.0023*, 0.0059*, 0.0119*, 0.0157*
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Saxagliptin 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs. Placebo
		Mean difference from Placebo	-14.7, -14.0, -15.8, -11.2

		95% CI	(-27.2, -2.3), (-26.4, -1.6), (-28.3, -3.4), (-23.6, 1.2)
		P-value	0.0204*, 0.0271*, 0.0130*, 0.0759
	Secondary endpoint: HbA1c <7.0% (percent)	Comparison groups	Saxagliptin 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs. Placebo
		Difference from Placebo	0.5, 9.6, 8.2, 3.3
		95% CI	(-15.9, 16.7), (-7.1, 25.8), (-8.5, 24.3), (-12.9%, 19.5)
		P-value	1.0000, 0.2968, 0.3832, 0.7267
	Secondary endpoint: PPG AUC (mg•min/dL)	Comparison groups	Saxagliptin 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs. Placebo
		Mean difference from Placebo	-4927, -5130, -4694, -2961
		95% CI	(-8416, -1437), (-8630,-1630), (-8210, -1178), (-6550, 629)
		P-value	0.0059[b], 0.0043 [b], 0.0091 [b], 0.1055

Analysis description	**Secondary analysis (76-week ST + LT phase)**					
Analysis population and time point description	Randomised subjects dataset, consisting of all randomised subjects who took at least one dose of double-blind study medication during the short-term (24 week) double-blind period					
Descriptive statistics and estimate variability	Treatment group	Saxagliptin 2.5 mg (QAM)	Saxagliptin 5 mg (QAM)	Saxagliptin 2.5/5 mg (QAM)	Saxagliptin 5 mg (QPM)	Placebo
	Number of subjects (randomised subjects dataset)	74	74	71	72	74
	Rescue/ discontinuation (percent)	43.9	39.8	40.1	45.0	44.8
	HbA1c (%) (adjusted mean change)	-0.84	-0.41	-0.60	-0.34	-0.29
	Standard error	0.122	0.108	0.118	0.117	0.114
	FPG (mg/dL) (adjusted mean change)	-11.9	-1.4	-14.5	1.0	0.1
	Standard error	5.03	4.43	4.89	4.77	4.61
	HbA1c <7.0% (percent)	40.3	31.9	43.5	31.4	33.8
	PPG AUC (mg•min/dL) (adjusted mean change)	-5859	-4163	-8511	-4700	-3788
	Standard error	1498.3	1429.2	1571.7	1547.4	1465.6
Notes	Source: CV181038 ST CSR; CV181038 ST + LT CSR The evaluation period for the LT efficacy analyses included the ST + LT period; therefore, subjects who had an efficacy evaluation during the ST period contributed data for the analyses of both the ST and ST + LT periods of the study. The statistical analysis plan specified that the ANCOVA LOCF analysis was the primary presentation of the efficacy endpoints (e.g., HbA1c, FPG, and PPG AUC) and a repeated measures analysis was performed as a sensitivity analysis. This was the approach taken in the ST CSR. However, in light of the large and increasing amount of missing data over time in the LT extension period, the					

	repeated measures analysis represented a more comprehensive approach to address the challenge of handling the missing data than the LOCF analysis. Hence, the repeated measures analysis was presented as the primary analysis of LT efficacy data in the ST + LT CSR (for HbA1c, FPG, and PPG AUC; LOCF was used for HbA1c <7.0%). Note: The efficacy results between the ST and LT periods of CV181038 cannot be compared directly because during the LT period, the saxagliptin dose could be titrated upward to a maximum of 10 mg; thus, approximately 70% of the subjects did not remain on the same dose of saxagliptin throughout the ST + LT periods. Additionally, all subjects who received placebo during the ST period received metformin during the LT period; thus, any comparisons for the saxagliptin doses during the LT period would be versus active controls (metformin) rather than placebo controls. [a] All Saxagliptin 5 mg QPM group results were a secondary efficacy endpoint. [b] The differences in mean reductions were nominally statistically significant for all saxagliptin QAM treatment groups; however, the placement of this endpoint in the sequential testing procedure prohibited interpretation of statistical significance. [c] Since subjects in the placebo group were switched to metformin at Week 24, no formal comparisons between treatment groups were planned for the LT treatment period. [d] Subjects discontinued due to lack of efficacy or rescued through Week 76 * Statistically significant at pre-specified level. For the primary endpoint, comparisons were performed in a 2-step sequential testing procedure. For Saxagliptin 2.5 mg QAM and 5 mg QAM, comparisons vs. placebo were significant at $\alpha = 0.027$, applying Dunnett's adjustment. For Saxagliptin 2.5/5 mg QAM, significance test was performed at the 0.027 level if 2.5 mg QAM or 5 mg QAM showed statistical significance and at 0.05 if both 2.5 mg QAM and 5 mg QAM groups showed statistical significance. All secondary endpoints were tested (sequentially) at the 0.05 significance level and only for groups where the primary endpoint showed statistical significance. AUC Area under the curve; CI Confidence interval; FPG Fasting plasma glucose; HbA1c Glycosylated haemoglobin; LT Long-term; NC Not calculated; OGTT Oral glucose tolerance test; PPG Postprandial glucose; ST Short-term;

Table 9 Summary of Efficacy for Study D1680C00005

Title: A 24-Week international, multicentre, randomised, parallel-group, double-blind, placebo-controlled, Phase III study to evaluate the efficacy and safety of saxagliptin in adult patients with Type 2 Diabetes who have inadequate glycaemic control with diet and exercise			
Study identifier	Study code: D1680C00005 ClinicalTrials.gov identifier: NCT00698932		
Design	International, multicentre, randomised, parallel group, double-blind, placebo-controlled; treatment-naive subjects		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 4 weeks NA	
Hypothesis	Superiority after 24 weeks		
Treatment groups	Saxagliptin 5 mg		Saxagliptin 5 mg, 24 weeks, 284 randomised
	Placebo		Placebo, 24 weeks, 284 randomised
Endpoints and definitions	Primary endpoint	HbA1c	Adjusted mean change from baseline to Week 24
	Secondary endpoint	FPG	Adjusted mean change from baseline to Week 24
	Secondary endpoint	PPG AUC	Adjusted mean change from baseline to Week 24 in AUC from 0 to 180 minutes for the PPG response to an MMTT

	Secondary endpoint	HbA1c <7.0%	Therapeutic glycaemic response, defined as the proportion of subjects achieving HbA1c <7.0% at Week 24
Database lock	05 November 2009		

Results and Analysis

Analysis description	**Primary Analysis (24-weeks)**		
Analysis population and time point description	Full analysis set, consisting of all subjects who took at least 1 dose of study medication and had both baseline and post-baseline efficacy data during the 24-week double blind treatment period.		
Descriptive statistics and estimate variability	Treatment group	Saxagliptin 5 mg	Placebo
	Number of subjects (full analysis set)	280	280
	HbA1c (%) (adjusted mean change)	-0.84	-0.34
	Standard error	0.067	0.065
	FPG (mg/dL) (adjusted mean change)	-16.13	-3.01
	Standard error	2.586	2.544
	PPG AUC (mg•min/dL) (adjusted mean change)	-7534	-4255
	Standard error	657.4	726.4
	HbA1c <7.0% (percent)	45.8	28.8

Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Saxagliptin 5 mg vs. Placebo
		Mean difference from Placebo	-0.50
		95% CI	(-0.65, -0.34)
		P-value	<0.0001*
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Saxagliptin 5 mg vs. Placebo
		Mean difference from Placebo	-13.12
		95% CI	(-19.12, -7.13)
		P-value	<0.0001*
	Secondary endpoint: PPG AUC (mg•min/dL)	Comparison groups	Saxagliptin 5 mg vs. Placebo
		Difference from Placebo	-3280
		95% CI	(-5214, -1345)
		P-value	0.0010*
	Secondary endpoint: HbA1c <7.0% (percent)	Comparison groups	Saxagliptin 5 mg vs. Placebo
		Mean difference from Placebo	17.0
		95% CI	(8.9, 24.9)
		P-value	<0.0001*
Notes	Source: D1680C00005 CSR The statistical analysis plan specified that the ANCOVA LOCF analysis was the primary presentation of the efficacy endpoints (e.g., HbA1c, FPG, and PPG AUC) and a repeated measures analysis was performed to assess the robustness of the primary efficacy analysis. * Between group comparison significant after controlling overall alpha of the study. All secondary endpoints were tested (sequentially) at the 0.05 significance level. AUC Area under the curve; CI Confidence interval; FPG Fasting plasma glucose; HbA1c Glycosylated haemoglobin; MMTT Mixed meal tolerance test; NC Not calculated; PPG Postprandial glucose;		

Table 10 Summary of Efficacy for Study D1680C00008

Title: A 24-Week, multicentre, randomised, parallel-group, double-blind, placebo-controlled, Phase IIIb study in India to evaluate the efficacy and safety of saxagliptin in adult patients with Type 2 Diabetes who have inadequate glycaemic control with diet and exercise				
Study identifier	Study code: D1680C00008 ClinicalTrials.gov identifier: NCT00918879			
Design	Multicentre, randomised, parallel group, double-blind, placebo-controlled; treatment-naive subjects			
	Duration of main phase:	24 weeks		
	Duration of Run-in phase:	4 weeks		
	Duration of Extension phase:	NA		
Hypothesis	Superiority after 24 weeks			
Treatment groups	5 mg		Saxagliptin 5 mg, 24 weeks, 107 randomised	
	Placebo		Placebo, 24 weeks, 106 randomised	
Endpoints and definitions	Primary endpoint	HbA1c	Adjusted mean change from baseline to Week 24	
	Secondary endpoint	FPG	Adjusted mean change from baseline to Week 24	
	Secondary endpoint	HbA1c <7.0%	Therapeutic glycaemic response, defined as the proportion of subjects achieving HbA1c <7.0% at Week 24	
Database lock	20 August 2010			
Results and Analysis				
Analysis description	**Primary Analysis (24-weeks)**			
Analysis population and time point description	Full analysis set, consisting of all subjects who took at least 1 dose of study medication and had both baseline and post-baseline efficacy data during the 24-week double blind treatment period.			
Descriptive statistics and estimate variability	Treatment group		Saxagliptin 5 mg	Placebo
	Number of subjects (full analysis set)[a]		106	105
	HbA1c (%) (adjusted mean change)		-0.51	-0.05
	Standard error		0.098	0.098
	FPG (mg/dL) (adjusted mean change)		-10.35	-0.16
	Standard error		3.827	3.863
	HbA1c <7.0% (percent)		22.1	13.3
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Saxagliptin 5 mg vs. Placebo	
		Mean difference from Placebo	-0.46	
		95% CI	(-0.73, -0.18)	
		P-value	0.0011*	
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Saxagliptin 5 mg vs. Placebo	
		Difference from Placebo	-10.19	
		95% CI	(-20.91, 0.53)	
		P-value	0.0623	
	Secondary endpoint: HbA1c <7.0% (percent)	Comparison groups	Saxagliptin 5 mg vs. Placebo	
		Mean difference from Placebo	8.8	
		95% CI	(-1.7, 19.3)	
		P-value	0.1059	

Notes	Source: D1680C00008 CSR The statistical analysis plan specified that the ANCOVA LOCF analysis was the primary presentation of the efficacy endpoints (e.g., HbA1c, FPG, and PPG AUC) and a repeated measures analysis was performed to assess the robustness of the primary efficacy analysis. * Statistically significant at pre-specified level. All secondary endpoints were tested (sequentially) at the 0.05 significance level. AUC Area under the curve; CI Confidence interval; FPG Fasting plasma glucose; HbA1c Glycosylated haemoglobin;

Supportive studies

One Phase 2b study and 4 Phase 3 additional studies contribute to this evaluation of saxagliptin as a monotherapy. All of these studies have been previously submitted to the EU. All dosing in these studies was QD, unless otherwise noted. Two of these studies (CV181008 and CV181039) included at least 1 saxagliptin monotherapy treatment group and were included in the original MAA.

Study CV181008

Study CV181008 was a 12-week placebo-controlled Phase 2b dose-finding study of saxagliptin monotherapy similar to the Phase 3 studies and provides information on both saxagliptin 5 mg and 2.5 mg doses. Study CV181008 was designed to evaluate the safety and efficacy of saxagliptin monotherapy in treatment-naïve subjects with T2DM who had inadequate glycaemic control. Subjects were randomized to receive 1 of 5 doses of saxagliptin (2.5, 5, 10, 20, or 40 mg) or placebo once daily for 12 weeks. An additional 85 subjects were randomized to receive saxagliptin 100 mg or placebo once daily for 6 weeks. Results from the cohort of subjects receiving 100 mg are not included in this assessment report. The Phase 2b study CV181008 is included in this submission to provide supportive efficacy data for the change from baseline in HbA1c at Week 12. In the 0-40 mg cohort, mean exposure (SD) was 80 days (20.1) for placebo and 81 (16.4), 77 (20.1), 80 (17.8), 77 (17.9), and 81 (16.6) days for saxagliptin 2.5, 5, 10, 20, and 40 mg, 2.7.3 respectively. In the 0/100 mg cohort, mean (SD) exposure was 37 (11.4) days for placebo and 42 (2.6) days for saxagliptin 100 mg. The adjusted mean change from baseline to Week 12 in HbA1c (LOCF) was statistically significantly larger in each saxagliptin group (-0.72%, -0.90%, -0.81%, -0.74%, and -0.80% for the saxagliptin 2.5, 5, 10, 20, and 40 mg groups, respectively) compared with the placebo group (-0.27%). For the saxagliptin 100 mg group, the adjusted mean change from baseline to Week 6 in HbA1c (LOCF) was statistically significantly larger (-1.09%) compared to placebo (-0.36%).

Study CV181039

Study CV181039 was designed to investigate saxagliptin as an initial combination therapy with metformin, but included a saxagliptin 10 mg monotherapy group as well as a metformin monotherapy group. This allowed for a post-hoc comparison between saxagliptin monotherapy and metformin monotherapy in treatment-naïve subjects. There was no placebo monotherapy control and saxagliptin monotherapy was at a higher dose (10 mg) than currently proposed for use (5 mg). Clinically meaningful within group changes from baseline in HbA1c [95% CI] were observed for both the saxagliptin 10 mg monotherapy group (-1.69% [-1.82, -1.55]) and the metformin monotherapy group (-1.99% [-2.12, -1.85]) after 24 weeks. A post-hoc analysis indicated that 10 mg monotherapy was inferior (nominal p-value = 0.0022) to the metformin monotherapy, with a mean (95% CI) difference in change from baseline in HbA1c of 0.30% (0.11, 0.49). The adjusted mean changes in HbA1c achieved in the saxagliptin/metformin combination groups of this study were similar (-2.49% for saxagliptin 10 mg + metformin and -2.53% for saxagliptin 5 mg + metformin).

Study D1680C00007

Study D1680C00007 provides perspective on how saxagliptin acts in an important subpopulation of the restricted indication proposed for saxagliptin monotherapy, i.e. in subjects for whom metformin is contraindicated because of renal impairment. Study D1680C00007 was included in a Type 2 Variation and supported the use of saxagliptin 2.5 mg in patients with moderate or severe renal impairment. Although subjects were randomized to saxagliptin and placebo treatment groups, subjects were allowed to take concurrent anti-diabetic medicines (98.2% did so at some point in the study), so this was not a monotherapy study. In this study, the primary analysis demonstrated the superior efficacy of saxagliptin 2.5 mg QD over placebo. There was a reduction in adjusted mean HbA1c from baseline in both treatment groups at week 12 (LOCF). The adjusted mean (SE) change from baseline was -0.86% (0.112%) for the saxagliptin group and -0.44% (0.109%) for the placebo group. The change from baseline was statistically significantly greater for saxagliptin than for placebo, with a mean treatment difference (95% CI) of -0.42% (-0.71% to -0.12).

Two other supportive studies (D1680C00001 and D1680C00002) were conducted with saxagliptin as an add-on to metformin (in patients who had inadequate glycaemic control on metformin therapy alone) and did not include treatment with saxagliptin monotherapy. However, they provide perspective on how saxagliptin compares to other alternatives for the restricted indication proposed for saxagliptin monotherapy. Study D1680C00001 compared saxagliptin with an SU (glipizide, QD or BID), both in combination with metformin, and supported an indication for saxagliptin as add-on therapy to metformin. Study D1680C00002 compared saxagliptin with another DPP4 inhibitor (sitagliptin, which is approved in the EU as a monotherapy) as an add-on to metformin. Final clinical study reports (CSRs) for these studies have been previously submitted to the EU.

Study D1680C00001

Study D1680C00001 compared saxagliptin with glipizide (an SU) in the setting of add-on therapy with metformin. The primary efficacy analysis was to establish the non-inferiority of saxagliptin + metformin compared with glipizide + metformin in the change in HbA1c from baseline to Week 52, in patients who had inadequate glycaemic control on metformin therapy alone. Both treatments resulted in a reduction from baseline in HbA1c (adjusted mean change from baseline -0.74% for saxagliptin + metformin and -0.80% for glipizide + metformin). The benefits of saxagliptin compared to an SU may be relevant to a monotherapy setting, particularly regarding a lower risk of hypoglycaemia and no weight gain, as these are known concerns for SUs both as monotherapy and as combination therapy.

Study D1680C00002

Study D1680C00002 compared saxagliptin to another DPP4 inhibitor, sitagliptin, in the setting of add-on therapy to metformin, in patients who had inadequate glycaemic control on metformin therapy alone. Both treatments resulted in a reduction from baseline in HbA1c (adjusted mean change from baseline -0.52% for saxagliptin + metformin and -0.62% for sitagliptin + metformin). Because they are in the same pharmacologic class, the similar efficacy of saxagliptin 5 mg compared with sitagliptin 100 mg in the add-on to metformin setting may also be relevant in the monotherapy setting (for which sitagliptin is approved in the EU).

CHMP's comments:

The additional studies have been assessed before. They are of limited support as most of these studies do not investigate monotherapy with saxagliptin. The only additional study that investigates saxagliptin monotherapy is study CV181008. This was a monotherapy dose-finding study, but treatment duration

was only 12-weeks. The other additional studies combine saxagliptin with metformin and/or other oral anti-hyperglycaemic drugs. As a comparator, placebo, SU or sitagliptin were used.

In study CV181039, a post-hoc comparison between saxagliptin monotherapy and metformin monotherapy in treatment-naïve subjects was performed. Saxagliptin was used in a higher dose (10 mg) than the dose that has been approved (5 mg). Saxagliptin 10 mg monotherapy was inferior (nominal p-value = 0.0022) to the metformin monotherapy, with a mean (95% CI) difference in change from baseline in HbA1c of 0.30% (0.11, 0.49).

2.2.4. Discussion on Clinical Efficacy

The focus of this submission was on 4 Phase 3 monotherapy studies (CV181011, CV181038, D1680C00005, and D1680C00008), which comprise all of the Phase 3 controlled studies of saxagliptin as a monotherapy.

Study CV181011 and Study CV181038 were already assessed in the original saxagliptin registration dossier. Study D1680C00005 and study D1680C00008 are new monotherapy studies performed in Asians. BMI was considerably lower in the studies in Asians (25.9 and 26.8 kg/m2) as compared to the studies in White individuals (31.7 and 30.5 kg/m2). Results in Asians may have therefore been different from results in White populations.

The applicant has not given further reasons for not including the 2.5 mg in the new monotherapy studies. Considering the lack of difference in clinical efficacy and safety seen for saxagliptin 2.5 mg and 5 mg seen in the previous assessed monotherapy studies, it was considered unfortunate, but acceptable, not having included a 2.5 mg treatment group in the new monotherapy studies.

Considering the large number of sites and the small number of subjects enrolled at most sites a centre effect could not be excluded. Hence, an analysis of centre effects in D1680C00005 and D1680C00008 was requested and provided by the applicant. In study D1680C00005, the centres were grouped by country and did not reveal evidence of a treatment-by-country interaction effect. The point estimates for the different countries (ranging from -0.34 to -0.62, HbA1c change from baseline at week 24 difference between saxagliptin and placebo) were relatively close together, especially given the fact that even when grouped by country, the number of subjects is still rather low. In study D1680C00008, the centres were grouped by region. The subsequent analysis did not reveal statistical evidence of a region-by-region interaction effect. However, the point estimates for the different regions (ranging from -0.20 to -0.96) were quite different. However, as there was no statistically significant region-by-centre interaction and with so many centres involved, an outlier not unexpected, this was considered a finding by chance.

During the procedure, the CHMP requested supplementary information how the data was pooled and whether raw or pre-processed data have been pooled. The applicant provided details about the pooling and confirmed that pre-processed data have been pooled in all cases. The pooled studies were designed generally in the same way, including the same type of patients, and using the same control treatment, and endpoints. Thus the pre-processing likely also had yielded the same results, and this was found to be satisfactory by CHMP.

The results of the pooled analysis should be interpreted as a summary of the data from the individual studies and be used as supportive evidence. The proof of efficacy was concluded from the individual studies.

The changes in HbA1c were accompanied by changes in the percentage of subjects achieving therapeutic glycaemic response (HbA1c <7%) and fasting and postprandial glucose values.

The additional studies included in the dossier have been assessed during the initial assessment, but are of limited support as most of these studies did not investigate monotherapy with saxagliptin and are therefore of minor relevance compared with the 4 main studies submitted.

In all studies, saxagliptin monotherapy was associated with a modest, but significant effect on HbA1c that could be clinically relevant. For the pooled analyses, the treatment effect was –0.51% (-0.62%, -0.39%). There were differences between the races; the adjusted mean change from baseline in HbA1c (95% CI) difference from placebo was –0.40% (-0.63, -0.16) for Whites (n=138) and –0.51% (-0.64, -0.38) for Asians (n=402). Non-inferiority compared to metformin has not been demonstrated, but effects on HbA1C appear comparable with that of glipizide and sitagliptin in an add-on design with metformin.

2.2.4.1. Conclusions on the clinical efficacy

This submission did seek approval for the use of saxagliptin as monotherapy when metformin is inappropriate due to contraindications or intolerance. Contraindications may include cardiac and/or renal failure. Intolerance is usually due to gastrointestinal side effects. All four studies were performed in individuals without any contraindication or intolerance for metformin. Although results in these individuals may not be fully applicable to the intended population, there appears no reason to believe that this would influence efficacy, however. Saxagliptin was superior to placebo in lowering HbA1c with a modest, but still statistically significant and clinically relevant effect.

2.3. Clinical Safety aspects

2.3.1.1. Introduction

This submission included newly submitted saxagliptin monotherapy safety data from 2 studies (D1680C00005 and D1680C00008), all at 5 mg. Compared with the saxagliptin monotherapy ST (24-week period) data summarized in the original MAA, this increases the ST exposure to saxagliptin monotherapy at 5 mg by an additional 391 subjects, to 643 subjects. This submission does not include new long-term safety data. As of July 2012, the overall safety experience with saxagliptin (monotherapy and combination studies) included over 16,800 subjects. The overall safety profile of saxagliptin is described in the Investigator's Brochure for saxagliptin and is reflected in the saxagliptin Summary of Product Characteristics (SmPC).

The focus of the description of the safety profile of saxagliptin monotherapy in this Clinical Overview and submission is on pooled ST (24-week, randomized, placebo-control double blind) period data from the 4 Phase 3 monotherapy studies (CV181011, CV181038, D1680C00005, and D1680C00008). These studies had similar study designs and study populations (including anti-diabetic treatment naïve subjects and baseline HbA1c) and were pooled to provide a more robust understanding of the safety and tolerability of saxagliptin 5 mg as monotherapy. Only data collected prior to initiation of rescue therapy were included in the safety analyses, to avoid the potential confounding effects of concomitant rescue therapy.

Although all 4 Phase 3 monotherapy studies had placebo and saxagliptin 5 mg treatment groups in common, they differed in regard to other saxagliptin treatment groups. The pooling strategy for the safety analyses was to provide both an inclusive and conservative summary.

Thus, the 2.5/5 mg titration group in Study CV181038 was pooled with the 2.5 mg treatment groups in this study and Study CV181011, and the 5 mg QPM (evening) treatment group of Study CV181038 was pooled with 5 mg morning treatment group in this and the other studies. Study CV181011 also included saxagliptin 10 mg treatment groups (double blind and open-label), but this dose was not included in any

of the other of the Phase 3 monotherapy studies and thus not included in the pooling. The approach to the pooling of safety data for saxagliptin monotherapy studies in this submission is similar to that used in the original saxagliptin MAA.

2.3.2. Methods – analysis of data submitted

Patient exposure

In the 4 Phase 3 monotherapy pooled safety data, a total of 890 subjects were exposed to saxagliptin (247 at 2.5 mg, 643 at 5 mg) and 559 to placebo. This increases the short-term (24-week) exposure to saxagliptin monotherapy by an additional 391 subjects (from Studies D1680C00005 and D1680C00008) compared with the original MAA saxagliptin monotherapy ST pooled exposure to 2.5 mg and 5 mg of 499 (from Studies CV181011 and CV181038).The exposure to study treatment during the 24-week ST treatment period was calculated regardless of interruptions in treatment and excluding days on or after rescue medication, consistent with the presentation of efficacy data in this submission. The mean duration of exposure was similar (20 to 21 weeks) in the 2.5 mg (143.96 days), 5 mg (152.68 days), and placebo (146.48 days) groups. The majority of subjects were exposed to treatment (prior to rescue) for .166 days (i.e., essentially the duration of the 168-day, or 24-week ST period), 70.4% in the saxagliptin 2.5 mg group, 77.6% in the saxagliptin 5 mg group, and 71.9% in the placebo group.

Demographic characteristics were generally balanced between the saxagliptin 5 mg and placebo treatment groups in the pooled monotherapy safety population (Table 11). Racial imbalances across treatment groups (the proportion of Asian patients was much higher in the 2.7.4 Summary of 5 mg group while the proportion of White subjects was higher in the 2.5 mg group), along with differences with respect to body weight and body mass index (BMI), resulted from the fact that Studies D1680C00005 and D1680C00008 were conducted exclusively in Asia and included only the 5 mg dose.

Table 11 Selected demographic and baseline disease characteristics (Pooled monotherapy safety population)

	Saxa 2.5 mg (N=247)	Saxa 5 mg (N=643)	All Saxa (N=890)	Placebo (N=559)
Mean age (yr) (SD)	54.15 (10.42)	52.14 (10.29)	52.70 (10.36)	51.88 (10.77)
Age category, n (%):				
<65 yr	208 (84.2)	576 (89.6)	784 (88.1)	490 (87.7)
≥65 yr	39 (15.8)	67 (10.4)	106 (11.9)	69 (12.3)
≥75 yr	4 (1.6)	8 (1.2)	12 (1.3)	6 (1.1)
Gender, n (%):				
Female	127 (51.4)	301 (46.8)	428 (48.1)	259 (46.3)
Male	120 (48.6)	342 (53.2)	462 (51.9)	300 (53.7)
Race, n (%):				
Asian	37 (15.0)	431 (67.0)	468 (52.6)	410 (73.3)
Black/African American	12 (4.9)	18 (2.8)	30 (3.4)	10 (1.8)
Other	5 (2.0)	4 (0.6)	9 (1.0)	7 (1.3)
White	193 (78.1)	190 (29.5)	383 (43.0)	132 (23.6)
Mean weight (kg) (SD)	87.69 (17.90)	76.20 (17.54)	79.39 (18.37)	74.65 (15.47)
Mean BMI (kg/m^2) (SD)	31.07 (4.83)	28.07 (4.93)	28.90 (5.08)	27.67 (4.60)
BMI category, n (%):				
<30 kg/m^2	105 (42.5)	446 (69.4)	551 (61.9)	400 (71.6)
≥30 kg/m^2	142 (57.5)	197 (30.6)	339 (38.1)	159 (28.4)
Mean duration of T2DM (yr) (SD)	2.2 (3.0)	1.3 (2.6)	1.6 (2.8)	1.4 (2.5)
Mean HbA1c (%) (SD)	8.0 (1.0)	8.1 (0.9)	8.1 (0.9)	8.1 (0.9)
Mean FPG (mg/dL) (SD)	169.9 (43.2)	162.8 (39.4)	164.8 (40.6)	162.0 (43.9)

A relatively large number of patients has been treated with saxagliptin monotherapy. However, the majority of these patients is Asian.

2.3.3. Results

Adverse events

The pooled safety data from the 4 Phase 3 monotherapy studies demonstrate that the overall incidence of AEs for saxagliptin 5 mg (53.0%) was numerically higher than placebo (45.3%). The AEs with the highest incidence in the saxagliptin 5 mg group were Upper Respiratory Tract Infection (6.1% vs. 7.3% for placebo), Urinary Tract Infection (4.2% vs. 4.7%, respectively), and Nasopharyngitis (3.9% vs. 3.0%, respectively). The only AE (excluding Hypoglycaemia, see section on AEs of special interest) with an incidence in the saxagliptin 5 mg group ≥2% and ≥1 percentage point higher than the incidence in the placebo group was Arthralgia (2.6% vs. 1.3%).

The incidences of AEs of special interest are presented in Table 12.

Table 12 Incidence of any AE of special interest, by area of interest (Pooled monotherapy safety analysis set)

	Number (%) of subjects with an AE			
Area of interest[a]	Saxa 2.5 mg (N=247)	Saxa 5 mg (N=643)	All Saxa (N=890)	Placebo (N=559)
Hypoglycemia	10 (4.0)	19 (3.0)	29 (3.3)	9 (1.6)
Infections and infestations	75 (30.4)	142 (22.1)	217 (24.4)	101 (18.1)
Opportunistic infections	0	1 (0.2)	1 (0.1)	0
GI disorders	45 (18.2)	80 (12.4)	125 (14.0)	45 (8.1)
CV events	2 (0.8)	5 (0.8)	7 (0.8)	1 (0.2)
Hypersensitivity reactions	7 (2.8)	11 (1.7)	18 (2.0)	3 (0.5)
Lymphopenia	2 (0.8)	5 (0.8)	7 (0.8)	3 (0.5)
Thrombocytopenia	2 (0.8)	1 (0.2)	3 (0.3)	1 (0.2)
Pancreatitis	0	0	0	0
Skin disorders	1 (0.4)	2 (0.3)	3 (0.3)	0
Bone fracture	2 (0.8)	1 (0.2)	3 (0.3)	0

The overall incidence of AEs for saxagliptin 5 mg (53.0%) was numerically higher than placebo (45.3%). The incidences of serious AEs (SAEs) and of AEs leading to discontinuation of study treatment (DAEs) were also higher for saxagliptin 5 mg compared to placebo (SAE incidence 2.8% vs. 1.6%, respectively; DAE incidence 1.1% vs. 0.5%, respectively).

The incidence of gastrointestinal side effects was higher with saxagliptin compared to placebo.

Serious adverse events/deaths

Across the 4 Phase 3 monotherapy studies 4 deaths were reported, all of which were considered by the Investigator to be unrelated to Investigational Product. Subject narratives for these 4 deaths are provided in the individual CSRs. Note that only the 2 deaths that occurred during ST treatment are included in the pooled monotherapy safety analysis set (see Table 13).

Deaths during ST treatment:

- In Study CV181038, a 47-year-old male in the saxagliptin 2.5/5 mg QAM group (2.5 mg group in the pooled monotherapy safety analysis set) died on Day 54 as a result of pneumococcal sepsis.
- In Study D1680C00005, a 58-year-old male in the saxagliptin 5 mg group with a history of obesity died as a result of a myocardial infarction on Day 62 of the study.
- Deaths occurring after the ST period:
- In Study CV181011, a 75-year-old female in the placebo group (therefore receiving metformin in the LT period) had a myocardial infarction on Day 853 and underwent angioplasty the same day. Study medication was interrupted on Day 853. On Day 854, cerebral haemorrhage was detected, and the subject died due to cerebral haemorrhage on Day 861.
- In Study CV181038, a 61-year-old female in the saxagliptin 2.5/5 mg QAM group (2.5 mg group in the pooled monotherapy safety analysis set) was diagnosed with pancreatic and hepatic cancer

on Days 13 and 18 of the study, respectively, and died due to her cancers on Day 502, 484 days after discontinuing study medication.

The incidence of SAEs was 2.8% for saxagliptin 5 mg and 1.6% for placebo (Table 13). The SAEs were distributed across various PTs with no single PT predominating.

Table 13 SOCs and PTs with SAEs reported for >1 saxagliptin-treated subject (Pooled monotherapy safety analysis set)

	Number (%) of subjects			
SOC/PT	**Saxa 2.5 mg (N=247)**	**Saxa 5 mg (N=643)**	**All Saxa (N=890)**	**Placebo (N=559)**
Subjects with any SAE	**12 (4.9)**	**18 (2.8)**	**30 (3.4)**	**9 (1.6)**
CARDIAC DISORDERS	2 (0.8)	5 (0.8)	7 (0.8)	1 (0.2)
Angina unstable	1 (0.4)	2 (0.3)	3 (0.3)	0
Atrial fibrillation	1 (0.4)	1 (0.2)	2 (0.2)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	4 (0.6)	4 (0.4)	0
Osteoarthritis	0	2 (0.3)	2 (0.2)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.8)	3 (0.5)	5 (0.6)	0
Overdose	1 (0.4)	1 (0.2)	2 (0.2)	0
NERVOUS SYSTEM DISORDERS	0	3 (0.5)	3 (0.3)	2 (0.4)
Cerebrovascular accident	0	2 (0.3)	2 (0.2)	0
GASTROINTESTINAL DISORDERS	0	2 (0.3)	2 (0.2)	1 (0.2)
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS	1 (0.4)	1 (0.2)	2 (0.2)	0
Chest pain	1 (0.4)	1 (0.2)	2 (0.2)	0
INFECTIONS AND INFESTATIONS	4 (1.6)	0	4 (0.4)	4 (0.7)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	2 (0.8)	0	2 (0.2)	0

The incidences of serious AEs (SAEs) and of AEs leading to discontinuation of study treatment (DAEs) were also higher for saxagliptin 5 mg compared to placebo (SAE incidence 2.8% vs. 1.6%, respectively; DAE incidence 1.1% vs. 0.5%, respectively).

AEs of special interest

Hypoglycaemia

The incidence of any hypoglycaemia event was 3.0% for saxagliptin 5 mg and 1.6% for placebo. Events were reported for 2 of the specified hypoglycaemia PTs: the incidence of Hypoglycaemia was 3.0% in the 5 mg group and 1.4% in the placebo group; the corresponding incidences for Blood Glucose Decreased were 0% and 0.2%. The numerical difference for incidence of any hypoglycaemia was not considered to be clinically meaningful considering the absence of reports of confirmed hypoglycaemia, i.e., symptoms of hypoglycaemia confirmed with finger stick glucose reading ≤50 mg/dL. None of the hypoglycaemia AEs was considered serious or led to discontinuation of study drug, and no subject required medical assistance or help from any others to manage a hypoglycaemic event.

Infections

The overall incidence of AEs in the Infections and Infestations System Organ Class (SOC) for saxagliptin 5 mg (22.1%) was not meaningfully different from placebo (18.1%). There were no SAEs or DAEs in the saxagliptin 5 mg group. The most common Infections and Infestations AEs in all treatment groups were Upper Respiratory Tract Infection (6.1% and 7.3% incidence in the saxagliptin 5 mg and placebo groups, respectively), Urinary Tract Infection (4.2% and 4.7%, respectively), and Nasopharyngitis (3.9% and 3.0%, respectively).

Gastrointestinal

The overall incidence of AEs in the Gastrointestinal Disorders SOC was 12.4% for saxagliptin 5 mg and 8.1% for placebo. The most common GI AEs in the 5 mg group were Diarrhoea (2.5% and 1.6% incidence in the saxagliptin 5 mg and placebo groups, respectively), Constipation (1.6% and 1.4% incidence, respectively), and Nausea (1.4% and 0.2%, respectively). There were 2 GI SAEs (Abdominal Pain and Intestinal Obstruction) in the saxagliptin 5 mg group, and 1 (Small Intestinal Obstruction) in the placebo group. There were 2 GI DAEs (Dry Mouth and Gastric Disorder) in the saxagliptin 5 mg group, and none in the placebo group.

Hypersensitivity reactions

The overall incidence of any hypersensitivity events was 1.7% in the 5 mg group and 0.5% in the placebo group. PTs that were reported for >1 subject in any treatment group were urticaria (0.8% and 0% incidence, respectively) and Hypersensitivity (0.5% and 0% incidence, respectively). None of the hypersensitivity events was considered serious or resulted in discontinuation of study drug.

CV events

The overall incidence of specified CV AEs was 0.8% (5/643) in the saxagliptin 5 mg group and 0.2% (1/559) in the placebo group. The individual PTs reported were Angina Unstable (0.3% and 0% incidence in the saxagliptin 5 mg and placebo groups, respectively), Cerebrovascular Accident (0.3% and 0%, respectively), Myocardial Infarction (0.2% and 0%, respectively), and Cerebral Infarction (0% and 0.2%, respectively). Five of these cases were reported as SAEs in the saxagliptin 5 mg group, and none in the placebo group. For each SAE, the Investigators' causality assessment was "not related" or "unlikely to be related" and the subject had either pre-existing CV disease or multiple CV risk factors predisposing to the event. None of the CV AEs, other than 1 fatal AE, led to discontinuation of study treatment. A previous analysis of pooled data from Phase 2/3 studies of saxagliptin monotherapy and combination therapy (N=4607) does not indicate increased CV risk in patients who are taking saxagliptin.

Other AEs of special interest

The incidence of each of the following AEs of special interest, based on specified PTs, was low (<1%), similar across all treatment groups including placebo, and did not raise any safety concerns for saxagliptin monotherapy: opportunistic infections, lymphopenia, thrombocytopenia, pancreatitis, skin disorders, and bone fracture.

Overall, the analyses of adverse events demonstrate that the incidences of all of these adverse events were higher with saxagliptin monotherapy compared to placebo in line with what is already known from saxagliptin in the original dossier

The incidence of any hypoglycaemia event was 3.0% for saxagliptin 5 mg and 1.6% for placebo. The overall incidence of AEs in the Infections and Infestations System Organ Class (SOC) for saxagliptin 5 mg (22.1%) was higher with placebo (18.1%). The overall incidence of AEs in the Gastrointestinal Disorders SOC was 12.4% for saxagliptin 5 mg and 8.1% for placebo. The overall incidence of any hypersensitivity events was 1.7% in the 5 mg group and 0.5% in the placebo group. The overall incidence of specified CV AEs was 0.8% (5/643) in the saxagliptin 5 mg group and 0.2% (1/559) in the placebo group.

A higher incidence of several of these adverse events may not be unexpected. Although, the higher incidence of cardiovascular adverse events could be serious, the numbers were very small and other data do not suggest an increased risk with saxagliptin and other DPP-4 inhibitors. A CV outcome study is at the time of this procedure on-going.

The pooled Phase 3 monotherapy studies safety data were evaluated for the following subgroups: age, gender, and race. There was no apparent differential effect of saxagliptin monotherapy compared with placebo on AE incidence based on age, gender, or race. In regard to gender, which was an area of interest during the review of the initial MAA, the incidences of AEs for saxagliptin 5 mg compared with placebo for males (49.1% vs. 42.0%, respectively) and females (56.8% vs. 47.9%, respectively) were similar. Compared with Whites, Asians had lower incidences of AEs across both saxagliptin and placebo treatment groups (saxagliptin 5 mg: 65.3% vs. 46.4%; placebo 63.6% vs. 38.8%).

Within the 2 studies that evaluated both doses, the incidences of AEs for saxagliptin 5 mg and 2.5 mg appeared to be similar. The incidences of all AEs (including hypoglycaemia) for saxagliptin 5 mg compared with saxagliptin 2.5 mg for Study CV181011 were 75.5% vs. 74.5%, respectively, and for saxagliptin Study CV181038 were 59.5% vs. 52.7%, respectively.

In the Phase 3 pooled monotherapy studies, the 2.5 mg group had a higher incidence of AEs than the 5 mg group. This resulted from the fact that only Studies CV181011 and CV181038 included a 2.5 mg group, and the AE rates in these studies were generally higher than in Studies D1680C00005 and D1680C00008. Therefore, in the pooled monotherapy safety analysis, comparisons of the AE incidences for saxagliptin 2.5 mg group with either the saxagliptin 5 mg or placebo groups need to be interpreted carefully.

Long term safety

Two of the Phase 3 monotherapy studies (CV181011 and CV181038) included LT (beyond 24 weeks) safety data on saxagliptin monotherapy. These LT data have been previously submitted to the EU as follow-up measures (10 June 2010). The LT periods of these studies differed sufficiently (e.g., 52 vs. 182 weeks in duration, fixed vs. flexible [up to 10 mg] saxagliptin dosing) so that pooling the data would not be informative.

For both studies, the primary safety analyses for the combined ST and LT period were performed on data collected inclusive of rescue. These analyses, including exposure and safety data, have been previously submitted and the details can be found in the individual CSRs. This submission presents exposure and safety data collected prior to rescue in keeping with the focus of this submission on a saxagliptin monotherapy indication. The interpretability of these analyses may be limited relative to analyses inclusive of rescue due to the additional proportion of subjects with censored data as a result of rescue.

The evaluation of long-term safety is also limited by a decreasing number of subjects on saxagliptin monotherapy over time (in part due to progressively stricter rescue criteria) and the absence of placebo control (placebo treatment subjects switched to metformin during the long-term extension).

Laboratory findings

Clinical laboratory data were collected (Table 14). There were no discernible consistent effects of saxagliptin treatment on platelet counts or absolute lymphocyte counts. Nor was there any clinically meaningful effect on laboratory safety parameters indicative of hepatic function.

Table 14 Marked laboratory abnormalities with an incidence >1% in any treatment group (Pooled monotherapy safety analysis set)

	n/No (%) of subjects			
Parameter/criterion	**Saxa 2.5 mg (N=247)**	**Saxa 5 mg (N=643)**	**All Saxa (N=890)**	**Placebo (N=559)**
Eosinophils >0.9 X 1000 c/uL	6/242 (2.5)	26/626 (4.2)	32/868 (3.7)	22/545 (4.0)
Lymphocytes ≤ 0.75 X 1000 c/uL	2/242 (0.8)	9/626 (1.4)	11/868 (1.3)	2/545 (0.4)
Alkaline Phosphatase >1.5 X ULN	2/242 (0.8)	6/628 (1.0)	8/870 (0.9)	12/547 (2.2)
Bilirubin, Total >1.5 X ULN	2/242 (0.8)	9/628 (1.4)	11/870 (1.3)	6/547 (1.1)
Glucose, Plasma Unspecified <50 mg/dL	3/242 (1.2)	3/633 (0.5)	6/875 (0.7)	1/550 (0.2)
Potassium, Serum ≥1.2 X pretreatment and ≥6.0 mEq/L	8/242 (3.3)	7/628 (1.1)	15/870 (1.7)	8/547 (1.5)
Protein Urine: if pretreatment=0 use ≥2, if pretreatment=0.5 or 1 use ≥3, if pretreatment=2 use 4	4/237 (1.7)	16/624 (2.6)	20/861 (2.3)	24/542 (4.4)
Blood Urine: if pretreatment=0 use ≥2, if pretreatment=0.5 or 1 use ≥3, if pretreatment=2 use 4	9/237 (3.8)	38/624 (6.1)	47/861 (5.5)	31/542 (5.7)
RBC Urine: if pretreatment=0 use ≥2, if pretreatment=0.5 or 1 use ≥3, if pretreatment=2 use 4	5/119 (4.2)	34/205 (16.6)	39/324 (12.0)	26/169 (15.4)
WBC Urine: if pretreatment=0 use ≥2, if pretreatment=0.5 or 1 use ≥3, if pretreatment=2 use 4	10/128 (7.8)	37/235 (15.7)	47/363 (12.9)	15/188 (8.0)

Vital signs and physical findings

As shown in Table 15, there were small reductions from baseline in mean heart rate, systolic blood pressure, diastolic blood pressure, and body weight across treatment groups, including the placebo group.

Table 15 Change from baseline to Week 24 in vital signs, weight, and waist circumference (Pooled monotherapy safety analysis set)

	Saxa 2.5 mg		Saxa 5 mg		All Saxa		Placebo	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Systolic blood pressure (mmHg)	176	-2.79 (0.966)	521	-4.34 (0.561)	697	-3.94 (0.486)	415	-5.28 (0.672)
Diastolic blood pressure (mmHg)	176	-0.59 (0.601)	521	-2.56 (0.346)	697	-2.06 (0.301)	415	-2.67 (0.430)
Heart rate (beats per minute)	176	-0.88 (0.739)	521	-0.38 (0.410)	697	-0.50 (0.359)	415	-1.22 (0.431)
Body weight (kg)	170	-0.92 (0.251)	519	-0.38 (0.137)	689	-0.52 (0.121)	411	-1.25 (0.136)
Waist circumference (cm)	165	3.47 (5.442)	514	0.53 (0.636)	679	1.24 (1.405)	406	-0.14 (0.725)

Overall, here were no relevant changes in laboratory findings, vital signs and physical findings.

Additional studies

CV181008: Phase 2b monotherapy dose-finding study

Although similar in design to the Phase 3 monotherapy studies, Study CV181008 was a Phase 2b dose-finding (2.5 to 100 mg) study limited to 12 weeks and was not pooled with the Phase 3 monotherapy studies, similar to the pooling strategy employed in the original saxagliptin MAA. The safety and tolerability profile for all doses of saxagliptin below 20 mg was similar to that for placebo.

The other additional studies (CV181039: saxagliptin and metformin initial combination active comparator study, D1680C00007: saxagliptin in subjects with renal impairment and the add-on Studies D1680C00001 and D1680C00002) have submitted and assessed previously

These additional studies have been assessed before. The additional studies are of limited support as most of these studies do not investigate monotherapy with saxagliptin. The only additional study that investigates saxagliptin monotherapy is study CV181008. This was a monotherapy dose-finding study, but treatment duration was only 12-weeks. The other additional studies combine saxagliptin with metformin and/or other oral anti-hyperglycaemic drugs. As a comparator, placebo, SU or sitagliptin were used.

2.3.4. Discussion and Conclusion

A relatively large number of patients (n=643) have been treated with saxagliptin monotherapy 5 mg. However, the majority of these patients were Asian (n=431). The overall incidence of AEs for saxagliptin 5 mg (53.0%) was numerically higher than placebo (45.3%). The incidences of serious AEs (SAEs) and of AEs leading to discontinuation of study treatment (DAEs) were also higher for saxagliptin 5 mg compared to placebo (SAE incidence 2.8% vs. 1.6%, respectively; DAE incidence 1.1% vs. 0.5%, respectively).

The analyses of adverse events of special interest demonstrate that the incidences of all of these adverse events were higher with saxagliptin monotherapy compared to placebo. The incidence of any hypoglycaemia event was 3.0% for saxagliptin 5 mg and 1.6% for placebo. The overall incidence of AEs in the Infections and Infestations System Organ Class (SOC) for saxagliptin 5 mg (22.1%) was higher with placebo (18.1%). The overall incidence of AEs in the Gastrointestinal Disorders SOC was 12.4% for saxagliptin 5 mg and 8.1% for placebo. The overall incidence of any hypersensitivity events was 1.7% in

the 5 mg group and 0.5% in the placebo group. The overall incidence of specified CV AEs was 0.8% (5/643) in the saxagliptin 5 mg group and 0.2% (1/559) in the placebo group.

The incidence of gastrointestinal side effects was higher with saxagliptin compared to placebo.

A higher incidence of several of these adverse events may not be unexpected. Although, the higher incidence of cardiovascular adverse events could be serious, the numbers were very small and other data do not suggest an increased risk with saxagliptin and other DPP-4 inhibitors. A CV outcome study is at the time of this procedure on-going.

Overall, more drug-related AEs were reported in the all saxagliptin group than in the placebo group (8.9% vs. 6.3%). Most of the related AEs, e.g. dizziness, headache and fatigue, are already reflected in the SmPC for the monotherapy indication. However, the CHMP had concerns whether an increase in blood creatine phosphokinase and blood creatinine should also be included and requested supplementary information from the applicant during the procedure. However, Blood creatine phosphokinase and Blood creatinine events were uncommon in the monotherapy pool, and the differences between saxagliptin and placebo were <1%. Incidence was lower or equal to the 5-study pool of placebo-controlled studies. In addition, in the renal study, there was no evidence of a safety signal for an increase in blood creatinine. Therefore, the CHMP considered that there was no need including these events in the SmPC.

There was a numerical difference in the results for white blood cells (WBC) in urine between the saxagliptin and placebo groups in the monotherapy pool (studies CV181011, CV181038, D1680C00005, and D1680C00008). However, this difference did not translate into an overall clinical difference in the proportion of subjects with urinary tract AEs. In addition, no consistent findings of urine laboratory abnormalities have been observed in the overall saxagliptin program. Therefore, CHMP considered that there is no merit for inclusion of these findings in the SmPC.

In the program, one case of drug-related skin lesion was reported. Taking into account the population in question and the fact that skin lesions have been reported in monkeys, the CHMP requested supplementary information from the applicant during the procedure. The reported event was as mild in intensity, required no treatment, and based on the lack of correlation between the monkey toxicity findings and observations in the saxagliptin clinical trial program, and considering that he current SmPC includes statements on skin lesions, no further concern did arise.

In conclusion, the safety data were acceptable and no further update of the SmPC was considered necessary by the CHMP.

2.4. Risk management plan

No update of the Risk Management Plan had been submitted within this procedure. The current version 2 of the saxagliptin risk management plan had previously been assessed during procedure EMEA/H/C/xxxx/WS/0295, in which the MAH applied for extension of indication to include triple oral therapy (metformin+SU+saxagliptin). This RMP already included data from each of the studies that are part of the monotherapy pool (CV181011, CV181038, D1680C00005 and D1680C00008), appropriately summarizing important identified and potential risks for saxagliptin in the context of the approved indications as well as the proposed change in indication with this type II variation (use as monotherapy in adults with type 2 diabetes mellitus), and the risk management system therefore was considered acceptable by CHMP.

2.5. Changes to the Product Information

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

(bold underlined = new text, strikethrough = deleted text):

SmPC

Section 4.1 Therapeutic indications

Onglyza is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control:

as monotherapy

- **in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance**

as dual oral therapy in combination with

. . .

Section 5.1 Pharmacodynamic properties of the SmPC

. . .

Saxagliptin as monotherapy
Two double-blind, placebo-controlled studies of 24-week duration were conducted to evaluate the efficacy and safety of saxagliptin monotherapy in patients with type 2 diabetes. In both studies, once-daily treatment with saxagliptin provided significant improvements in HbA1c **(see Table 3). The findings of these studies were confirmed with two subsequent 24-week regional (Asian) monotherapy studies comparing saxagliptin 5 mg with placebo.**

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

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of several member states.

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

Benefits

Beneficial effects

This submission requested approval for the use of saxagliptin as monotherapy in adult patients aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control in patients inadequately controlled by diet and exercise alone, and for whom metformin is inappropriate due to contraindications or intolerance. The focus of this submission was on 4 Phase 3 monotherapy studies (CV181011, CV181038, D1680C00005, and D1680C00008), which comprise all of the Phase 3 controlled studies of saxagliptin as a monotherapy.

Study CV181011 and Study CV181038 were already assessed in the original saxagliptin registration dossier. Study D1680C00005 and study D1680C00008 were performed in Asians and have not been submitted previously. In all of the main studies, saxagliptin monotherapy was associated with a modest effect on HbA1c. For the pooled analyses, the treatment effect was –0.51% (-0.62%, -0.39%). However, there were differences between the races; the adjusted mean change from baseline in HbA1c (95% CI) difference from placebo was –0.40% (-0.63, -0.16) for Whites (n=138) and –0.51% (-0.64, -0.38) for Asians (n=402). Efficacy in Whites was therefore of borderline magnitude, but still significant. There is a growing body of evidence that the pathophysiology of type 2 diabetes differs between Whites and Asians (Kim et al. Diabetologia, January 2013), and the differences in efficacy between Whites and Asians are in line with previous findings with other DPP-4 inhibitors.

The changes in HbA1c were accompanied by changes in the percentage of subjects achieving therapeutic glycaemic response (HbA1c <7%) and fasting and postprandial glucose values.

In an additional study (CV181039), a post-hoc comparison demonstrated that saxagliptin 10 mg monotherapy was inferior to metformin monotherapy, with a mean (95% CI) difference in change from baseline in HbA1c of 0.30% (0.11, 0.49). The dose of 10 mg was twice as high as the recommended dose.

Uncertainty in the knowledge about the beneficial effects

The requested indication is the use of saxagliptin as monotherapy when metformin is inappropriate due to contraindications or intolerance. Main contraindications for metformin are moderate and severe renal impairment, hepatic impairment, heart failure and recent myocardial infarction. Intolerance is usually due to gastrointestinal side effects. All four main studies were not specifically performed in individuals with a contraindication or intolerance for metformin. Although results in these individuals may not be fully applicable to the intended population, there appears no reason to assume that this will influence efficacy in terms of HbA1c reduction. Cardiovascular effects are currently being studied in an outcome study.

When saxagliptin was used as combination therapy, both in combination with metformin, SUs and TZD, the 5 mg dose did somewhat better in the core Phase 3 combination trials than the 2.5 mg dose, while the safety profile between both doses was comparable. The approved recommended combination dose was 5 mg. When used as monotherapy, the efficacy of the 5 mg dose, with respect to the primary endpoint, has not been proven to be greater than the 2.5 mg dose. However the new Phase 3 studies included saxagliptin 5 mg only, which therefore did not provide any further direct comparisons of the efficacy between of 2.5 mg QD and 5 mg QD.

Risks

Unfavourable effects

The overall incidence of AEs for saxagliptin 5 mg (53.0%) was numerically higher than placebo (45.3%). The incidences of serious AEs (SAEs) and of AEs leading to discontinuation of study treatment (DAEs) were also higher for saxagliptin 5 mg compared to placebo (SAE incidence 2.8% vs. 1.6%, respectively; DAE incidence 1.1% vs. 0.5%, respectively).

The analyses of AEs of special interest demonstrate that the incidences of all of these AEs were higher with saxagliptin monotherapy compared to placebo. The incidence of any hypoglycaemia event was 3.0% for saxagliptin 5 mg and 1.6% for placebo. The overall incidence of AEs in the Infections and Infestations System Organ Class (SOC) for saxagliptin 5 mg (22.1%) was higher with placebo (18.1%). The overall

incidence of AEs in the Gastrointestinal Disorders SOC was 12.4% for saxagliptin 5 mg and 8.1% for placebo. The overall incidence of any hypersensitivity event was 1.7% in the 5 mg group and 0.5% in the placebo group. The overall incidence of specified CV AEs was 0.8% (5/643) in the saxagliptin 5 mg group and 0.2% (1/559) in the placebo group.

Uncertainty in the knowledge about the unfavourable effects

The incidence of gastrointestinal side effects was higher with saxagliptin compared to placebo. This is of special interest as saxagliptin monotherapy is intended for use patients with gastrointestinal intolerance with metformin. This has not been specifically studied, similar to patients in whom metformin is inappropriate due to contraindications, in particular patients with severe renal insufficiency and cardiac disease. During the procedure the Applicant was requested to provide supplementary information with regard to safety in renally and hepatically impaired patients. Results did not reveal unexpected issues. However, the number of patients, especially in the severe and end-stage renal impairment groups was limited.

More drug-related AEs were reported in the All saxagliptin group than in the placebo group (8.9% vs. 6.3%). Most of the related AEs, e.g. dizziness, headache and fatigue, are already reflected in the SmPC for the monotherapy indication. However, the increases in blood creatine phosphokinase and blood creatinine are not included, and the CHMP requested supplementary information to that regard. The Applicant answered that both events were uncommon in the monotherapy pool, and the differences between saxagliptin and placebo were <1%. Incidence was lower or equal to the 5-study pool of placebo-controlled studies. In addition, in the renal study, there was no evidence of a safety signal for an increase in blood creatinine. Therefore, the MAH had adequately justified the reasons for not including these events in the SmPC.

One case of drug-related skin lesion was reported. Taking into account the population in question and the fact that skin lesions have been reported in monkeys, any relevance to the lesions seen in non-clinical studies should be discussed and CHMP requested supplementary information. The applicant justified that skin lesions are adequately described in the SmPC. More patients in the saxagliptin group had increase in WBC (urine) compared to the placebo group (12.9% vs. 8.0%). However, this difference did not translate into an overall clinical difference in the proportion of subjects with urinary tract AEs. Therefore, CHMP considered that there is no merit for inclusion of these findings in the SmPC.

Benefit-risk balance

Importance of favourable and unfavourable effects

The "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" (CPMP/EWP/1080/00 Rev. 1) states that 'approval of a first or a second line monotherapy indication will be a case by case decision taking into account the observed efficacy of the drug in the target population, as well as the size of the safety database and the safety profile.' None of the main four studies with saxagliptin 5 mg was specifically performed in subjects with contraindications or intolerance for metformin. Although results in these individuals may not be fully applicable to the intended population, there appears no reason to believe that this would influence efficacy, however. Effects on HbA1c were modest, varying from -0.40% in Whites to -0.51% in Asians, but were statistically significant and considered as clinically relevant. Non-inferiority compared to metformin has not been demonstrated, but effects on HbA1c appear comparable with those of glipizide and sitagliptin in an add-on design with

metformin. Saxagliptin could therefore be an alternative for SU-derivatives, in particular when symptoms of weight gain or hypoglycaemia occur using one of these agents.

With regard to safety, saxagliptin has not been studied specifically in patients with gastrointestinal intolerance to metformin nor in patients with contraindications to metformin. However, it should be noted that saxagliptin is already approved in combination with SU in patients when use of metformin is considered inappropriate. Main contraindications for metformin are moderate and severe renal impairment, hepatic impairment, heart failure and recent myocardial infarction. These are conditions for which there is limited experience for saxagliptin. So far, three DPP-4 inhibitors have a monotherapy indication. Linagliptin monotherapy has been approved in patients for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment. A study comparing linagliptin monotherapy and placebo was specifically performed in patients with gastrointestinal intolerance for metformin and in addition. For linagliptin, a study in patients with renal insufficiency was performed. Sitagliptin has been approved in patients for whom metformin is inappropriate due to contraindications or intolerance, as sitagliptin showed better gastrointestinal tolerability compared to metformin and could be administered in patients with hepatic and severe renal impairment. Vildagliptin has also been accepted for this indication.

With respect to gastrointestinal adverse events of saxagliptin, the mechanism of action behind the GI events in saxagliptin and metformin is different and as such, saxagliptin can still be an option in patients with intolerance to metformin. As mentioned above, this has also been shown for other DPP-IV inhibitors. Thus, no specific studies with saxagliptin were considered necessary in these patients. Safety needed to be specified further for patients with contraindications for metformin and in particular patients with hepatic and severe renal insufficiency. The Applicant has provided data on renally impaired patients. No unexpected safety issues were seen although the number of patients, especially in the severe and end-stage renal impairment groups was limited. Based on PK data and clinical experience with saxagliptin, specific precautions for saxagliptin administration were not considered necessary for hepatically impaired patients.

Benefit-risk balance

The overall B/R for saxagliptin as monotherapy when metformin is inappropriate due to contraindications or intolerance is considered positive.

During the assessment of this application, a review under article 5(3) of Regulation (EC) 726/2004 was initiated on 26 March 2013 to assess the findings of an independent academic group of researchers following publication of a paper entitled "Marked Expansion of Exocrine and Endocrine Pancreas with Incretin Therapy in Humans with increased Exocrine Pancreas Dysplasia and the potential for Glucagon-producing Neuroendocrine Tumors", by Butler AE et al. which was published online on March 22 in the journal "Diabetes".

To date the assessment performed under Art.5(3) has not reached any conclusions and the impact of these findings on the benefit/risk balance of medicinal products containing saxagliptin is unknown at this stage.

The CHMP opinion with regard to the overall B/R for saxagliptin as monotherapy when metformin is inappropriate due to contraindications or intolerance is therefore without prejudice to the future outcome of the Art. 5(3) procedure.

Discussion on the benefit-risk balance

The overall B/R for saxagliptin as monotherapy when metformin is inappropriate due to contraindications or intolerance is considered 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 4.1and 5.1 of the SmPC in order to extend the indication to include monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance . The Package Leaflet is updated accordingly.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Furthermore, the PI is being brought in line with the latest QRD template version 9.0.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II 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 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.

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

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

Not applicable.