EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

Komboglyze

International non-proprietary name: **saxagliptin / metformin**

Procedure No. **EMEA/H/C/002059**

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AUC	Area under the curve
BMS	Bristol-Myers Squibb
CI	Confidence interval
CK	Creatine kinase
C_{max}	Maximum plasma concentration
CSR	Clinical study report
DPP4	Dipeptidyl peptidase 4
EC	European Commission
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide-1
HbA1c	Glycosylated hemoglobin
IR	Immediate release
LOCF	Last observation carried forward
LT	Long-term
MWG	Mean weighted glucose
PK	Pharmacokinetic(s)
PPG	Postprandial glucose
QAM	Once daily in the morning
QPM	Once daily in the evening
SAE	Serious adverse event
SOC	System organ class
ST	Short-term
T2DM	Type 2 diabetes mellitus
US	United States
XR	Extended release

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb / AstraZeneca EEIG submitted on 21 July 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Komboglyze, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 July 2009.
The applicant applied for the following indication:

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

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC, as amended – fixed combination application
The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/240/2009 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice

The applicant did not seek scientific advice.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 21 July 2010.
- The procedure started on 18 August 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 November 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 November 2010.
- During the meeting on 13-16 December 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 December 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 and 15 July 2011.
- During the CHMP meeting on 18-21 July 2011 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 6 September 2011.
- During the meeting on 19-22 September 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Komboglyze on 22 September 2011.

2. Scientific discussion

2.1. Introduction

Problem statement

The prevalence of type 2 diabetes mellitus (T2DM) is steadily increasing in almost every region of the world and in the European region it is about 9% (International Diabetes Federation). T2DM has a diverse physiopathology including inappropriate hepatic glucose production, reduced insulin sensitivity, pancreatic islet dysfunction (reduced ß-cell mass combined with ß-cell dysfunction) and inappropriately elevated glucagon secretion. The chronic hyperglycaemia is associated with microvascular and macrovascular complications and subsequent increases in morbidity and mortality. Glucose control detoriates progressively over time, and after failure of diet and exercise, needs on average a new intervention with glucose-lowering agents every 3-4 years to obtain/retain good control. The recommended first line treatment is metformin. Sulfonylureas may be used as an alternative to patients intolerant to metformin, or as an addition to metformin. Other oral treatment alternatives include alpha-glucosidase inhibitors, meglitinides, thiazolidindiones and DPP-4 inhibitors.
A fixed dose combination tablet containing 2 anti-hyperglycaemic agents, i.e. one DPP-4 inhibitor (saxagliptin) and one biguanide (metformin) with complementary mechanism of action for lowering glucose, has the potential to provide new treatment option for patients with T2DM. As a fixed dose combination tablet, it is assumed that it may improve patient compliance.

About the product

The applicant proposed the FDC product of saxagliptin/metformin IR of 2.5/850 and 2.5/1000 with a fixed dose of metformin taken twice daily, instead of a once daily 5 mg dose of saxagliptin as add on to metformin, for adequate coverage of T2DM. A single tablet dosing can be considered more convenient than the dosing of separate tablets for each mono-component.
The once daily 5 mg dose of saxagliptin has been approved as add on to metformin for the treatment of T2DM via the EU Centralised Procedure.

Metformin hydrochloride is a well characterised drug. The IR dosage forms are widely approved for the treatment of T2DM, with tablet strengths of 500 mg, 850 mg and 1000 mg approved in several countries as Merck-Serono-branded Glucophage tablets, as well as generic products.
The proposed combination therapy with metformin and the DPP-4 inhibitor saxagliptin is expected to lower glucose due to the different mechanisms of action.

The applied dose strengths are 2.5 mg/850 mg and 2.5 mg/1000 mg, and the applied dose is one tablet twice daily.

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

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

Type of application and other comments on the submitted dossier

The legal basis for this application referred to: Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for fixed combination products.

Most of the studies presented in the dossier had been already submitted and evaluated in the previous MAA, which lead to the approval of Onglyza (saxagliptin), which is approved for the combined use of saxagliptin with metformin.

The dossier submitted initially did not provide a sufficient comparison between 2 x 2.5 mg dosing and 1 x 5 mg dosing of saxagliptin. Therefore, the applicant has conducted a pharmacokinetic (PK)/pharmacodynamic (PD) study after the start of the procedure, which was then submitted and evaluated during the procedure.

2.2. Quality aspects

2.2.1. Introduction

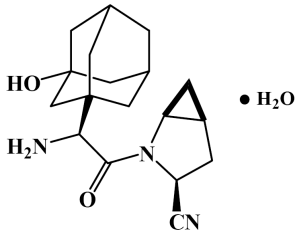
Saxagliptin has been approved as add on to metformin for the treatment of T2DM via the EU Centralised Procedure. Information about saxagliptin in the present dossier is the same as for the approved product *Onglyza*, updated with stability data.
Metformin hydrochloride is a well characterised drug. The IR dosage forms are widely approved for the treatment of T2DM, with tablet strengths of 500 mg, 850 mg and 1000 mg approved in several countries.

The product is an immediate release fixed dose combination, film-coated tablet containing two drug substances: saxagliptin and metformin hydrochloride. It is available in two strengths 2.5/850 and 2.5/1000 saxagliptin / metformin respectively. Komboglyze is indicated for treatment of type 2 diabetes mellitus. The maximum daily dose according to the SPC is 5 mg saxagliptin and 2 gram metformin hydrochloride.
Komboglyze is presented in alu/alu blisters. For a full list of excipients refer to the SmPC.

2.2.2. Active Substance

Saxagliptin

The INN name of the active substance is saxagliptin and the chemical name (IUPAC) (1S,3S,5S)-2-((2S)-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. Its molecular formula and weight are $C_{18}H_{25}N_3O_2 \cdot H_2O$ and 333.43 (315.41 anhydrous), respectively. Its structure is shown below.



The substance is soluble in water, and very soluble at low pH showing a minimum solubility of 17.6 mg/ml over the pH range 0.7 to 8.7. The pKa value of saxagliptin was determined to be 7.3. The distribution coefficient octanol / water (Do/w) is at pH 7.0 is 0.607. It appears as a white to off-white, non-hygroscopic, crystalline powder that exists as a stable monohydrate. To date, only one polymorphic form of saxagliptin (free base monohydrate) has been observed.

Manufacture

The synthesis is performed in five reactions carried out as three steps with isolation of two intermediates. Reprocessing steps have been laid down for cases when the acquired intermediate is not sufficient pure; in these steps the same solvents are used as in the step in question or in other steps of the synthesis. The evolution from Process A to the intended Process D is characterized by changes in the use of reagents and/or solvents in the reaction, work-up, and crystallization/isolation. Process C and D can be considered essentially equivalent and representative for the proposed synthesis route.
The manufacturing process of the drug substance is thoroughly described and sufficient information is given on the syntheses of the starting materials.
A Quality by Design (QbD) approach has been utilized during development of the manufacturing process. The Critical Quality Attributes (CQAs) of the drug substance were defined and their impact on the product quality and the associated control strategies for these CQAs were presented.
Critical process parameters (CPP) were identified based on the risk assessments of the process and uni- and multivariate experiments were utilized to define the design space within the studied ranges.
Critical Process Parameters (CPPs), as well as Key Process Parameters (KPPs), have been identified and acceptable ranges for all process parameters have been established to ensure that the manufacturing process reproducibly meets the defined CQAs of the drug substance.This was studied through a five-batch campaign, conducted within the defined design space at scale at the commercial manufacturing site.

The CPP limits, IPCs and batch size ranges (including molar ratio's) for the materials used during the process and acquired drug substance are acceptable based on the QbD data and CQAs submitted. The temperature ranges of the process laid down are within the CPP limits. The process is considered to be sufficently under control.

In summary, the QbD approach to the manufacturing process for saxagliptin drug substance has provided enhanced process knowledge and resulted in a manufacturing design space which will consistently deliver high quality drug substance.

Specification

The drug substance specification includes tests for appearance (visual), colour (visual) identification (IR or Raman and HPLC), assay (HPLC), impurities/ degradants (HPLC) and residual solvents (GC).
It has been shown that the stereochemical purity is maintained during manufacture and storage.
The levels of heavy metals and trace metals are found < 20 ppm (ICP-MS) and for this reason no test or limit is included as part of specification. Finally, given the process chemistry, including aqueous extractions as well as a wash of the drug substance that contains water, the levels of inorganic materials are expected to be appreciably low. Also the results regarding residue on ignition are below

the generally applied limit in Ph. Eur. Monographs, therefore quality control of the drug substance without a test and limit for sulphated ash and residue on ignition is considered acceptable.
Sufficient evidence has been provided to justify why polymorphism is not controlled in the product specification
Results for 9 batches of "process D" manufactured according to the proposed manufactured process, at the proposed manufacturing site have been presented. The results of these batches can be considered as representative for evaluation of batch-to-batch consistency of the proposed manufacturing process.
In addition, results of 11 batches of "process C", manufactured at a different site which were provided are considered supportive, as "process C" is essentially equivalent to "D". The batch data of "process C" and "D" are within the specified limits.

Stability

A stability study on two batches manufactured by Process D at the commercial site covers 36 months at refrigerated conditions (5°C) and 6 months at accelerated conditions (25°C/60%RH). For the Process D batches, a study without an outer container has also been started at the long-term condition (the data cover 36 months) as well as at -20°C for 12 months. The results were within specifications at the long-term condition.
Results from another stability study for three batches of saxagliptin manufactured by Process C at a former site have been provided as supportive data. The data cover 37 months at refrigerated conditions and 12 months at accelerated conditions.
The differences between Process C and Process D are minor. After 12 months at long-term conditions and 6 months at accelerated conditions the level of degradants in Process D batches is lower than or similar to the level seen in Process C batches.
For powder X-ray diffraction no change from initial was observed for any batch. The sample stereochemistry remained the same and the drug substance form remained unchanged. All other tested parameters remained the same.

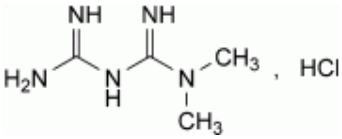
Photostability study
Photostability was investigated in accordance with ICH Q1B and it was shown that saxagliptin is not sensitive to light.

Forced degradation studies
Forced degradation studies were performed with the drug substance in solution at several pH's. Based on the results a potential degradation pathway has been identified and submitted in the dossier.
Oxidative studies have also been performed. Some other degradation products than the already discussed have been encountered, which are not likely to be present, considering that they degrade further. Adequate, qualified limits are already present for contents of these oxidation degradants in the drug substance.

In conclusion the re-test period and the proposed packaging material are accepted.

Metformin hydrochloride

The INN name of the active substance is metformin and the chemical name (IUPAC) N,N-Dimethylimidodicarbonimidic diamide monohydrochloride. Its molecular formula and weight are C4H12ClN5 and 165.63. Its structure is shown below.



The substance is white or almost white crystals freely soluble in water, slightly soluble in alcohol. There is no evidence of polymorphism for metformin hydrochloride. The dossier refers to the Ph. Eur. Monograph and the CEP provided by the metformin active substance supplier.

Manufacture

The applicant has submitted a CEP provided by the metformin active substance supplier. Description of manufacturing process and process controls, Control of materials, Control of critical steps and intermediates, Process validation and/or evaluation and Manufacturing process development are covered by the CEP
It is noted that the metformin is sourced as a blend with magnesium stearate from the manufacturer. The magnesium stearate is added as a lubricant to prevent the metformin HCl from caking and forming lumps during routine bulk storage in drums. The blend comprises 99.5% metformin HCl and 0.5% magnesium stearate.

Specification

As per the submitted CEP the drug substance specification complies with that of the Ph. Eur with an additional limit for 'any other impurity', in comparison with the Ph. Eur. Monograph. The CEP also states the absence of use of material of human or animal origin in the manufacturing of the substance.

Stability

According to the CEP, a retest period of 5 years is justified when stored in the proposed material.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was a fixed-dose combination of saxagliptin and metformin hydrochloride. The dissolution of the drug substances should be similar to that of the commercial mono-component drug products.
The product is an immediate release, film-coated tablet with two drug substances, provided in two product strengths: saxagliptin/metformin HCl 2.5 mg/850 mg and 2.5 mg/1000 mg respectively.
The design of the tablet is based on the recently approved product Onglyza 5 mg film-coated tablet, containing 5 mg saxagliptin/tablet.
The tablet consists of a tablet core with metformin HCl as drug substancecovered by a number of film-coat layers. The drug substance saxagliptin is embedded within the middle layer.
The composition of the 2.5mg/1000mg product strength is based on the same tablet core granulate as of the 2.5mg/850mg strength: the two core compositions are proportionally equal. The compositions of the coatings are the same except regarding the colouring materials.

Metformin is mixed with magnesium stearate in order to improve flowability and prevent lumping on storage. Metformin's particle size is not critical to solubility or dissolution considering its high solubility in water, and throughout the physiological pH range as well as its pharmacokinetics.
For the core tablet manufacturing stage, proven acceptable range (PAR) has been established for batch size, mixing, lubrication, tablet hardness, -thickness and -weight. The operating parameters were found not to affect the CQAs within the ranges investigated.

Saxagliptin is prone to undergo an intra-molecular cyclisation reaction in solution and solid states to form a cyclic amidine. To minimise this phenomenon a tablet formulation was developed with saxagliptin embedded within a film coat of Opadry.
Considering that the drug substance dissolved in a coating suspension during manufacturing, particle size is not relevant. In addition, the effect of large aggregates of the free base in the preparation of the coating solution on the dissolution of the tablet was investigated. The drug product formulation has been demonstrated to perform identically with aggregate levels several hundred times larger than what the drug substance process typically produces and thus also no control on particle size in the product is needed.
There are no unusual excipients included. Compatibility of saxagliptin with several coating materials has been investigated.
During formulation development, several prototype formulations were manufactured by different processes. Bridging studies for the various formulations used in phase I, II and III and the commercial one were presented and are considered acceptable from a chemical-pharmaceutical point of view.

Quality by Design concepts and a risk-based approach was employed in the manufacturing process development to identify the critical quality attributes (CQA) of the drug product. All identified CQAs relate to the coating stage. Proven acceptable ranges have been established for several of the processes at three specified scales. An investigation has been performed to determine the effect of the active layer on the CQAs. The parameters and factors affecting drug product CQA have been investigated and proven acceptable ranges established. The ratio of active substance to coating material in the suspension has been defined. Chemical stability of the coating suspension and absence of microbial growth were confirmed, and an appropriate holding time has been established.
The predictive active coating model (RSD model) establishing the process parameters ranges and the effect on saxagliptin content uniformity of the proposed product, which was originally developed, has been adapted for the Komboglyze. This model was used extensively in the manufacturing process development for several strengths of the proposed product. It was indeed demonstrated experimentally that the model accurately predicts the impact of active coating variables on saxagliptin content uniformity and is suitable for the proposed product.
However, the model is not intended to be used alone to support future expansions. Model maintenance is considered covered by GMP and does not trigger a variation application unless the established PARs are narrowed or expanded. However if future batch analysis indicate that the prediction model fails to provide a satisfactory estimate of the content uniformity of the batch the applicant will take proper action to resolve the issue.
Finally, a cause and effect diagram has been developed with regard to the risks to the commercial manufacturing of drug product and the factors potentially affecting manufacture. Based on all experiments an extensive list with the control strategy and proven acceptable ranges for production of the product has been submitted, which includes the intended operating ranges, IPC's etc. for all manufacturing steps. The system response over the Proven Acceptable Ranges was confirmed by multiple batches at each scale.
Comparative in vitro dissolution studies at pH 1.2, 4.5 and 6.8 between the saxagliptin 2.5 mg/metformin HCl 850 mg tablets (used in BE study CV181121) and the saxagliptin 2.5 mg/metformin HCl 1000 mg tablets (for which a biowaiver is requested) was presented.
In view of the comparative dissolution results and the f2 results for metformin, and the requirements for f2-calculation in the guideline on Bioavailability, similarity regarding metformin dissolution between the two strengths at the three pHs have been demonstrated. Regarding saxagliptin as this substance remains a very rapidly dissolving component for both strengths at the three pH's so these profiles are considered similar. Therefore the in vitro data support the biowaiver as discussed in section 2.4 Clinical Aspects.

Adventitious agents

Lactose monohydrate is the only material of animal origin derived from bovine milk sourced from healthy cows in the same condition as milk collected for human consumption and comply with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) .

Manufacture of the product

The components of the metformin core tablets are blended and tablets are compressed. The manufacturing process then involves active coating of saxagliptin onto the core tablet. The tablets are printed and packaged..The metformin-magnesium stearate blend is an intermediate product for which validation studies regarding homogeneity/content uniformity have been conducted.
A prospective validation study will be performed in line with the presented protocol. It is noted that the application of the drug substance saxagliptin as a coating layer may be considered as a non-standard manufacturing process. However, considering that a total of 11 commercial scale batches have been manufactured for three strengths of the drug product, and the enhanced approach to pharmaceutical development and the manufacturer's experience with the similar drug product Onglyza, it is considered acceptable that the results of the process validation study will be completed in a prospective way.

Product specification

The drug product release and shelf life specification includes tests and limits for description (visual), identification (saxaglipin: HPLC, TLC, metformin: HPLC, IR), assay (HPLC), uniformity of dosage units

(Ph.Eur., at release), impurities/ degradants (HPLC), dissolution (Ph.Eur. HPLC,) and microbial attributes (Ph. Eur., not routinely).

Analytical results have been presented for two batches of the 2.5 mg/ 850 mg strength and five batches of the 2.5 mg/ 1000 mg strength. In addition results for four batches of the 2.5 mg/ 500 mg strength (outside the scope of the present application) have been presented as supportive data. Batch sizes correspond to the commercial batch size. The results comply with the specification.

Stability of the product

Stability data were presented for seven commercial scale batches (three batches of each of the 2.5 mg/ 500 mg and the 2.5 mg/ 1000 mg strengths and one batch of the 2.5 mg/ 850 mg strength). The data cover 24 months at 5 °C, 25°C/ 60% RH and 30°C/ 75% RH, and 6 months at 40°C/75% RH. Under long term conditions from all the tested parameters only a slight increase in total impurities was observed but remained within specifications. At accelerated conditions all the tested parameters remained within specifications with the exception of total or individual impurities (saxagliptin) at the six-month timepoint.

In addition, the results from a one month stress stability study (50 °C), 12 months open dish study (25°C/ 60% RH), photostability study (1.2 million lux hours) and temperature cycling study (7 x -20°C to 40°C) have been presented.

Stability data on the metformin hydrochloride/magnesium stearate blend, demonstrated excellent stability for up to 5 years.

Overall, the presented stability information supports the proposed shelf life and storage conditions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

Komboglyze is a fixed dose combination product containing two approved products, saxagliptin (Onglyza) and metformin.

The preclinical safety of the individual products has also been fully evaluated in the context of other marketing authorisation applications by regulatory agencies.

The non-clinical primary and secondary pharmacodynamics (PD) of saxagliptin have been previously fully evaluated in the context of the marketing authorisation application of Onglyza.

No new pharmacology studies have been submitted for saxagliptin, metformin or saxagliptin/metformin and no new dedicated safety pharmacology studies have been performed as part of this application. However, because of the limited experience of concomitant use of saxagliptin and metformin a 3-month repeat oral dose toxicity study in dogs was performed.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A prominent theory in the pathogenesis of type 2 diabetes is that there is reduced modulation of insulin and glucagon homeostasis by incretins, hormones that increase insulin secretion in response to a meal. Based on the finding that infusion of the glucagon-like peptide-1 (GLP-1) incretin may alleviate some of the metabolic abnormalities in diabetic patients, there has been intense interest in increasing incretin levels therapeutically by using incretin mimetics or by inhibiting dipeptidyl peptidase 4 (DPP4). DPP4 is the primary enzyme responsible for inactivation of many incretins, specifically GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Saxagliptin is a potent inhibitor of human DPP4. By inhibiting DPP4 saxagliptin increases the level of GLP-1, thereby augmenting postprandial insulin secretion and subsequently lowering the postprandial plasma glucose levels.

Metformin is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes by lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production and intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Secondary pharmacodynamic studies

Saxagliptin has been evaluated In vitro for the potential to antagonize the binding of appropriate radioligands to 42 receptor and ion-channels or to inhibit 11 different enzymes. No significant effects were observed (<25% inhibition at 10 µM).

Metformin has in humans, independently of its action on glycaemia, favourable effects on lipid metabolism as shown at therapeutic doses in controlled, medium-term or long-term clinical studies, where metformin reduces total cholesterol, LDLc and triglyceride levels.

No new studies have been performed. With saxagliptin/metformin combination the applicant considered that no adverse pharmacologic interactions are anticipated due to different mechanisms of action for the two substances, and no additional pharmacology studies were therefore performed with the combination, which was found to be justified.

Safety pharmacology programme

No significant findings were reported from the saxagliptin safety pharmacology studies included in the MAA submission for Onglyza.

Extensive use of metformin in patients with T2DM has not revealed any specific safety pharmacology concern.
No dedicated safety pharmacology studies with saxagliptin/metformin have been performed. However, potential cardiovascular, central nervous and respiratory effects were evaluated as part of the 3-month repeat oral dose toxicity study in dogs.

Cardiovascular system

The potential effects of saxagliptin in combination with metformin on the cardiovascular system were evaluated as a component of the pivotal dog repeat-dose toxicity study and provided no findings of any concern for humans.

Consistent with the individual compounds, the combination of saxagliptin and metformin did not produce any haemodynamic or electrocardiographic effects in dogs dosed for 3 months in the non-clinical toxicity study (5 mg/kg/day saxagliptin, 20 mg/kg/day metformin, and 1/20 and 5/20

mg/kg/day saxagliptin/metformin). The benign cardiovascular safety profile of the combination in dogs was found to indicate a similarly favorable profile in humans.

Central nervous system
Metformin-related tremors/shivers occurred in the 3-month dog study at a slightly higher incidence in dogs given 5/20 mg/kg/day saxagliptin/metformin compared to metformin alone. These observations were considered toxicologically insignificant based on the sporadic nature and low incidence.

Respiratory system
The potential effects of saxagliptin in combination with metformin on the respiratory system were evaluated as a component of the dog repeat-dose toxicity study. Consistent with the individual compounds, the combination of saxagliptin and metformin did not produce effects on mean arterial oxygen saturation or respiratory rate.

Pharmacodynamic drug interactions

Due to different mechanisms of action for saxagliptin and metformin no interaction is anticipated with the fixed combination, and no dedicated non-clinical studies were therefore conducted, which was acceptable.

2.3.3. Pharmacokinetics

Pharmacokinetic endpoints for saxagliptin and metformin were previously assessed in non-clinical and clinical settings. Based on those assessments, no adverse pharmacokinetic interactions were expected. Therefore no additional non-clinical studies were conducted with the compounds in combination.

Although no interaction is suspected, C_{max} values for saxagliptin and the saxagliptin metabolite BMS-510849 were decreased by 46-70% in the oral combination study of embryo-fetal development in rats when saxagliptin (25 mg/kg) was co-administered with metformin at 600 mg/kg, suggesting a weak-to-moderate interaction between metformin and saxagliptin. AUC exposures were generally comparable or slightly increased. No signs of interaction was observed in rats (25/200 mg/kg/day), rabbits (40/50 mg/kg/day), or in dogs (5/20 mg/kg/day) at metformin/saxagliptin ratios ≤ 8. In a clinical drug-drug interaction study, co-administration of 1000 mg metformin with 100 mg saxagliptin resulted in a 21% decrease in the geometric mean C_{max} of saxagliptin, while the AUC(inf) of saxagliptin remained unchanged (study CV181017). These findings may indicate that a potential interaction may occur between metformin and saxagliptin at dosing ratios >8, but considering that AUC levels remain unchanged, the reduced C_{max} levels were considered of minimal clinical relevance.

Toxicokinetics was assessed as a part of the toxicity studies.

Absorption
Bioavailability following oral administration of saxagliptin was determined to be 75% in rat, 76% in dog and 51% in monkey,. Saxagliptin exhibits a high volume of distribution at steady state in rat, dog and monkey (1.3-5.2 l/kg). Saxagliptin is cleared rapidly in rats (115 ml/min/kg) and at a moderate rate in dogs (9.3 ml/min/kg) and monkeys (14.5 ml/min/kg).The elimination half-life estimates of saxagliptin are comparable for rat, dog, monkey and human (2.1-4.4 h).

Distribution
The protein binding of saxagliptin was very low in all species tested. The highest concentrations (1-12 h) after oral dosing of saxagliptin related material were found in gastro-intestinal tissues, liver, urinary bladder and kidney. For both saxagliptin and metformin, red blood cells are likely to represent a secondary compartment of distribution at later times. No data was provided on the distribution of metformin or of saxagliptin in combination with metformin.

Placental transfer
Saxagliptin-derived radioactivity was widely distributed in both maternal and fetal tissues in rats. This demonstrates that saxagliptin-derived components cross the placenta in rats. A limited amount of human data suggests the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with

respect to pregnancy, embryonic or foetal development, parturition or postnatal development. No data was provided on the placental transfer of metformin or of saxagliptin in combination with metformin.

Metabolism
The biotransformation of saxagliptin is primarily mediated by CYP3A4/5. The major metabolite of saxagliptin (BMS-510849) is also a selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin. Metformin is excreted unchanged in the urine in humans. No metabolites have been identified in humans.

Excretion
Saxagliptin and its metabolites are mainly excreted via urine, with the renal clearance of saxagliptin greater than the GFR, suggesting active excretion. Metformin is also actively excreted via urine, but no data on excretion percentages via faeces or urine was provided by the applicant. In the SPC it is stated that in humans metformin is excreted unchanged in urine, indicating that excretion via faeces is a minor excretion route. Thus, saxagliptin, its metabolites and metformin are mainly excreted via urine.
Studies in animals have shown excretion of both saxagliptin and/or metabolite and metformin in breast milk. It is unknown whether saxagliptin is excreted in human milk, but metformin is excreted in human milk in small amounts.

2.3.4. Toxicology

The toxicological properties of saxagliptin were assessed as part of the MAA for Onglyza, and the toxicological properties of metformin are well known from previous animal studies and extensive clinical use. The nonclinical safety of the combination of saxagliptin and metformin was evaluated in a repeat-dose oral toxicity study in dogs and a series of embryo-fetal development studies in rats and rabbits. All pivotal studies were conducted in compliance with GLP regulations and according to International Conference of Harmonization (ICH) guidelines.

Single dose toxicity

A (non-GLP) single dose combination toxicity study in dogs was performed in order to determine the toxicokinetic profile of saxagliptin and metformin, and to assess the tolerability of both compounds.
Beagle dogs were administered saxagliptin (1, 5, or 10 mg/kg), metformin (10, 20 or 40 mg/kg) or saxagliptin/metformin (5/20 mg/kg) individually and in combination. Clinical signs in the single dose toxicity study in dogs were limited to faecal findings (unformed faeces, etc.) with saxagliptin and metformin dosed separately. The faecal observations in dogs given the combination were comparable to those in the dogs given high dose metformin alone. Therefore, there were no unique or synergistic toxicities resulting from the combination.

Repeat dose toxicity

A three month, GLP-compliant combination toxicity study of saxagliptin in combination with metformin has been provided, in accordance with the Guideline on the non-clinical development of fixed-combinations of medicinal products (EMEA/CHMP/SWP/258498/2005). The dose selection was based on a 2-week range-finding study. The dog was selected as the species for evaluation since studies with saxagliptin had demonstrated increased sensitivity in dog including dose-limiting gastrointestinal toxicity and at very high doses, enteropathy.

The combinations of saxagliptin and metformin at 1/20 and 5/20 mg/kg/day were well tolerated. Soft, liquid, and/or red faeces were noted with comparable incidence in all groups. Saxagliptin-related findings consisted of mucoid material (faecal/non-faecal) in both sexes and clear eye discharge predominately in females. Both findings showed comparable incidence across all groups given the combination of saxagliptin and metformin. Metformin-related findings consisted of salivation and sporadic tremors/shivers. Salivation occurred at a comparable incidence across all groups given metformin alone and together with saxagliptin. Transient tremors/shivers were increased in dogs in the combination group of the toxicology study. In the group receiving only saxagliptin, no tremors were observed. In the groups metformin only, and metformin in combination with 1 mg/kg/day saxagliptin, one dog had a single incidence of tremors. In the high dose combination however, three males and two females had four and seven occurrences of tremors respectively. The finding was sporadic and at the

beginning of the study only, it was assessed to be behaviour based and no histological change was observed, the tremors were not associated with hypoglycaemia, and no such effect was seen in pregnant rats or rabbits. It has been shown before that metformin causes adverse effects on the brain in dogs, when dosed with 50 mg/kg/day or higher. It could therefore be possible that the combination with high dose saxagliptin can exaggerate this effect, and that tremors and shivers occur before there is any sign of damage. Since this only occurs in combination with very high dose saxagliptin (80-fold the human exposure), a relevance for humans is unlikely. Furthermore, this observation was not considered toxicologically relevant due to low incidence, sporadical at the beginning of the study, were not associated with hypoglycaemia or neurological effects or histological changes.

Decreases in mean body weight gain (up to 9% body weight difference at dose completion) were observed in females dosed with saxagliptin/metformin at 5/20 mg/kg/day and in males in all 3 groups given metformin (alone or in combination) compared to dogs given saxagliptin alone. This effect was considered related to metformin since it was observed at a similar magnitude in male dogs given metformin alone or in combination with saxagliptin.

NOAEL for the combination of saxagliptin and metformin was 5/20 mg/kg/day (mean $AUC_{(0-T)}$ levels for saxagliptin, BMS-510849, and metformin of ≤ 5530, ≤ 7130, and ≤ 30000 ng•h/mL, equating to ≤68×, 16×, and 1.5× the MRHD).

Genotoxicity

The combination saxagliptin/metformin has not been tested for genotoxicity. As both separate substances have been shown to have no genotoxic potential, this was acceptable.

Carcinogenicity

Saxagliptin was not carcinogenic in 2-year rat and mouse studies. Metformin showed an increase in benign stromal uterine polyps in rats at high doses. Extensive clinical experience does not indicate a relevance for humans. Consequently, further studies on the combination product were not necessary and the combination saxagliptin/metformin has not been tested for carcinogenicity.

Reproduction Toxicity

A complete battery of reproductive and developmental toxicity studies were conducted with saxagliptin as part of the MAA for Onglyza. A similar battery of studies had been performed with metformin. Although metformin was associated with mortality in rabbits, none of the substances were associated with reproductive or developmental toxicity. Effects of saxagliptin and metformin alone and in combination were evaluated in embryo-fetal development studies in rats and rabbits.
Embryo-fetal toxicity studies in rats and rabbits were performed by individual and combined dosing of saxagliptin and metformin. In rabbits, co-administration of saxaliptin and metformin was poorly tolerated by the does, but no teratogenic effects were observed. In rats, craniorachischisis was observed in 2 fetuses from a single litter when saxagliptin and metformin were administered at 25/200 mg/kg/day. One of these fetuses also had a cleft palate. The occurrence of craniorachischisis was considered to be within historical control levels. These findings were not reproduced in a second rat study at saxagliptin/metformin doses of 25/600 mg/kg/day.
As metformin showed no effect on fertility in previous studies, and for saxagliptin effects were only seen at doses far in excess of the recommended human dose, additional studies to assess toxicity of the fixed combination to fertility and early embryonic development, parturition, pre- and postnatal development, or on juvenile animals were deemed unnecessary.
The reproductive/developmental toxicological profile of saxagliptin and metformin were considered sufficiently characterised; studies on fertility and pre- and postnatal development were therefore seen not warranted.

Toxicokinetic data

Toxicokinetics were assessed as part of the three month toxicity study in dogs, and in the embryo-fetal developmental studies in rats and rabbits. Systemic plasma exposures to saxagliptin, its major active metabolite BMS-510849, and metformin were assessed in dogs and pregnant rats and rabbits following

oral administration of saxagliptin in combination with metformin. Validated LC-MS/MS methods were used for determination of plasma levels of saxagliptin, the saxagliptin metabolite BMS-510849, and metformin in dog, rat and rabbit plasma. At steady state, increases in saxagliptin AUC levels were approximately dose proportional in the 1/20 and 5/20 mg/kg/day saxagliptin/metformin combination groups. Exposures to BMS-510849 were approximately 0.9 to 2.24× those of saxagliptin. Exposures to saxagliptin, BMS-510849, and metformin were similar regardless of individual or combination dosing, with no gender-related difference or accumulation.

Exposure levels for metformin in the repeat dose combination study were only ≥ 1.4 times human exposure at maximum recommended human dose. According to the Guideline on the non-clinical development of fixed-combinations of medicinal products, the non-clinical studies should be designed in such a way that the exposure range encompasses the anticipated human clinical situation while avoiding high-dose non-clinical effects that may be irrelevant to human safety assessment. The dose level in the repeat dose study fulfilled this and was therefore considered acceptable.

Local Tolerance

The intended clinical route of administration is oral, and studies of local tolerance have therefore not been performed.

Other toxicity studies

No additional studies have been conducted with the combination.

2.3.5. Ecotoxicity/environmental risk assessment

As this application concerned two known active substances that substitute the use of the separate substances, the use of the substances will not increase and no new ERA is required. The ERA for the separate active substances can be used for this combination.

The risk of adverse environmental impacts from use of saxagliptin has been evaluated in Phase I, Phase II Tier A, and Tier B (on sediment dwelling organisms) environmental risk assessments. Based on the results presented, saxagliptin is not expected to pose a risk to the environment.
A partial ERA has been presented for metformin. Due to PEC surface water > 0.01, a Phase II assessment has been performed. Two of the tests in Phase II (adsorption/desorption test and ready biodegradability) were not performed in accordance with the protocols recommended in the guideline, and three other tests (Aerobic and Anaerobic Transformation Test (OECD 308), the Early Life Stage Toxicity Test in Fish (OECD 210), and the Activated Sludge, Respiration Inhibition Test (OECD 209)) were omitted. Consequently, the ERA for metformin was not in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00). However, based on the submitted data, the applicant argued that no appreciable risk has been identified for metformin, which was acceptable.

2.3.6. Discussion on non-clinical aspects

The MAA concerned two known substances that are already approved as free combination therapy. As such, new non-clinical studies were not required (Guideline on the non-clinical Development of Fixed Combinations of Medicinal Products, EMEA/CHMP/SWP//258498/2005).
The pharmacodynamic properties of saxagliptin and metformin suggest an additive effect when used in combination for treatment of type 2 diabetes. The exact mechanism of action for the anti-hyperglycaemic effects of metformin is not known. However, interaction with saxagliptin is not expected, as indicated by overall different mechanisms of action between saxagliptin and metformin. This was further substantiated by existing clinical experience with the free combination of saxagliptin and metformin, and by other, marketed gliptin/metformin combinations, and therefore pharmacology studies and pharmacodynamic interaction studies with saxagliptin/metformin were not considered as needed.

Based on the known pharmacokinetic properties of saxagliptin and metformin, no adverse pharmacokinetic interactions were expected. The lack of additional pharmacokinetic studies was therefore accepted.

No dedicated safety pharmacology studies were performed with saxagliptin/metformin. However, since the experience of concomitant use of saxagliptin and metformin is limited, a 3-month repeat oral dose toxicity study in dogs has been performed and potential cardiovascular, central nervous and respiratory effects were evaluated. No significant effects were seen following single and repeated doses of saxagliptin, metformin or saxagliptin/metformin. Single incidences of slight tremors were observed in all males administered saxagliptin/metformin at 5/20 mg/kg/day, and in some females administered metformin alone or saxagliptin/metformin. A potential metformin relation could not be excluded. However, due to the mild level of tremors, sporadic occurrence, and extensive clinical experience with the use of metformin, the tremors were not considered clinically relevant.

No additional findings were reported in the combined saxagliptin/metformin dosing groups compared with the saxagliptin or metformin dosing groups, and NOAEL for saxagliptin/metformin in the 3-month toxicity study is ≥ 5/20 mg/kg/day. Exposure levels for metformin in the repeat dose combination study were only ≥ 1.4 times human exposure at maximum recommended human dose. However, according to the Guideline on the non-clinical development of fixed-combinations of medicinal products, the non-clinical studies should be designed in such a way that the exposure range encompasses the anticipated human clinical situation while avoiding high-dose non-clinical effects that may be irrelevant to human safety assessment. The dose level in the repeat dose study is therefore considered acceptable.

The reproductive/developmental toxicological profile of saxagliptin and metformin is considered sufficiently characterised, and studies on fertility and pre- and postnatal development were therefore not required. In support of the fixed dose MAA, effects of saxagliptin and metformin alone and in combination were evaluated in embryo-fetal development studies in rats and rabbits. While no teratogenic effects were observed in rabbits, craniorachischisis was observed in rats, but the occurrence appeard to be within historical control levels, and was not observed in a second rat study. Overall, the reproductive/developmental toxicological profile of saxagliptin and metformin were considered sufficiently characterised; studies on fertility and pre- and postnatal development were therefore seen not warranted.

Based on the results from the submitted ERA, saxagliptin is not considered to pose a risk to the environment. A marketing authorisation for Komboglyze is not expected to cause a significant increase of environmental exposure to metformin, and a formal ERA for metformin was not required.

2.3.7. Conclusion on the non-clinical aspects

The MAA for Komboglyze concerns two known substances that are already approved as free combination therapy. As such, new non-clinical studies were generally not required (Guideline on the non-clinical Development of Fixed Combinations of Medicinal Products, EMEA/CHMP/SWP/258498/2005), and the applicant provided sufficient data to support that view.

2.4. Clinical aspects

2.4.1. Introduction

The applicant has submitted an application in accordance with Directive 2001/83/EC Article 10b for a European Marketing Authorisation for their product, film coated tablets, containing a fixed dose combination (FDC) of saxagliptin and metformin.

Saxagliptin (Onglyza), a dipeptidyl peptidase 4 - (DPP-4) inhibitor, was approved for marketing in EU in October 2009 for the treatment of type 2 diabetes mellitus (T2DM) in combination with metformin, sulfonylurea or thiazolidinedione. The recommended dose is 5 mg once daily.

Metformin is a biguanide and the most commonly used first-line agent in patients with T2DM worldwide.

Metformin is approved in adults as monotherapy and in combination with other anti-diabetic agents or insulin, and in children and adolescents from 10 years of age as monotherapy or in combination with insulin.

Most of the studies presented in the dossier had been already submitted and evaluated in the previous MAA, which lead to the approval of Onglyza (saxagliptin), which is approved for the combined use of saxagliptin with metformin.
The dossier submitted initially did not provide a sufficient comparison between 2 x 2.5 mg dosing and 1 x 5 mg dosing of saxagliptin. Therefore, following a Major Objection raised by the CHMP in the day 120 list of questions, the applicant has conducted Study CV181152, a pharmacokinetic (PK)/pharmacodynamic (PD) study, in response to the request, which was then submitted and evaluated during the procedure.
A BE study has been conducted with the EU metformin formulation for 2.5/850 mg.

Children were not included in the clinical studies. A paediatric investigation plan, including a product specific waiver, was granted 1 December 2009 (EMEA-000644-PIP01-09).

The most relevant guidelines for this application are:

- Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus (CPMP/EWP/1080/00)
- Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus (CPMP/EWP/1080/00 Rev. 1) (draft guideline)
- Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr *)
- Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP//240/95 Rev. 1)

No formal CHMP Scientific Advice was given specifically for this fixed combination product.

The clinical development program included data from 7 phase 3 studies. A total of 4326 subjects were randomised and treated, including 2158 receiving saxagliptin plus metformin. Data included in this submission reflect up to 102 weeks total duration of treatment.

Table 1: overview of Phase 3 studies included in this application

Study No.	Study objectives	Randomised and treated All/Saxa	Duration	Saxagliptin (mg) dose
Saxagliptin + Metformin				
CV181014	Safety and efficacy (A1C 7%-10%)	743/564	24 weeks (206 weeks)	2.5, 5, or 10 QD (+metformin)
Saxagliptin + Metformin Initial Combination				
CV181039	Safety and efficacy (A1C 8%-12%)	1306/978	24 weeks (76 weeks)	5 or 10 QD (+metformin) or 10 mg QD
Saxagliptin + Metformin versus Glipizide + metformin				
CV181054 (D1680C00001)	Safety and efficacy (A1C 6.5%-10%)	838 / 419	52 weeks (104 weeks)	5 mg (+ metformin IR)
Saxagliptin + Metformin vs Sitagliptin + Met				
CV181056 (D1680C00002)	Safety and efficacy (A1C 6.5%-10%)	710 / 355	18 weeks	5 mg (+ metformin IR)
Saxagliptin 2.5 mg BID + Metformin vs placebo + metformin				
CV181080	Safety and efficacy (A1C 7%-10%)	160/74	12 weeks	2x2.5 mg (+ metformin IR)
Saxagliptin + Metformin XR (PM dosing)				
CV181066	Safety and efficacy (A1C 7%-10%)	93/46	4 weeks	5 mg (+ metformin XR)
Saxagliptin Monotherapy (with PM dosing arm)				
CV181038	Safety and efficacy (A1C 7%-10%)	365/291	24 weeks (52 weeks)	2.5 QAM, 5QAM, 2.5/5 QAM, 5 QPM, all titratable to 10 mg

The 7 main studies are summarized at the end of the efficacy section.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.
The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Saxagliptin/metformin FDC IR tablets have been developed at dose strengths of 2.5 mg saxagliptin/850 mg metformin, and 2.5 mg saxagliptin/1000 mg metformin.
The FDC tablet is formulated by coating a metformin core tablet with saxagliptin and uses similar coating technology as the commercial saxagliptin tablet (ONGLYZA), with the exception that for the FDC, the saxagliptin coating layers are applied to a metformin core, rather than onto an inert core.
The application contained initially six clinical PK studies, with a total of 118 healthy adult subjects receiving saxagliptin, 72 of those receiving the combination of saxagliptin and metformin. One study is a PK and PD study with saxagliptin BID, three studies are bioequivalence studies with saxagliptin and metformin, and two studies are drug-drug-interaction studies with saxagliptin. No study compared the previously approved posology of 5 mg QD with the applied posology of 2.5 mg BID. Thus a direct comparison between these doses was not possible and a new study comparing saxagliptin 5 mg QD to 2.5 mg BID was requested druing the procedure as part of the day 120 list of questions.

Bioquivalence between the fixed-dose saxagliptin/metformin combination formulation and the dosing of saxagliptin and metformin with separate tablets was found under both fasted and fed states. Peak and total exposures for saxagliptin and metformin were similar in three studies with different metformin doses. However, only in one study (CV181121 with 850 mg metformin) the metformin tablet was EU-sourced (Glucophage®). The 500 mg and 1000 mg metformin tablets, used in the two other studies, were US-marketed and these studies are therefore of less significance.

Therefore, study CV181121 was considered pivotal, as it compared the rate and extent of absorption of both saxagliptin and metformin administered as the individual tablets (2.5 mg saxagliptin and 850 mg metformin [EU-sourced]) to the 2.5 mg saxagliptin/850 mg metformin FDC under fed and fasting conditions.
In accordance with guidance from the Committee for Medicinal Products for Human Use (see CHMP Guidance on the Investigation of Bioequivalence 2010), a waiver for demonstrating in vivo bioequivalence of the 2.5 mg saxagliptin/1000 mg metformin strength FDC compared with 2.5 mg saxagliptin plus 1000 mg EU-sourced metformin is based on:

- Demonstration of bioequivalence of the 2.5 mg saxagliptin/850 mg metformin FDC tablet (study CV181121) to co-administered 2.5 mg saxagliptin and EU-sourced 850 mg metformin
- Formulation composition proportionality of the 2.5 mg saxagliptin/1000 mg metformin FDC to the 2.5 mg saxagliptin/850 mg metformin FDC, on which bioequivalence testing was undertaken
- Similar in vitro dissolution profiles with regard to both saxagliptin and metformin for the 2.5 mg saxagliptin/850 mg metformin FDC and 2.5 mg saxagliptin/1000 mg metformin FDC tablets

Based on these results and assessments, the Applicant was requesting a waiver for demonstrating in vivo bioequivalence of the 2.5 mg saxagliptin/1000 mg metformin FDC versus 2.5 mg saxagliptin plus EU-sourced 1000 mg metformin. Since metformin has a non-linear saturation kinetics due to saturable intestinal absorption and the test and reference products do not contain any excipients that may affect gastrointestinal motility or transport proteins, it is sufficient to demonstrate bioequivalence at the lowest strength. Therefore, this approach for a biowaiver for the 2.5 mg saxagliptin/1000 mg metformin strength FDC compared with 2.5 mg saxagliptin plus 1000 mg EU-sourced metformin was acceptable.

The analytical methods were validated and are adequate for accurate analysis of saxagliptin and metformin in human plasma. The bioanalytical and validation reports were submitted.

Bioequivalence study CV181121 showed that the criteria for bioequivalence of saxagliptin and metformin from the 2.5 mg saxagliptin/850 mg metformin FDC compared to co-administered 2.5 mg saxagliptin and 850 mg EU-sourced metformin under both fed and fasted conditions were met for C_{max}, AUC(INF) and AUC(0-T). The 90% confidence intervals for the point estimates of C_{max}, AUC(INF), and AUC(0-T), were within the acceptance criteria of 0.8 to 1.25 to conclude bioequivalence under fasted and fed conditions. The CV found in the bioequivalence study was moderate with a CV for saxagliptin and metformin C_{max} and AUC being between 18 and 24%.

Influence of food

Food causes a slightly increased T_{max} (4 hours instead 3 hours) of metformin in the FDC tablet. Additionally, the AUC decreases with approximately 4% and the C_{max} with 11%. This is in accordance with the results obtained with the separate metformin tablets, SPC of Glucophage, and literature reports, where even higher numbers of 25% and 40%, respectively are reported. This food interaction is of low clinical significance as metformin should be given concomitantly or just after a meal to prevent gastro-intestinal side effects. The new combination tablet is also to be given in combination with a meal according to the SPC.

Comparison of the 5 mg once daily with the twice daily 2.5 mg saxagliptin treatment

The steady-state pharmacokinetics of saxagliptin and BMS-510849 following BID administration of saxagliptin were investigated in an open label study in healthy subjects (CV181091). The pharmacokinetic data were compared with study CV181034, in which a single 10 mg dose of saxagliptin was administered with a high-fat breakfast (CV181034).

The total daily exposure to saxagliptin and BMS-510849, as expressed by dose-normalized AUC, during administration of saxagliptin 2.5 mg BID for 7 days with meals, were approximately similar to that achieved when saxagliptin 5 mg was given as a single dose with a meal. Also, as would be expected, when extrapolation is made to the C_{max} value following the 5 mg dose the C_{max} will be approximately twice as high as the C_{max} value following the 2.5 mg dose (see table below).

Table 2 Dose-normalized Pharmacokinetics of Saxagliptin and BMS-510849 Following Administration of a Single Saxagliptin Dose or Saxagliptin BID for 7 Days With Food in Studies CV181091 and CV181034

Pharmacokinetic Parameter	CV181091[a] (2.5 mg saxagliptin BID with meals; n=12)		CV181034[b] (Day 1; 10 mg saxagliptin with a high fat breakfast; n=14)
	First Dose (with breakfast)	Second Dose (with dinner)	
Saxagliptin			
Cmax per 2.5 mg saxagliptin (ng/mL) Geo mean (%CV)	13.44 (25)	11.73 (28)	12.49 (26)
Tmax (h) Median (Min, Max)	1.50 (1.00-3.03)	1.26 (1.00-5.00)	0.99 (0.50, 4.00)
AUC per 5 mg saxagliptin (ng·h/mL) Geo mean (%CV)	109.35 (19)		95.34 (26)
BMS-510849			
Cmax per 2.5 mg saxagliptin (ng/mL) Geo mean (%CV)	26.18 (29)	19.81 (22)	22.06 (37)
Tmax (h) Median (Min, Max)	2.00 (1.50-3.03)	2.01 (1.50-5.00)	1.98 (1.47, 4.00)
AUC per 5 mg saxagliptin (ng·h/mL) Geo mean (%CV)	260.64 (20)		251.54 (26)

Notes:
[a]For study CV181091, AUC is the sum of AUC(TAU) values of the first and second doses on Day 7
[b]For study CV181034 Cmax and AUC(INF) were dose-normalized for 2.5 mg and 5 mg, respectively
Source: Tables 9.2 and 9.3 of the CV181091 CSR and Tables 11.2.1A and 11.2.2A of the CV181034 CSR

Results from these two studies were chosen for pharmacokinetic comparisons between once and twice daily administration because saxagliptin was administered as a tablet with food in both studies. The applicant gave several reasons to indicate validity of this comparison.
The Applicant has conducted one additional the PK/PD study **CV181152** comparing saxagliptin 2.5 mg BID with 5 mg QD. The Applicant had submitted initially an intermediate analysis of this PK/PD study but a final report was provided during the procedure and was found to be satisfactory. Results of the study indicate the bioequivalence of daily exposures of saxagliptin 2.5 mg BID and 5 mg QD. Geometric mean C_{max} values following the AM and PM doses of the 2.5 mg BID treatment were, as expected, approximately half of those observed in the 5 mg QD treatment. The CHMP agreed that the lower C_{max} is of no clinical concern, as the total exposure (AUC) of saxagliptin for the 2 regimens were bioequivalent. Furthermore, PD effects of the 2 regimens met the well-established standard for concluding bioequivalence (see also pharmacodynamic and clinical sections below).

Table 3: Summary Statistics of Saxagliptin Pharmacokinetic Parameters on Day 7 and Results of Bioequivalence Testing

Parameter	Statistics	Treatment A (5 mg QD) (N=16)	Treatment B (2.5 mg BID) AM (N=16)	Treatment B (2.5 mg BID) PM (N=16)
C max (ng/mL)	Geo. Mean (CV%)	24.01 (22.54%)	12.75 (21.80%)	10.87 (34.33%)
T max (h)	Median (Range)	1.50 (0.53-2.00)	1.78 (0.50-3.00)	2.00 (1.00-5.00)
AUC(TAU) (ng•h /mL)	Geo. Mean (CV%)	99.27 (15.15%)	51.10 (13.83%)	52.17 (15.72%)
AUC(0-24h) (ng•h /mL)	Geo. Mean (CV%)	99.27 (15.15%)	103.32 (14.45%)	
	Ratio (%) (Treatment B/A) of geometric LS Mean for AUC(0-24 h)	104.08%		
	(90% CI)	(101.03-107.22%)		

Abbreviations: CV = coefficient of variation, Geo. Mean = geometric mean from summary statistics, CI = confidence interval

As an interaction study between saxagliptin and metformin (see CV181017 CSR) with the orginal MAA for Onglyza has shown no clinically meaningful effect of saxagliptin on metformin PK and vice versa, no

additional studies were needed with that regard for the subsequent section on pharmacokinetics with the fixed dose combination product beyond the data available for the individual components.

Absorption

No absolute bioavailability clinical studies were conducted for the saxagliptin/metformin IR development program.

Saxagliptin is rapidly absorbed after oral administration in the fasted state, with maximum plasma concentrations (C_{max}) of saxagliptin and its major metabolite attained within 2 and 4 hours (T_{max}), respectively.
Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with food (a high-fat meal) resulted in no change in saxagliptin C_{max} and a 27% increase in AUC compared with the fasted state. These changes were not considered to be clinically meaningful.
Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution

No additional studies were conducted for the saxagliptin/metformin IR development program.

The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is negligible. Thus, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

Elimination

No additional studies were conducted for the saxagliptin/metformin IR development program.

The biotransformation of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin.
The mean plasma terminal half-life ($t_{1/2}$) values for saxagliptin and its major metabolite are 2.5 hours and 3.1 hours respectively, and the mean $t_{1/2}$ value for plasma DPP-4 inhibition was 26.9 hours. Saxagliptin is eliminated by both renal and hepatic pathways.

Dose proportionality and time dependencies

No specific PK study was conducted with regard to dose proportionality and time dependency with the saxagliptin/metformin FDC tablet. In general this is acceptable for this kind of application.

Special populations

No additional studies were conducted for the saxagliptin/metformin IR development program.

Renal impairment
In subjects with mild (> 50 to ≤ 80 ml/min), moderate (≥ 30 to ≤ 50 ml/min), or severe (19-30 ml/min) renal impairment the exposures to saxagliptin were 1.2-, 1.4- and 2.1-fold higher, respectively, and the exposures to BMS-510849 were 1.7-, 2.9-, and 4.5-fold higher, respectively, than those observed in subjects with normal renal function (> 80 ml/min). However, Komboglyze is contraindicated in moderate and severe renal impairment (creatinine clearance < 60 ml/min) in any case due to the metformin component (see section 4.4 of the SPC)

Hepatic impairment

In subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment the exposures to saxagliptin were 1.1-, 1.4- and 1.8-fold higher, respectively, and the exposures to BMS-510849 were 22%, 7%, and 33% lower, respectively, than those observed in healthy subjects. Komboglyze is contraindicated in hepatic impairment (see section 4.4 of the SPC)

Elderly patients (≥ 65 years)
Elderly patients (65-80 years) had about 60% higher saxagliptin AUC than young patients (18-40 years). This was not considered clinically meaningful, therefore, in the SPC no dose adjustment for Komboglyze is recommended on the basis of age alone.

Pharmacokinetic interaction studies

As reported in the original saxagliptin registration dossier, a 2-way drug-drug interaction study between saxagliptin and metformin (see CV181017 CSR) has shown no clinically meaningful effect of saxagliptin on metformin PK and vice versa.

No additional studies were conducted for the saxagliptin/metformin IR development program for this application

Saxagliptin exerted no relevant effect on the pharmacokinetics of the estrogenic and progestational components of a combined oral contraceptive. When saxagliptin was co-administered with rifampicin, the geometric mean Cmax and AUC(INF) values for saxagliptin were 53% and 76% lower, respectively, compared to when saxagliptin was administered alone, and the corresponding values for BMS-510849 were 39% and 3% higher, respectively. These findings are consistent with the *in vivo* induction of CYP3A- mediated metabolism of saxagliptin by rifampicin.

Studies examining metformin only were not conducted as part of the saxagliptin/metformin IR development program because metformin IR has been extensively characterized already, and is a widely approved and established agent for treating Type 2 diabetes.

This approach was found to be acceptable for this kind of application by CHMP.

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

The product combines two antihyperglycaemic products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: saxagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.
The mechanism of action of saxagliptin was summarised in the original saxagliptin submission. The results demonstrated plasma DPP4 activity inhibition in support of a 5 mg once daily dose.

Primary and Secondary pharmacology

Saxagliptin is a highly potent, selective, reversible, competitive, DPP-4 inhibitor. In patients with type 2 diabetes, administration of saxagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load, this DPP-4 inhibition resulted in a 2-to 3-fold increase in circulating levels of active incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), decreased glucagon concentrations and increased glucose-dependent beta-cell responsiveness, which resulted in higher insulin and C-peptide concentrations. The rise in insulin from pancreatic beta-cells and the decrease in glucagon from pancreatic alpha-cells were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. Saxagliptin improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes.

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. The mechanism of action is unknown, but the following mechanisms have been suggested: reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis in muscle; modestly increasing insulin sensitivity, improving peripheral glucose uptake and utlisation; delaying intestinal glucose absorption. Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Pharmacodynamic studies

In support of the BID dosing of saxagliptin 2.5 mg originally one study was submitted (CV181091). This was an open-label, non-randomized, single-sequence study in 12 healthy subjects. Subjects received 2.5 mg saxagliptin with breakfast and dinner for 7 days. The main pharmacodynamic variables measured were plasma DPP-4 activity and post-prandial GLP-1 plasma concentrations.

Plasma DPP-4 inhibition

In Study CV181091 following twice daily administration of 2.5-mg saxagliptin with meals for 7 days, the plasma DPP-4 activity was almost completely inhibited as compared to the baseline DPP-4 activity (Day -1).

Plasma DPP-4 inhibition and PD parameters on Day 7 are summarized by morning (with breakfast) and evening (with dinner) doses in the Table 4.

Pharmacodynamic steady-state is achieved after 7 days of BID dosing of saxagliptin. Trough DPP-4 inhibition is similar (~80% inhibited from baseline) from each dose on Day 7. As compared to baseline values, plasma DPP-4 activity is almost completely inhibited after BID (morning and evening) dosing with 2.5-mg saxagliptin with meals. On Day 7, the mean peak DPP-4 inhibition from baseline was > 85% after the morning and evening doses.

Table 4: Summary Statistics for Plasma DPP-4 Inhibition Pharmacodynamic Parameters Study181091

Treatment	Imax (% inhibited) Geo. Mean [N] (%CV)	AUEC(TAU) (% inhibited.h) Geo. Mean [N] (%CV)	AUEC(0-24 h) (% inhibited.h) Geo. Mean [N] (%CV)	Tmax(DPP) (h) Median [N] (Min-Max)	Trough DPP-4 (% inhibited) Geo. Mean [N] (%CV)
Day 7 1st Dose (with breakfast)	87.20 [12]	889.49 [12]	NA	1.75 [12]	79.83 [12]
	(5)	(4)	NA	(0.00-8.00)	(6)
Day 7 2nd Dose (with dinner)	86.19 [12]	992.32 [12]	1882.19 [12]	3.00 [12]	80.44 [12]
	(1)	(3)	(3)	(0.00-5.00)	(6)

Note: Trough DPP-4 is % DPP-4 inhibition with respect to baseline value on Day -1 in the last plasma sample collected on Day 7 following first dose (with breakfast) and second dose (with dinner)

Abbreviations: CV = coefficient of variation, Geo. Mean = geometric mean from summary statistics, h = hours, NA = not applicable

Plasma GLP-1 Activity

In Study CV181091 compared with Day -1, the geometric means AUC(0-3 h) for plasma GLP-1 were 2.44-, 2.17- and 3.13-fold higher on Day 7 for breakfast, lunch and dinner, respectively. Plasma GLP-1 PD parameters are summarized by meal and study day in the **Table 5**. Results indicate that the DPP-4 inhibitory effects of 2.5-mg saxagliptin when given BID result in an increase in post-prandial plasma GLP-1 concentrations.

Table 5: Summary Statistics for Plasma iGLP-1 Pharmacodynamic Parameters Following BID Administration of Saxagliptin with Breakfast and Dinner Study181091

Meal	Study Day	Cmax (pM) Geo. Mean [N] (%CV)	AUC(0-3h) (pM.h) Geo. Mean [N] (%CV)	Tmax (h) Median [N] (min-max)
Breakfast	Day -1 (without saxagliptin)	8.17 [12] (74)	10.19 [12] (66)	0.26 [12] (0.25-2.00)
	Day 7 (with saxagliptin)	17.13 [12] (86)	24.84 [12] (120)	0.33 [12] (0.25-2.00)
Lunch	Day -1 (without saxagliptin)	9.01 [12] (98)	13.07 [12] (60)	0.42 [12] (0.25-2.00)
	Day 7 (with saxagliptin)	22.55 [12] (67)	28.33 [12] (50)	0.31 [12] (0.25-0.42)
Dinner	Day -1 (without saxagliptin)	11.11 [12] (72)	14.19 [12] (66)	0.42 [12] (0.25-0.53)
	Day 7 (with saxagliptin)	25.44 [12] (49)	44.38 [12] (46)	0.42 [12] (0.25-3.02)

Comparison of saxagliptin PD following a single 5 mg dose of saxagliptin (Study CV181059) versus 2.5 mg saxagliptin BID (Study CV181091).

The cross study comparison was made with data of the **CV181059** study that has been submitted during the Onglyza (saxagliptin) MAA review. In this study one of the secondary objectives was to assess the safety and tolerability of a single 5 mg dose of saxagliptin in the presence and absence of rifampin in healthy subjects. The data obtained in the absence of rifampin are used in table 6 for comparison with 2.5 mg saxagliptin BID dosing for 7 days. Plasma DPP4 was inhibited when saxagliptin was administered as a single 5 mg dose or 2.5 mg BID for 7 days. Similar Imax and AUEC(0-24 h) values were observed when saxagliptin was administered as a single 5 mg dose or 2.5 mg BID for 7 days.

Table 6: Comparison of plasma DPP4 inhibition PD parameters of saxagliptin when administered as a single dose versus BID for 7 days in studies CV181091 and CV181059

Pharmacodynamic Parameter	CV181091[a] 2.5 mg saxagliptin BID; Day 7; (n=12)		CV181059[b] A single 5 mg saxagliptin Dose; (n=13)
	First Dose (with breakfast)	Second Dose (with dinner)	(fasted)
Imax (% inhibited) Mean (SD)	87.32 (4.7)	86.20 (1.2)	83.07 (3.5)
Tmax(DPP) (h) Median (Min, Max)	1.75(0.00-8.00)	3.00 (0.00-5.00)	2.00 (1.00, 8.00)
AUEC(0-24 h)[c] Mean (SD)	1883.08 (61)		1711.61 (72)

[a] For Study CV181091, AUEC(0-24 h) is the sum of AUEC(TAU) values of the first and second doses on Day 7.
[b] For Study CV181059, AUEC(0-24 h) is the AUEC over a 24 h period on Day 1.
[c] AUEC(0-24)= % inhibited/hour.

Pharmacodynamic results from the new study CV181152:

DPP4 inhibition:

Summary statistics of PD parameters of DPP4 percentage inhibition on Day 7 following 2.5 mg BID and 5 mg QD dosing of saxagliptin are presented in table 7.

On Day 7, following multiple dosing of saxagliptin, geometric mean Imax values of DPP4 inhibition were 82.00%, 82.03% and 81.36% following the 5 mg QD, 2.5 mg BID AM and PM doses, respectively, indicating that the plasma DPP4 activity was almost completely inhibited regardless of whether a 2.5 mg BID or 5 mg QD dose was administered. Thus, despite the fact that plasma saxagliptin Cmax after administration of 2.5 mg BID was approximately half that of 5 mg QD dosing, the Imax of DPP4 activity was similar between these 2 dosing regimens. The DPP4 inhibition following 2.5 mg BID dosing of saxagliptin is equivalent to the 5 mg saxagliptin QD dosing.

Table 7: Summary Statistics of DPP4 Percentage Inhibition Following 5 mg QD and 2.5 mg BID Dosing of Saxagliptin on Day 7 Study CV181152

Parameter	Statistics	Treatment A (5 mg QD) (N=16)	Treatment B (2.5 mg BID) AM (N=16)	Treatment B (2.5 mg BID) PM (N=16)	Ratio (%) (Treatment A/ B-AM) of geometric LS Mean for I_{max} (90% CI)
I_{max} (%inhibited)	Geo. Mean	82.00	82.03	81.36	100.03
	(CV%)	(1.92)	(3.11)	(2.69)	(98.65-101.43)
T_{max} (h)	Median	2.00	2.00	3.00	
	(Range)	(1.50-5.00)	(0.25-5.00)	(1.00-12.00)	
Trough (%inhibited)	Geo. Mean	62.05	72.66	75.07	
	(CV%)	(6.15)	(5.78)	(5.16)	
AUEC(TAU) (% inhibited•h)	Geo. Mean	1740.00	906.83	930.89	
	(CV%)	(6.04)	(6.08)	(3.31)	
AUEC(0-24h) (%inhibited•h)	Geo. Mean	1740.00	1838.45		
	(CV%)	(6.04)	(4.02)		
	Ratio (%) (Treatment B/A) of geometric LS Mean for AUC(0-24 h)	105.66			
	(90% CI)	(102.23-109.20)			

Abbreviations: CV = coefficient of variation, Geo. Mean = geometric mean from summary statistics, CI = confidence interval

iGLP-1 activity:
The baseline iGLP-1 activity [Cmax and AUEC(0-3h)] on Day -1 was similar between saxagliptin regimen of 2.5 mg BID and 5 mg QD; as expected, large inter-subject variation was observed. The iGLP-1 activity elevation by multiple-dose administration of saxagliptin 5 mg QD is equivalent to multiple-dose administration of saxagliptin 2.5 mg BID.

Discussion on pharmacodynamics
The applicant has demonstrated in the new Study CV181152, comparing saxagliptin 5 mg QD with 2.5 mg BID that saxagliptin 2.5 mg BID is equivalent to saxagliptin 5 mg QD in terms of PD.

Conclusions on pharmacodynamics
Therefore study CV181152 established that the fixed dose combination (FDC) of 2.5 mg saxagliptin and metformin BID can be used in patients who are already treated with the combination of 5 mg saxagliptin OD and metformin as separate components (**switch indication**).

2.4.4. Discussion on clinical pharmacology

In Study CV181091 the pharmacodynamics of 2.5-mg saxagliptin administered BID with meals was assessed by determining plasma DPP-4 activity and plasma concentrations of its substrate, GLP-1. Saxagliptin 2.5 mg twice daily resulted in trough DPP-4 inhibition of 80%. However, in this study no direct comparison was made with 5 mg saxagliptin administered once daily. The applicant argued that in the literature for other DPP-4 inhibitors, non-clinical studies have shown that DPP-4 inhibition of 80% or more was related to maximum effects in incretin response and glucose reduction (Roy RS et al. Diabetes 2009; 58(6) (Suppl), Abstr 2373-PO; Krishna R et al. AAPS J 2008; 10(2): 401-409), but this was based on experimental data and a direct comparison with as single 5 mg dose would have been preferred. Consequently, the applicant carried out a comparison with previously obtained data of **CV181059**. From this comparison it can be concluded that, when saxagliptin 2.5 mg is administered BID, this twice daily regimen of saxagliptin will achieve the same daily level of plasma DDP4 inhibition as the already approved once daily treatment of 5 mg. However, this comparison was made between day 1 of the 5 mg dose and day 7 of the 2x2.5mg dose. On day 1 of the 5 mg dose, steady-state has not yet been reached. In the original MAA and with this application, no data were included of multiple doses of 5 mg in healthy volunteers.
Therefore, as requested a new pharmacokinetic/pharmacodynamic study CV181152 comparing saxagliptin 5 mg QD with 2.5 mg BID was performed by the applicant. From the data provided in study CV181152 it could be concluded that the inhibition of DPP4 by saxagliptin after 2.5 mg BID regimen is equivalent to that by the 5 mg QD regimen. The increase in iGLP-1 activity by saxagliptin 2.5 mg BID was equivalent to the 5 mg QD regimen. There was a difference in saxagliptin plasma C_{max} values between the two dosing regimens. Nevertheless the effects of 2.5 mg BID and 5 mg QD on DPP4 and iGLP-1 activity were comparable. This is consistent with the conclusion that saxagliptin C_{max}, within this dose range, is less important for its activity. For pharmacokinetics, see separate section.

2.4.5. Conclusions on clinical pharmacology

The applicant has demonstrated in the new Study CV181152, comparing saxagliptin 5 mg QD with 2.5 mg BID that saxagliptin 2.5 mg BID is equivalent to saxagliptin 5 mg QD in terms of PD. Therefore the fixed dose combination (FDC) of 2.5 mg saxagliptin and metformin BID was found to be appropriate to be used in patients who are already treated with the combination of 5 mg saxagliptin OD and metformin as separate components (**switch indication**).

2.5. Clinical efficacy

2.5.1. Dose response studies

No new dose-response studies were submitted

Dose selection for the two components in the FDC was based upon results from several studies.
The previously submitted study **CV181014**, which was assessed in the original Onglyza MAA, specifically investigated different doses (2.5 mg, 5 mg and 10 mg) of saxagliptin when used as add-on to metformin. The 5 mg dose was concluded to provide the optimal benefit-risk ratio. This recommended daily dose is administered once daily, with or without food. However, the commonly used daily dose for metformin IR is 500 to 2000 mg administered with food in up to 3 divided doses. Therefore, the efficacy of saxagliptin 2.5 mg administered twice daily (morning and evening) was investigated to support the applied FDC product. Study **CV181038**, also assessed in the original Onglyza MAA, indicated that evening administration of saxagliptin (as monotherapy) is as effective as morning dosing in improving glycaemic control. In the pivotal **CV181080** study for the current application saxagliptin was administered twice daily as add-on to metformin IR just prior to the morning and evening meals.

Table 8: overview of Phase 3 studies included in this application

Study No.	Study objectives	Randomised and treated All/Saxa	Duration	Saxagliptin (mg) dose
Saxagliptin + Metformin				
CV181014	Safety and efficacy (A1C 7%-10%)	743/564	24 weeks (206 weeks)	2.5, 5, or 10 QD (+metformin)
Saxagliptin + Metformin Initial Combination				
CV181039	Safety and efficacy (A1C 8%-12%)	1306/978	24 weeks (76 weeks)	5 or 10 QD (+metformin) or 10 mg QD
Saxagliptin + Metformin versus Glipizide + metformin				
CV181054 (D1680C00001)	Safety and efficacy (A1C 6.5%-10%)	838 / 419	52 weeks (104 weeks)	5 mg (+ metformin IR)
Saxagliptin + Metformin vs Sitagliptin + Met				
CV181056 (D1680C00002)	Safety and efficacy (A1C 6.5%-10%)	710 / 355	18 weeks	5 mg (+ metformin IR)
Saxagliptin 2.5 mg BID + Metformin vs placebo + metformin				
CV181080	Safety and efficacy (A1C 7%-10%)	160/74	12 weeks	2x2.5 mg (+ metformin IR)
Saxagliptin + Metformin XR (PM dosing)				
CV181066	Safety and efficacy (A1C 7%-10%)	93/46	4 weeks	5 mg (+ metformin XR)
Saxagliptin Monotherapy (with PM dosing arm)				
CV181038	Safety and efficacy (A1C 7%-10%)	365/291	24 weeks (52 weeks)	2.5 QAM, 5QAM, 2.5/5 QAM, 5 QPM, all titratable to 10 mg

The efficacy results of all 7 main studies are summarized at the end of the efficacy section.

2.5.2. Main studies

In support of this FDC application seven studies have been submitted (see table 8). Five of these have been submitted during the MAA of Onglyza or thereafter, and have already been assessed. Key aspects of these studies are described below. Two studies (CV181080 and CV181066) are new. The metformin XR formulation used in study CV181066 is not approved in European countries. Therefore, this study is not taken into account in this report. Study CV181080 however is considered a pivotal study of this application and is therefore described in detail in the subsequent section.

Table 9 shows the baseline characteristics of the study population included in the phase 3 studies.

	CV181014 (N=743)	CV181039 (N=1306)	D1680C00001 (N=858)	D1680C00002 (N=801)	CV181080 (N=160)	CV181066 (N=93)	CV181038 (N=365)
Mean age (yr) (SD)	54.57 (9.98)	51.99 (10.73)	57.55 (10.31)	58.42 (10.32)	55.4 (10.20)	55.14 (9.14)	54.98 (10.31)
Age ≥65 (%)	15.7	12.7	25.5	28.8	17.5	16.1	17.5
Male (%)	51	49	52	49	53	53	46
Race (%):							
White	81.6	76.2	83.2	66.4	90.0	88.2	69.6
Black	5.4	1.8	0.1	7.4	6.9	5.4	6.6
Asian	2.7	16.3	16.1	9.2	2.5	3.2	23.3
Other	10.4	5.7	0.6	16.9	0.6	3.2	0.5
Mean weight (kg) (SD)	87.04 (17.79)	82.60 (16.89)	88.65 (19.12)	85.55 (17.83)	93.64 (20.63)	88.18 (16.61)	84.89 (17.70)
Mean baseline BMI (kg/m^2) (SD)	31.4 (4.85)	30.18 (4.81)	31.42 (5.94)	30.97 (5.41)	33.05 (6.08)	31.36 (4.25)	30.54 (4.95)
Region (%):							
North America	55.5	16.5	0	0	65.6	47.3	44.7
Latin America	42.7	28.3	0	31.6	11.3	31.2	0
Europe	0	39.4	84.7	51.1	23.1	19.4	34.0
Asia/Pacific	1.9	15.8	15.3	0	0	2.2	21.4
South Africa	0	0	0	17.4	0	0	0
Mean duration of T2DM (yr) (SD)	6.5 (5.1)	1.7 (3.1)	5.4 (4.6)	6.3 (4.9)	6.0 (5.3)	6.9 (5.6)	1.7 (3.2)
Previous T2DM treatment	Metformin	None	Metformin	Metformin	Metformin	Metformin	None
Mean baseline HbA1c (%) (SD)	8.0 (0.9)	9.5 (1.3)	7.7 (0.9)	7.7 (0.9)	8.0 (0.9)	8.1 (0.8)	7.9 (0.9)
Mean baseline FPG (mg/dL) (SD)	175.9 (46.4)	200.6 (57.4)	161.7 (40.2)	160.2 (44.5)	163.1 (44.2)	155.6 (34.5)	162.0 (42.7)

Source: Tables 5.3.1 and 5.3.2 in ST + LT interim CSR CV181014 and ST CSRs CV181039 and CV181038, and CSRs CV181080 and CV181066, Tables 13 and 15 in ST CSR D1680C00001, and Tables 9 and 10 in CSR D1680C00002.
BMI Body mass index; FPG Fasting plasma glucose; HbA1c Glycosylated hemoglobin; IR Immediate release; SD Standard deviation; T2DM Type 2 diabetes mellitus; XR Extended release

Study CV181014

This was a multicenter, randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of saxagliptin in combination with metformin in subjects with T2DM, who had inadequate glycaemic control on metformin alone.

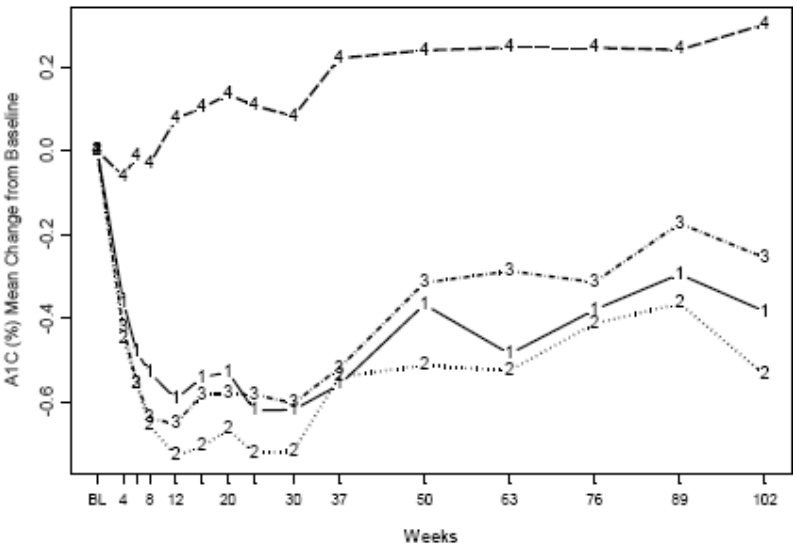
Subjects in this 24-week 4 treatment arm trial received saxagliptin 2.5 mg, saxagliptin 5 mg, saxagliptin 10 mg, or placebo in addition to open-label metformin (1500 mg to 2550 mg)
Those who met glycaemic rescue criteria during the short-term period (24 weeks) entered the long-term period, where they received OL pioglitazone (15-45 mg) in addition to blinded study medication and OL metformin. Completers of the short-term period, who did not need rescue, entered the long-term period and continued on the same treatment as in the short-term period.

This study was submitted and assessed in the original saxagliptin MAA. Results up to 24 weeks were assessed. At week 24, saxagliptin plus metformin led to a placebo-corrected HbA1c decrease for 2.5 mg, 5 mg and 10 mg saxagliptin of -0.73% (95%CI -0.92, -0.53), -0.83% (-1.02, -0.63), and -0.72% (-0.91, -0.52), respectively. Results from this study were published last year (DeFronzo et al., Diabetes Care 2009;32:1649-1655).

Data from the long-term extension (102 weeks) were assessed in variation EMEA/H/C/001039/II/07 for Onglyza. At Week 102, the difference in the adjusted mean (95% CI) change from baseline compared to placebo in HbA1c was -0.69% (-1.02, -0.35), -0.84% (-1.18, -0.49), and -0.56% (-0.90, -0.22) for the saxagliptin 2.5 mg, 5 mg and 10 mg treatment groups, respectively. Based on these results, the CHMP concluded that the treatment effect was sustained up to week 102. The MAH was, however, requested to state in the SmPC that only a very limited number of patients completed the long-term extension period.

Measured HbA1c values during the 102 weeks treatment period are presented in the figure below and might indicate a diminution of the treatment effect over time.

Figure 1: HbA1c Mean Changes from Baseline During ST + LT Treatment Period



1 = Saxa 2.5mg+Met, 2 = Saxa 5.0mg+Met, 3 = Saxa 10.0mg+Met, 4 = Placebo+Met
Source: Figure 7.2A of Final ST + LT CSR CV181014. Data set: Randomized Subjects

The 182-week LT extension was still ongoing at the writing of this report. Results up to 154 weeks were evaluated in EMEA/H/C/001039/FUM 011. The CHMP concluded that efficacy of saxagliptin in long term is attenuated. Whether this is due to reduction in efficacy or to disease progression can not be derived from the submitted data. Conclusions are hampered by the fact that there were only small numbers of subjects who continued in the study after 102 weeks.

Study CV181038

This study was a multicenter, randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of saxagliptin as monotherapy with titration in subjects with T2DM who had inadequate glycaemic control with diet and exercise.

Subjects were randomised to four treatment groups: two groups received fixed doses of saxagliptin 2.5 mg or 5 mg QAM; one group received saxagliptin 2.5 mg QAM, with the possibility of an uptitration to 5 mg; and one group received a fixed dose of saxagliptin 5 mg QPM.

This study was also submitted and assessed in the original saxagliptin application
The mean reduction from baseline to Week 24 in HbA1c (primary endpoint) was larger and statistically significant in all saxagliptin groups compared with the placebo group. The greatest decrease was observed in the 2.5 mg QAM group (-0.45%). The saxagliptin 5 mg QPM and QAM groups achieved similar decreases in HbA1c (-0.35% and -0.40%, respectively).

The efficacy results from the ST + LT periods, total of 76 weeks, are not presented in this report as the results between the two periods cannot be directly compared due to differences in dosing regimens implemented in the ST and LT periods.

The magnitude of the difference between saxagliptin and placebo in the monotherapy studies for Onglyza was questioned by the CHMP, however this was of limited relevance since Onglyza is not approved as monotherapy.

Study CV181039

This study was a multicenter, randomised, double-blind, active-controlled, phase 3 trial to evaluate the efficacy and safety of saxagliptin in combination with metformin IR as initial therapy compared to saxagliptin monotherapy and to metformin IR monotherapy in subjects with T2DM who had inadequate glycaemic control.

This study was assessed in the original MAA for Onglyza, and the long-term results were assessed in variation EMEA/H/C/001039/II/07. Based on these results, the CHMP concluded that addition of saxagliptin to metformin provided a sustained reduction in glycaemic parameters, including HbA1c, FPG, and PPG, without an increase in hypoglycaemia or hypoglycaemic symptoms. Still, it should be

noted that the -0.54%, change in HbA1c for saxagliptin 5 mg plus metformin compared with metformin plus placebo, though statistically significant, had a rather wide 95% CI (-0.73, -0.35). Consequently, the clinical relevance of this difference was questioned.
The results of the long-term analysis of this study demonstrated that administration of saxagliptin as initial combination therapy with metformin or as initial monotherapy for up to 76 weeks, both with and without pioglitazone, was well tolerated.

However this was of limited relevance since Onglyza is not approved for use as an initial combination therapy.

Study D1680C00001
This was a 52-week international, multi-center, randomised, parallel-group, double-blind, active-controlled, phase III study with a 52-week extension period to evaluate the safety and efficacy of saxagliptin in combination with metformin compared with sulfonylurea in combination with metformin in adult patients with T2DM who had inadequate glycaemic control on metformin therapy alone.

This study was assessed in variation EMEA/H/C/001039/II/05. The CHMP concluded that both treatments resulted in a reduction from baseline to week 52 in HbA1c. Treatment with saxagliptin plus metformin was non-inferior to treatment with glipizide plus metformin.
A delta of <0.35% might be too large for baseline HbA1c of 7.5%, however the difference in mean change from baseline between treatment groups was so small [0.06 (-0.05% to 0.16%)] that the conclusion of non-inferiority is acceptable. In the saxagliptin group the reduction of FPG was slightly less than in the glipizide group. More subjects in the saxagliptin group (15.3%) than in the glipizide group (12%) discontinued the study due to lack of efficacy by Week 52.
The proportion of subjects with at least 1 hypoglycaemic event was low (3.0%) in the saxagliptin group, much lower than the 36.3% in the glipizide group.
Mean body weight decreased from baseline to week 52 in the saxagliptin group and increased in the glipizide group, the differences were statistically significant.

Study D1680C0002
This was an 18-week, international, multi-centre, randomised, parallel-group, double-blind, active-controlled phase 3b study to evaluate the efficacy and safety of saxagliptin in combination with metformin in comparison with sitagliptin in combination with metformin in adult patients with T2DM who had inadequate glycaemic control on metformin therapy alone.

This study was assessed in variation EMEA/H/C/001039/II/06 for Onglyza. The CHMP concluded that HbA1c was reduced after 18 weeks of treatment in both groups: -0.52% for saxagliptin, versus -0.62% for sitagliptin. The reduction with saxagliptin was slightly lower, but according to predefined criteria, saxagliptin was non-inferior to sitagliptin. The same trend was seen in achievement of HbA1c goals: 26.3% of patients in the saxagliptin group achieved an HbA1c ≤6.5%, while 29.1% of the subjects in the sitagliptin group achieved this goal. Considering that slightly more patients in the saxagliptin group had a baseline HbA1c < 7%, the achievement seems to be very modest.

Furthermore, the sitagliptin group produced a numerically greater decrease from baseline in HbA1c compared with saxagliptin added to metformin in the subset of subjects with baseline HbA1c ≥7% (95% CI: 0.04 to 0.31%). All together, saxagliptin was non-inferior to sitagliptin in lowering HbA1c levels in this 18 week study. However, the reduction in HbA1c level and the percentage of patients achieving good glycaemic control (A1C ≤6.5%) was modest in this study. There was a trend of a lower efficacy of saxagliptin in comparison with sitagliptin. Secondary efficacy parameters confirmed the primary endpoint.

Study CV181080

Methods

Study CV181080 is a randomized, double-blind, two-arm, parallel-group, placebo-controlled, multi-centre trial comparing saxagliptin 2.5 mg BID with placebo BID administered concomitantly with metformin IR in subjects with T2DM who have inadequate glycaemic control with metformin IR monotherapy.

The duration of the study was 15 weeks, including:
1) Screening (Period A): 1 week.
2) Placebo Lead-in (Period B): 2-week continuation of subjects' pre-study stable metformin BID dose (≥ 1500 mg/day) in addition to single-blind placebo BID.
3) Double-blind (Period C): 12-week administration of either 2.5-mg saxagliptin BID or placebo BID concomitantly with their stable metformin IR BID dose.

Study Participants

The study population included male or female subjects with T2DM, aged between 18 and 78 years (inclusive), who had inadequate glycaemic control (defined as HbA1C levels ≥ 7.0% and ≤ 10.0% with diet and exercise) with daily monotherapy of at least 1500-mg metformin given BID. Subjects had a fasting C-peptide value of ≥ 0.8 ng/mL (0.34 nmol/L), and a body mass index (BMI) of ≤ 45.0 kg/m2. Excluded were subjects due to a number of criteria including those mainly based on contraindications for either saxagliptin or metformin.

Treatments

Screening (Period A)
Subjects had to receive a stable, baseline dose of metformin IR ≥ 1500 mg total daily dose (BID) for at least 8 weeks prior to enrolment, with diet and exercise.
Single-blind, Placebo Lead-in Period (Period B)
Eligible subjects entered the 2-week, single-blind, diet and exercise placebo lead-in period. Subjects continued to receive their individual twice daily metformin dose as prescribed by the investigator in addition to single-blind placebo and were instructed to take 1 tablet daily prior to the morning meal and 1 tablet daily prior to the evening meal, in addition to their prescribed metformin dose, BID as prescribed.
Double-blind Treatment Period (Period C)
Following completion of the lead-in period, eligible subjects entered the 12-week, double-blind treatment period. In addition to their basic treatment with metformin, subjects were randomized to 1 of 2 treatment arms (saxagliptin 2.5 mg BID or placebo). Metformin was to be taken twice daily, as prescribed, in addition to 1 tablet of saxagliptin or matching placebo prior to their morning and evening meal. No titration or adjustment of blinded saxagliptin or metformin was allowed during the study.

Objectives

The primary objective was to demonstrate superiority over placebo (+ metformin) as add-on of saxagliptin with regard to change in HbA1C.

Outcomes/endpoints

Primary Efficacy Endpoint was the change in HbA1c from baseline to Week 12 (or the last post-baseline measurement prior to Week 12, if no Week 12 assessment was available). The primary comparison was between the saxagliptin 2.5 mg BID (plus stable background metformin IR) and placebo (plus stable background metformin IR) treatment groups.

Secondary Efficacy Endpoints were comparison of saxagliptin 2.5 mg BID and placebo BID including change from baseline in FPG at Week 12, proportion of subjects achieving a therapeutic glycemic response at Week 12 (defined as HbA1c< 7.0%), and proportion of subjects achieving a therapeutic glycemic response at Week 12 (defined as HbA1c ≤ 6.5%).

Safety Endpoints were the incidences of AEs (including hypoglycemia events and events of special interest such as skin disorders, infections, localized edema, CV events, decreased lymphocytes, and decreased platelet count), serious AEs (SAEs), and discontinuations due to AEs, and results of ECGs, vital signs, physical examination, and clinical laboratory tests.

Sample size

The sample size of 72 per group was based on a projected difference in mean HbA1c of 0.6% with a standard deviation of 1.1% in individual HbA1c's and a power of 90% and 2-sided significance level of 0.05. To account for 5% unevaluable subjects (no week 12 measurement), this sample size was increased to 76 per group.

Randomisation

Randomization was performed in a 1:1 ratio (saxagliptin:placebo); 304 male and female subjects (target population HbA1c levels ≥ 7.0% and ≤ 10%) were screened to allow for randomization of 152 subjects (76 subjects per treatment group) in a 1:1 ratio.

Blinding (masking)

Precautions to not unnecessary break the blind were operational.

Statistical methods

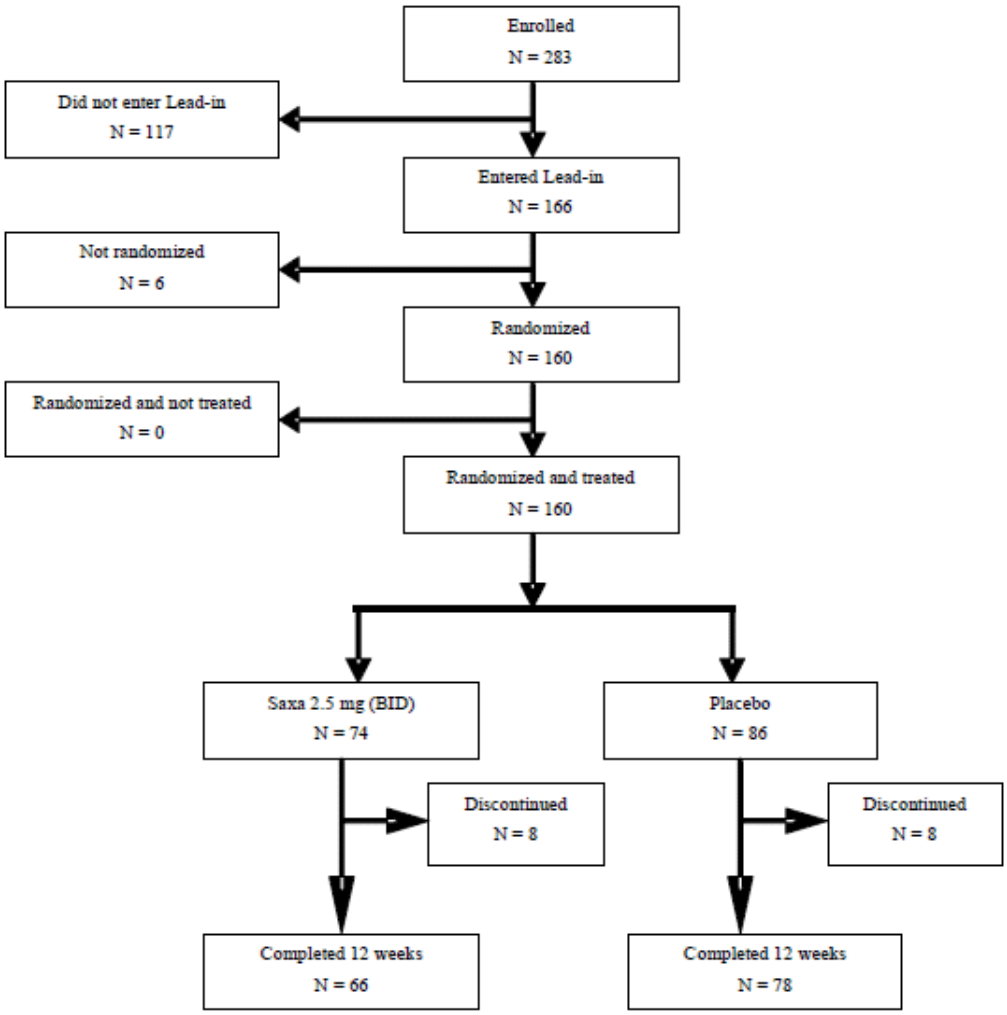
The analysis methods and multiple testing strategy are acceptable. Missing post baseline data (e.g. due rescue or discontinuation) was imputed via LOCF with complete cases analysis as sensitivity analysis.

Results

Participant flow

Of the 166 subjects who entered the lead-in period, 6 discontinued the study during the lead-in period. The most common reason for subject discontinuation during lead-in was withdrawal of consent (3 subjects, 1.8%). The remaining 3 subjects were not randomized because of poor/noncompliance, an AE (abdominal pain secondary to partial small bowel obstruction [which became an SAE when the subject was hospitalized]), and other: elevated liver enzymes. Of the 160 subjects who were randomized and treated with double-blind study drug, 144 completed 12 weeks of treatment; 74 subjects were randomized to saxagliptin and 86 were randomized to placebo.

Fig. 2: participant flow



Recruitment

Germany (21), Hungary (16) and Puerto Rico (18) contributed with 55 subjects, whereas USA contributed with the most (105) subjects to the 160 randomised and treated subjects.

Conduct of the study

Referring to the inclusion criteria, subjects should have baseline HbA1c values of ≥7.0 and ≤10%. However, in this study no subjects deviated from the HbA1c inclusion criteria to the extent considered relevant. There were 3 saxagliptin 2.5 mg BID subjects and 3 placebo subjects who continued in the study despite lack of glycaemic control at Week 8. However the number of subjects who had this protocol deviation was balanced between treatment groups.
Overall, according to the study report there were a few relevant protocol deviations; slightly more in the saxagliptin group than in the placebo group (2.7% vs. 2.3%).

Baseline data

53.1% were men and 90.0% were white. The mean age was 55.4 years (range 24 to 77 years), and 17.5% of the subjects were ≥ 65 years old. The proportion of hispanics/latinos in the study (40.0%) was similar to that of the non-hispanic/non-latino population (43.8%). Mean body weight was 93.6 kg (SD = 20.6 kg) and mean BMI was 33.1 kg/m2 (SD = 6.1 kg/m2), with heavier subjects in the saxagliptin treatment group than in the placebo group. Median BMI was 33.8 kg/m2 for saxagliptin-treated subjects and 31.1 kg/m2 in the placebo-treated group. A total of 25.7% of subjects in the saxagliptin group and 40.7% of subjects in the placebo group had a BMI of < 30 kg/m2.
The majority (55.6%) of subjects was diagnosed with T2DM ≥ 5 years before the start of the study.
The mean duration of diabetes was 6.0 years (median 5.3 years). There were no treatment naïve subjects, one subject had diabetes diagnosed for 0.1 year.
The mean baseline HbA1c was 7.95% (range, 6.5% to 10.1%) and the mean baseline FPG was 163.1 mg/d.

Numbers analysed

Of 86 participants in the placebo group, 78 were completing 12 weeks of treatment, of 74 participants in the saxagliptin group, 66 completed.

Outcomes and estimation

Table 10: Primary and Secondary Efficacy Endpoints - Summary at Week 12 (LOCF)

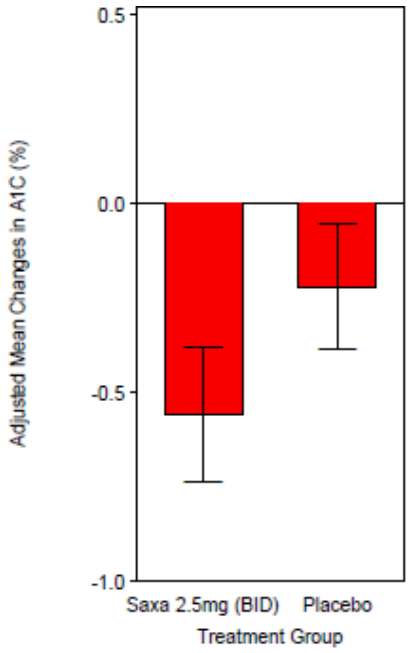
Efficacy Endpoint (Week 12)	Saxa 2.5 mg (BID)	Placebo
Statistics	N=74	N=86
A1C (%)		
n	74	84
Baseline Mean (SE)	7.92 (0.112)	7.97 (0.090)
Week 12 LOCF Mean (SE)	7.36 (0.132)	7.75 (0.117)
Change From Baseline (SE) (a)	-0.56 (0.089)	-0.22 (0.084)
Difference From Placebo (SE) (b)	-0.34 (0.122)	
P-Value (*)	0.0063	
FPG (MG/DL)		
n	73	84
Baseline Mean (SE)	164.22 (5.512)	161.25 (4.624)
Week 12 LOCF Mean (SE)	149.74 (6.182)	157.68 (4.037)
Change From Baseline (SE) (a)	-13.73 (4.506)	-4.22 (4.200)
Difference From Placebo (SE) (b)	-9.51 (6.162)	
P-Value (*)	0.1248	
Subjects Achieving A1C<7%		
n/N (%) (c)	29 / 74 (37.5)	19 / 84 (24.2)
Difference From Placebo (c)	13.22	
Subjects Achieving A1C<=6.5%		
n/N (%) (c)	19 / 74 (24.6)	8 / 84 (10.7)
Difference From Placebo (c)	13.84	

HbA1C

In CV 18080 the placebo group had a reduction of HbA1c of 0.22%, questioning whether subjects were truly diet/exercise/metformin failures or not. However life style modification, compliance and weight loss might well have contributed to this reduction of HbA1c in the placebo group.

There was a statistically significant reduction in adjusted mean change in HbA1C from baseline to Week 12 in the saxagliptin treatment group compared with placebo (P = 0.0063).

Figure 3: HbA1c Adjusted Mean Changes from Baseline at Week 12 (LOCF)



The mean change from baseline was –0.56% (95% CI [-0.74,-0.38]) for the saxagliptin treatment group and -0.22% (95% CI [-0.39, -0.06]) for placebo. The difference in the adjusted mean change from baseline versus placebo was -0.34% (95% CI [-0.58, -0.10]).

Changes from baseline in HbA1C observed values are in agreement with the LOCF data.

A greater proportion of subjects achieved a therapeutic glycaemic response (defined as HbA1C < 7.0% or HbA1c ≤ 6.5%) relative to placebo (37.5% versus 24.2%; 24.6% versus 10.7%). The difference in the proportions of subjects achieving HbA1C < 7% versus placebo was 13.2 % (95% CI [1.1, 25.4]), and HbA1c ≤ 6.5% 13.8% (95% CI [3.0, 24.7]).

The Applicant conducted analyses with several methods of handling missing data to evaluate the robustness of the primary HbA1c analysis results.

A post hoc repeated measures analysis was performed as an additional sensitivity analysis, and under the missing-at-random and ignorability assumptions. In addition, a Baseline Observation Carried Forward (BOCF) analysis was conducted to address the hypothetical scenario where subjects who discontinued from the study prior to Week 12 actually derived no benefit from participation in the study. The worst-case, multiple imputation analysis was proposed, using a "good" imputed value for a missing value in the placebo group and a "bad" imputed value for a missing value in the saxagliptin group. Therefore, the approach used for the placebo group was to randomly pick values from the placebo group observed at Week 12 and to impute values for subjects in this group with missing values. The approach used for the saxagliptin group was to impute a value that was worse than the mean value of the saxagliptin group at Week 12. To see how "bad" these values could be and still result in a significant effect for saxagliptin versus placebo, the analysis was performed in 5 steps, where the imputed values used for the saxagliptin group were worse for each step. This performed worse case

sensitivity analyses show that imputing unfavourable values of at most, on average, 9% for missing data of intervention patients still retains the statistical significance of the difference.
The results of each of these analyses for Study CV181080 are congruent for LOCF, observed case, and repeated measures analyses. The results of the BOCF analysis are also similar. For the multiple imputation analysis, results, up to imputation of HbA1c 9% values, were similar to those obtained using the other missing data handling approaches.

Fasting Plasma Glucose (FPG)
From baseline to Week 12 (LOCF) saxagliptin was associated with a numerically greater decrease in FPG compared with placebo. This was without statistical significance (P = 0.1248; 95% CI [-21.68, 2.66]). The adjusted mean change from baseline at Week 12 was -13.73 mg/dL (95% CI (-22.63, -4.83) in the saxagliptin group, and -4.22 mg/dL (95% CI [-12.52, 4.08]) for the placebo group.

Body Weight
Body weight was assessed post hoc. Baseline mean body weight was 95.59 kg for saxagliptin-treated subjects and 91.41 for placebo-treated subjects. At Week 12, mean change in body weight (LOCF) was -0.32 kg (95% CI [-0.97, 0.34]) for the saxagliptin group and -0.40 kg (95% CI [-0.83, 0.02]) for the placebo group.

Ancillary analyses

N/A

Summary of main studies

The following tables summarise the efficacy results from the 7 main studies and the PK/PD study 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 11. Summary of Efficacy for Study CV181014

Title: A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of saxagliptin (BMS-477118) in combination with metformin in subjects with type 2 diabetes who have inadequate glycemic control on metformin alone			
Study identifier	Study code: CV181014 ClinicalTrials.gov identifier: NCT00121667		
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group; metformin treatment failure subjects		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 2 weeks 182 weeks
Hypothesis	Superiority after 24 weeks		
Treatment groups	Saxa 2.5 mg + Met		Saxagliptin 2.5 mg on a background therapy of open-label metformin (at pre-study dose, ≤2500 mg), 24 weeks, 192 randomized[a]
	Saxa 5 mg + Met		Saxagliptin 5 mg on a background therapy of open-label metformin (at pre-study dose, ≤2500 mg), 24 weeks, 191 randomized[a]
	Saxa 10 mg + Met		Saxagliptin 10 mg on a background therapy of open-label metformin (at pre-study dose, ≤2500 mg), 24 weeks, 181 randomized[a]
	Plac + Met		Placebo on a background therapy of open-label metformin (at pre-study dose, ≤2500 mg), 24 weeks, 179 randomized[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 glycemic 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	22 November 2006 (ST CSR) 07 April 2010 (ST + LT CSR)		

Results and Analysis

Analysis description	**Primary Analysis (24-week ST phase)**				
Analysis population and time point description	Randomized subjects dataset, consisting of all randomized 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	Saxa 2.5 mg + Met	Saxa 5 mg + Met	Saxa 10 mg + Met	Plac + Met
	Number of subjects (randomized subjects dataset)	192	191	181	179
	HbA1c (%) (adjusted mean change)	-0.59	-0.69	-0.58	0.13
	Standard error	0.07	0.07	0.07	0.07
	FPG (mg/dL) (adjusted mean change)	-14.31	-22.03	-20.50	1.24
	Standard error	2.48	2.49	2.53	2.56
	HbA1c <7.0% (percent)	37.1	43.5	44.4	16.6
	PPG AUC (mg•min/dL) (adjusted mean change)	-8891	-9586	-8137	-3291
	Standard error	797.97	810.46	807.88	853.24

Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Saxa 2.5, 5, and 10 mg (+Met) vs Plac (+Met)
		Mean difference from Plac	-0.73, -0.83, -0.72
		95% CI	(-0.92, -0.53), (-1.02, -0.63), (-0.91, -0.52)
		P-value	<0.0001*, <0.0001*, <0.0001*
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Saxa 2.5, 5, and 10 mg (+Met) vs Plac (+Met)
		Mean difference from Plac	15.55, -23.28, -21.74
		95% CI	(-22.55, -8.55), (-30.29, -16.27), (-28.81, -14.68)
		P-value	<0.0001*, <0.0001*, <0.0001*
	Secondary endpoint: HbA1c <7.0% (percent)	Comparison groups	Saxa 2.5, 5, and 10 mg (+Met) vs Plac (+Met)
		Difference from Plac	20.5, 27.0, 27.9
		95% CI	(10.6, 30.5), (17.0, 36.7), (17.7, 37.7)

		P-value		<0.0001*, <0.0001*, <0.0001*	
	Secondary endpoint: PPG AUC (mg•min/dL)	Comparison groups		Saxa 2.5, 5, and 10 mg (+Met) vs Plac (+Met)	
		Mean difference from Plac		-5599, -6294, -4845	
		95% CI		(-7894, -3305), (-8606, -3983), (-7153, -2537)	
		P-value		<0.0001*, <0.0001*, <0.0001*	
Analysis description	**Secondary analysis (206-week ST + LT phase)[b]**				
Analysis population and time point description	Randomized subjects dataset, consisting of all randomized 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	Saxa 2.5 mg + Met	Saxa 5 mg + Met	Saxa 10 mg + Met	Plac + Met
	Number of subjects (randomized subjects dataset)	192	191	181	179
	Rescue/ discontinuation (percent)[c]	71.4	61.3	66.9	74.3
	HbA1c (%) (adjusted mean change)	-0.36	-0.42	-0.16	0.09
	Standard error	0.129	0.119	0.117	0.202
	FPG (mg/dL) (adjusted mean change)	-5.2	-4.4	-3.3	-0.1
	Standard error	5.14	4.74	4.63	7.97
	HbA1c <7.0% (percent)	18.8	24.1	28.3	13.1
	PPG AUC (mg•min/dL) (adjusted mean change)	-4517	-8547	-5398	-4180
	Standard error	1718.2	1487.2	1508.2	2479.8
Effect estimate per comparison	Rescue/ discontinuation (percent)[c]	Comparison groups		Saxa 2.5, 5, and 10 mg (+Met) vs Plac (+Met)	
		Difference from Plac		-2.9, -13.0, -7.5	
		95% CI		(-12.0, 6.2), (-22.4, -3.5), (-16.8, 2.0)	
		P-value		NC	
	HbA1c (%)	Comparison groups		Saxa 2.5, 5, and 10 mg (+Met) vs Plac (+Met)	
		Mean difference from Plac		-0.45, -0.51, -0.25	
		95% CI		(-0.92, 0.02), (-0.97, -0.05), (-0.70, 0.21)	
		P-value		NC	
	FPG (mg/dL)	Comparison groups		Saxa 2.5, 5, and 10 mg (+Met) vs Plac (+Met)	
		Mean difference from Plac		-5.2, -4.3, -3.3	
		95% CI		(-23.8, 13.4), (-22.5, 13.9), (-21.3, 14.8)	

		P-value	NC
	HbA1c <7.0% (%)	Comparison groups	Saxa 2.5, 5, and 10 mg (+Met) vs Plac (+Met)
		Difference from Plac	5.7, 10.9, 15.2
		95% CI	(-2.0, 13.3), (2.9, 18.9), (6.8, 23.6)
		P-value	NC
	PPG AUC (mg•min/dL)	Comparison groups	Saxa 2.5, 5, and 10 mg (+Met) vs Plac (+Met)
		Mean difference from Plac	-337, -4367, -1218
		95% CI	(-6261, 5586), (-10047, 1313), (-6912, 4476)
		P-value	NC
Notes	Source: CV181014 ST CSR; CV181014 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 (eg, 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%). [a] Subjects randomized and treated [b] The final assessment of efficacy endpoints during the ST + LT phase occurred at Week 154. [c] Subjects discontinued or rescued through Week 193 * Statistically significant at prespecified level. For primary endpoint, between-group comparisons significant at $\alpha = 0.019$, 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 hemoglobin; LT Long-term; Met Metformin; NC Not calculated; OGTT Oral glucose tolerance test; Plac Placebo; PPG Postprandial glucose; ST Short-term; Saxa Saxagliptin		

Table 12. **Summary of Efficacy for Study CV181038**

Title: A multicenter, randomized, 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 glycemic control with diet and exercise						
Study identifier	Study code: CV181038 ClinicalTrials.gov identifier: NCT00316082					
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group; treatment-naive subjects					
	Duration of main phase:	24 weeks				
	Duration of Run-in phase:	2 weeks				
	Duration of Extension phase:	52 weeks				
Hypothesis	Superiority after 24 weeks					
Treatment groups	Saxa 2.5 mg (QAM)	Saxagliptin 2.5 mg, QAM, 24 weeks, 74 randomized				
	Saxa 5 mg (QAM)	Saxagliptin 5 mg, QAM, 24 weeks, 74 randomized				
	Saxa 2.5/5 mg (QAM)	Saxagliptin titration from 2.5 to 5 mg, QAM, 24 weeks, 71 randomized				
	Saxa 5 mg (QPM)	Saxagliptin 5 mg, QPM, 24 weeks, 72 randomized				
	Plac	Placebo, QAM, 24 weeks, 74 randomized				
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 glycemic 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	Randomized subjects dataset, consisting of all randomized 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	Saxa 2.5 mg (QAM)	Saxa 5 mg (QAM)	Saxa 2.5/5 mg (QAM)	Saxa 5 mg (QPM)[a]	Plac
	Number of subjects (randomized 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	Saxa 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs Plac
		Mean difference from Plac	-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	Saxa 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs Plac
		Mean difference from Plac	-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	Saxa 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs Plac
		Difference from Plac	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	Saxa 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs Plac
		Mean difference from Plac	-4927, -5130, -4694, -2961
		95% CI	(-8416, -1437), (-8630, -1630), (-8210, -1178), (-6550, 629)
		P-value	0.0059[c], 0.0043 [c], 0.0091 [c], 0.1055

Analysis description	**Secondary analysis (76-week ST + LT phase)**					
Analysis population and time point description	Randomized subjects dataset, consisting of all randomized 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	Saxa 2.5 mg (QAM)	Saxa 5 mg (QAM)	Saxa 2.5/5 mg (QAM)	Saxa 5 mg (QPM)	Plac
	Number of subjects (randomized subjects dataset)	74	74	71	72	74
	Rescue/ discontinuation (percent)	33.8	33.8	32.4	36.1	37.8
	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

Effect estimate per comparison[b]	Rescue/ discontinuation (percent)	Comparison groups	Saxa 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs Plac
		Difference from Plac	NC
		95% CI	NC
		P-value	NC
	HbA1c (%)	Comparison groups	Saxa 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs Plac
		Mean difference from Plac	NC
		95% CI	NC
		P-value	NC
	FPG (mg/dL)	Comparison groups	Saxa 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs Plac
		Mean difference from Plac	NC
		95% CI	NC
		P-value	NC
	HbA1c <7.0% (%)	Comparison groups	Saxa 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs Plac
		Difference from Plac	NC
		95% CI	NC
		P-value	NC
	PPG AUC (mg•min/dL)	Comparison groups	Saxa 2.5, 5, 2.5/5 mg QAM, and 5 mg QPM vs Plac
		Mean difference from Plac	NC
		95% CI	NC
		P-value	NC
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 (eg, 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 Saxa 5 mg QPM group results were a secondary efficacy endpoint. [b] 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. [c] 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. * Statistically significant at prespecified level. For the primary endpoint, comparisons were performed in a 2-step sequential testing procedure. For Saxa 2.5 mg QAM and 5 mg QAM, comparisons vs placebo were significant at α = 0.027, applying Dunnett's adjustment. For Saxa 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 hemoglobin; LT Long-term; NC Not calculated; OGTT Oral glucose tolerance test; Plac Placebo; PPG Postprandial glucose; ST Short-term; Saxa Saxagliptin

Table 13. **Summary of Efficacy for Study CV181039**

Title: A multicenter, randomized, double-blind, active-controlled, phase 3 trial to evaluate the efficacy and safety of saxagliptin in combination with metformin IR as initial therapy compared to saxagliptin monotherapy and to metformin IR monotherapy in subjects with type 2 diabetes who have inadequate glycemic control					
Study identifier	Study code: CV181039 ClinicalTrials.gov identifier: NCT00327015				
Design	Multicenter, randomized, double-blind, active-controlled, parallel-group; treatment-naive subjects				
	Duration of main phase:	24 weeks			
	Duration of Run-in phase:	1 week			
	Duration of Extension phase:	52 weeks			
Hypothesis	Superiority after 24 weeks				
Treatment groups	Saxa 5 mg + Met		Saxagliptin 5 mg on a background therapy of metformin 500-2000 mg (titratable), 24 weeks, 320 randomized		
	Saxa 10 mg + Met		Saxagliptin 10 mg on a background therapy of metformin 500-2000 mg (titratable), 24 weeks, 323 randomized		
	Saxa 10 mg		Saxagliptin 10 mg plus placebo, 24 weeks, 335 randomized		
	Met		Metformin 500-2000 mg (titratable) plus placebo, 24 weeks, 328 randomized		
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 glycemic 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		
	Secondary endpoint	HbA1c ≤6.5%	Proportion of subjects achieving HbA1c ≤6.5% at Week 24		
	Secondary endpoint	Rescue/ discontinu-ation	Proportion of subjects requiring rescue for failing to achieve pre-specified glycemic targets or discontinuing for insufficient efficacy at Week 24		
Database lock	25 February 2008 (ST CSR) 02 April 2009 (ST + LT CSR)				
Results and Analysis					
Analysis description	**Primary Analysis (24-week ST phase)**				
Analysis population and time point description	Randomized subjects dataset, consisting of all randomized 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	Saxa 5 mg + Met	Saxa 10 mg + Met	Saxa 10 mg	Met
	Number of subjects (randomized subjects dataset)	320	323	335	328
	HbA1c (%) (adjusted mean change)	-2.53	-2.49	-1.69	-1.99
	Standard error	0.070	0.069	0.069	0.069

	FPG (mg/dL) (adjusted mean change)	-59.8	-62.2	-30.9	-47.3
	Standard error	2.34	2.34	2.30	2.33
	HbA1c <7.0% (percent)	60.3	59.7	32.2	41.1
	PPG AUC (mg•min/dL) (adjusted mean change)	-21080	-21336	-16054	-15005
	Standard error	836.5	869.6	826.7	857.0
	HbA1c ≤6.5% (percent)	45.3	40.6	20.3	29.0
	Rescue/ discontinuation (percent)	7.5	5.9	21.2	10.1

Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Mean difference from Saxa 10 mg	-0.84, -0.80
		95% CI	(-1.03, -0.65), (-0.99, -0.61)
		P-value	<0.0001*, <0.0001*
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Mean difference from Met	-0.54, -0.50
		95% CI	(-0.73, -0.35), (-0.70, -0.31)
		P-value	<0.0001*, <0.0001*
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Mean difference from Saxa 10 mg	-28.9, -31.3
		95% CI	(-35.3, -22.4), (-37.7, -24.9)
		P-value	<0.0001*, <0.0001*
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Mean difference from Met	-12.5, -14.9
		95% CI	(-19.0, -6.0), (-21.4, -8.5)
		P-value	0.0002*, <0.0001*
	Secondary endpoint: HbA1c <7.0% (percent)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Difference from Saxa 10 mg	28.1, 27.5
		95% CI	(20.4, 35.4), (19.8, 34.8)
		P-value	<0.0001*, <0.0001*
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Difference from Met	19.2, 18.6
		95% CI	(11.3, 26.8), (10.8, 26.2)
		P-value	<0.0001*, <0.0001*
	Secondary endpoint: PPG AUC (mg•min/dL)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Mean difference from Saxa 10 mg	-5027, -5282

		95% CI	(-7338, -2715), (-7639, -2925)
		P-value	<0.0001*, <0.0001*
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Mean difference from Met	-6075, -6330
		95% CI	(-8429, -3721), (-8728, -3932)
		P-value	<0.0001*, <0.0001*
	Secondary endpoint: HbA1c ≤6.5% (percent)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Difference from Saxa 10 mg	25.0, 20.3
		95% CI	(17.7, 32.0), (13.2, 27.3)
		P-value	<0.0001*, <0.0001*
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Difference from Met	16.3, 11.7
		95% CI	(8.7, 23.8), (4.2, 19.1)
		P-value	<0.0001*, 0.0026*
	Secondary endpoint: Rescue/ discontinuation (percent)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Difference from Saxa 10 mg	-13.7, -15.3
		95% CI	(-19.1, -8.5), (-20.5, -10.3)
		P-value	<0.0001*, <0.0001*
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Difference from Met	-2.6, -4.2
		95% CI	(-7.1, 1.9), (-8.5, -0.0)
		P-value	0.2693, 0.0597

Analysis description	**Secondary analysis (76-week ST + LT phase)**				
Analysis population and time point description	Randomized subjects dataset, consisting of all randomized 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	Saxa 5 mg + Met	Saxa 10 mg + Met	Saxa 10 mg	Met
	Number of subjects (randomized subjects dataset)	320	323	335	328
	Rescue/ discontinuation (percent)	23.1	26.0	47.2	34.1
	HbA1c (%) (adjusted mean change)	-2.31	-2.33	-1.55	-1.79
	Standard error	0.067	0.066	0.077	0.071
	FPG (mg/dL) (adjusted mean change)	-53.9	-55.3	-23.8	-40.3
	Standard error	2.60	2.61	3.03	2.79

	HbA1c <7.0% (percent)	51.1	50.8	25.0	34.7
	PPG AUC (mg•min/dL) (adjusted mean change)	-21174	-20308	-13913	-13601
	Standard error	781.4	821.5	907.4	833.4
	HbA1c ≤6.5% (percent)	38.4	38.1	16.3	20.1

Effect estimate per comparison	Rescue/ discontinuation (percent)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Difference from Saxa 10 mg	-24.0, -21.2
		95% CI	(-31.0, -16.8), (-28.3, -13.9)
		P-value	NC
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Difference from Met	-11.0, -8.1
		95% CI	(-17.9, -4.0), (-15.2, -1.1)
		P-value	NC
	HbA1c (%)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Mean difference from Saxa 10 mg	-0.76, -0.78
		95% CI	(-0.96, -0.56), (-0.98, -0.58)
		P-value	NC
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Mean difference from Met	-0.52, -0.54
		95% CI	(-0.71, -0.33), (-0.73, -0.35)
		P-value	NC
	FPG (mg/dL)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Mean difference from Saxa 10 mg	-30.2, -31.5
		95% CI	(-38.0, -22.3), (-39.4, -23.7)
		P-value	NC
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Mean difference from Met	-13.6, -14.9
		95% CI	(-21.0, -6.1), (-22.4, -7.5)
		P-value	NC
	HbA1c <7.0% (%)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Difference from Saxa 10 mg	26.1, 25.8
		95% CI	(18.6, 33.4), (18.4, 33.0)
		P-value	NC
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Difference from Met	16.4, 16.1

		95% CI	(8.6, 24.1), (8.3, 23.7)
		P-value	NC
	PPG AUC (mg•min/dL)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Mean difference from Saxa 10 mg	-7261, -6395
		95% CI	(-9615, -4907), (-8801, -3988)
		P-value	NC
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Mean difference from Met	-7573, -6707
		95% CI	(-9820, -5327), (-9007, -4407)
		P-value	NC
	HbA1c ≤6.5% (%)	Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Saxa 10 mg
		Difference from Saxa 10 mg	22.2, 21.8
		95% CI	(15.3, 28.9), (15.1, 28.5)
		P-value	NC
		Comparison groups	Saxa 5 mg + Met and Saxa 10 mg + Met vs Met
		Difference from Met	18.4, 18.0
		95% CI	(11.3, 25.4), (11.0, 25.0)
		P-value	NC
Notes	Source: CV181039 ST CSR; CV181039 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 (eg, 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% and HbA1c ≤6.5%). * Statistically significant at prespecified level. For primary endpoint, between-group comparisons significant at $\alpha = 0.027$, applying Dunnett's adjustment. All secondary endpoints were tested (sequentially) at the 0.05 significance level and only if comparison of the combination treatment group vs each monotherapy active-control group was significant. AUC Area under the curve; CI Confidence interval; FPG Fasting plasma glucose; HbA1c Glycosylated hemoglobin; LT Long-term; Met Metformin; NC Not calculated; OGTT Oral glucose tolerance test; PPG Postprandial glucose; ST Short-term; Saxa Saxagliptin		

Table 14. Summary of Efficacy for Study D1680C00001

Title: A 52-week international, multi-center, randomized, parallel-group, double-blind, active-controlled, phase III study with a 52-week extension period to evaluate the safety and efficacy of saxagliptin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone			
Study identifier	Study code: D1680C00001 ClinicalTrials.gov identifier: NCT00575588		
Design	Multicenter, randomized, double-blind, active-controlled, parallel-group; metformin treatment failure subjects		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks 2 weeks 52 weeks
Hypothesis	Non-inferiority after 52 weeks		
Treatment groups	Saxa 5 mg + Met		Saxagliptin 5 mg on a background therapy of open-label metformin (at pre-study dose, 1500-3000 mg), 52 weeks, 428 randomized
	Glip 5 mg + Met		Glipizide 5 mg (titratable to 20 mg [mean final glipizide dose was 15 mg and 50.5% of subjects were receiving 20 mg]) on a background therapy of open-label metformin (at pre-study dose, 1500-3000 mg), 52 weeks, 430 randomized
Endpoints and definitions	Primary endpoint	HbA1c	Adjusted mean change from baseline to Week 52
	Secondary endpoint	≥1 Hypo-glycemic event	Proportion of subjects reporting at least 1 hypoglycemic event at Week 52 (a safety outcome variable)
	Secondary endpoint	Body weight	Adjusted mean change from baseline in body weight at Week 52 (a safety outcome variable)
	Secondary endpoint	HbA1c Durability	Durability from Week 24 to Week 52 of the HbA1c effect observed at Week 24 (efficacy)
Database lock	25 September 2009 (ST CSR) 24 September 2010 (ST + LT CSR)		
Results and Analysis			
Analysis description	**Primary Analysis (52-week ST phase)**		
Analysis population and time point description	Per-protocol dataset, a subset of the Full analysis set (subjects who took at least 1 randomized dose of double-blind study medication, and had at least 1 non-missing baseline and 1 post-baseline efficacy data assessment) consisting of all subjects who completed the 52-week, randomized treatment period, had both a baseline and Week 52 HbA1c measurement, and had no significant protocol deviations		
Descriptive statistics and estimate variability	Treatment group	Saxa 5 mg + Met	Glip 5 mg + Met
	Number of subjects (per-protocol dataset)[a]	293	293
	HbA1c (%) (adjusted mean change)	-0.74	-0.80
	Standard error	0.038	0.038
	≥1 Hypo-glycemic event (percent)	3.0	36.3
	Body weight (kg) (adjusted mean change)	-1.1	1.1
	Standard error	0.17	0.17
	HbA1c Durability (mean slope of regression)	0.001	0.004

	Standard error	0.001	0.001
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Saxa 5 mg + Met vs Glip 5 mg + Met
		Mean difference from Glip 5 mg + Met	0.06
		95% CI	(-0.05, 0.16)[+]
		P-value	NC
	Secondary endpoint: ≥1 Hypoglycemic event (percent)	Comparison groups	Saxa 5 mg + Met vs Glip 5 mg + Met
		Difference from Glip 5 mg + Met	-33.2
		95% CI	(-38.1, -28.5)
		P-value	<0.0001*
	Secondary endpoint: Body weight (kg)	Comparison groups	Saxa 5 mg + Met vs Glip 5 mg + Met
		Mean difference from Glip 5 mg + Met	-2.2
		95% CI	(-2.7, -1.7)
		P-value	<0.0001*
	Secondary endpoint: HbA1c Durability (mean slope of regression)	Comparison groups	Saxa 5 mg + Met vs Glip 5 mg + Met
		Mean difference from Glip 5 mg + Met	-0.002
		95% CI	(-0.0046, -0.0001)
		P-value	0.040*
Analysis description	**Secondary analysis (104-week ST + LT phase)**		
Analysis population and time point description	Full analysis set consisting of all subjects who took at least 1 randomized dose of double-blind study medication, and had at least 1 non-missing baseline and 1 post-baseline efficacy data assessment		
Descriptive statistics and estimate variability	Treatment group	Saxa 5 mg + Met	Glip 5 mg + Met
	Number of subjects (full analysis dataset)[a]	426	426
	HbA1c (%) (adjusted mean change)	-0.41	-0.35
	Standard error	0.041	0.043
	≥1 Hypo-glycemic event (percent)	3.5	38.4
	Body weight (kg) (adjusted mean change)	-1.47	1.29
	Standard error	0.200	0.205
	HbA1c Durability (mean slope of regression)	0.0041	0.0076
	Standard error	0.0005	0.0005
Effect estimate per comparison	HbA1c (%)	Comparison groups	Saxa 5 mg + Met vs Glip 5 mg + Met
		Mean difference from Glip 5 mg + Met	-0.05
		95% CI	(-0.17, 0.06)
		P-value	NC
	≥1 Hypoglycemic event (percent)	Comparison groups	Saxa 5 mg + Met vs Glip 5 mg + Met
		Difference from Glip 5 mg + Met	-34.9

		95% CI	(-39.8, -30.0)
		P-value	NC
	Body weight (kg)	Comparison groups	Saxa 5 mg + Met vs Glip 5 mg + Met
		Mean difference from Glip 5 mg + Met	-2.76
		95% CI	(-3.32, -2.20)
		P-value	NC
	HbA1c Durability (mean slope of regression)	Comparison groups	Saxa 5 mg + Met vs Glip 5 mg + Met
		Mean difference from Glip 5 mg + Met	-0.0035
		95% CI	(-0.0048, -0.0022)
		P-value	NC
Notes	Source: D1680C00001 ST CSR; D1680C00001 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 for the ST CSR specified that the ANCOVA LOCF analysis was the primary presentation of the endpoints and a repeated measures analysis was performed as a sensitivity analysis. The statistical analysis plan for the ST + LT CSR specified that a repeated measures analysis be used for the primary presentation of the results from the ST + LT period because, compared with the LOCF analysis, it represented a more comprehensive approach to address the challenge of handling the large and increasing amount of missing data over time in the LT extension period (partially due to the increasingly stringent protocol-mandated discontinuation criteria relating to glycemic control). [+] Achieved the prespecified level for non-inferiority. Saxa + Met was considered non-inferior to Glip + Met if the upper confidence limit of the estimate of the between-group difference was <0.35%. * Between group comparison significant after controlling overall alpha of the study. [a] The safety analysis dataset (Saxa + Met: 428 subjects; Glip + Met: 430 subjects) was used for the analysis of ≥1 hypoglycemic event and body weight. CI Confidence interval; Glip Glipizide; HbA1c Glycosylated hemoglobin; LT Long-term; Met Metformin; NC Not calculated; Plac Placebo; ST Short-term; Saxa Saxagliptin		

Table 15. Summary of Efficacy for Study D1680C00002

Title: An 18-week, international, multi-centre, randomized, parallel-group, double-blind, active-controlled phase IIIb study to evaluate the efficacy and safety of saxagliptin in combination with metformin in comparison with sitagliptin in combination with metformin in adult patients with type 2 diabetes who have inadequate glycaemic control on metformin therapy alone			
Study identifier	Study code: D1680C00002 ClinicalTrials.gov identifier: NCT00666458		
Design	Multicenter, randomized, double-blind, active-controlled, parallel-group; metformin treatment failure subjects		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	18 weeks 2 weeks NA	
Hypothesis	Non-inferiority after 18 weeks		
Treatment groups	Saxa 5 mg + Met		Saxagliptin 5 mg on a background therapy of open-label metformin (at pre-study dose, 1500-3000 mg), 18 weeks, 403 randomized
	Sita 100 mg + Met		Sitagliptin 100 mg on a background therapy of open-label metformin (at pre-study dose, 1500-3000 mg), 18 weeks, 398 randomized
Endpoints and definitions[a]	Primary endpoint	HbA1c	Adjusted mean change from baseline to Week 18
	Secondary endpoint	FPG	Adjusted mean change from baseline to Week 18
	Secondary endpoint	HbA1c ≤6.5%	Therapeutic glycemic response, defined as the proportion of subjects achieving HbA1c ≤6.5% at Week 18
Database lock	07 April 2009		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Per-protocol dataset, a subset of the Full analysis set (subjects who took at least 1 randomized dose of double-blind study medication, and had at least 1 non-missing baseline and 1 post-baseline efficacy data assessment) consisting of all subjects who completed the 18-week, randomized treatment period, and had no significant protocol deviations		
Descriptive statistics and estimate variability	Treatment group	Saxa 5 mg + Met	Sita 100 mg + Met
	Number of subjects (per-protocol dataset)	334	343
	HbA1c (%) (adjusted mean change)	-0.52	-0.62
	Standard error	0.039	0.038
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Saxa 5 mg + Met vs Sita 100 mg + Met
		Mean difference from Sita 100 mg + Met	0.09
		95% CI	(-0.01, 0.20)[+]
		P-value	NC
Analysis description	**Secondary analysis**		
Analysis population and time point description	Full analysis set consisting of all subjects who took at least 1 randomized dose of double-blind study medication, and had at least 1 non-missing baseline and 1 post-baseline efficacy data assessment		
Descriptive statistics and estimate variability	Treatment group	Saxa 5 mg + Met	Sita 100 mg + Met
	Number of subjects (full analysis dataset)	400	395

	FPG (mg/dL) (adjusted mean change)	-10.75	-16.16
	Standard error	1.455	1.464
	HbA1c ≤6.5% (percent)	26.3	29.1
Effect estimate per comparison[a]	FPG (mg/dL)	Comparison groups	Saxa 5 mg + Met vs Sita 100 mg + Met
		Mean difference from Sita 100 mg + Met	5.42
		95% CI	(1.37, 9.47)
		P-value	NC
	HbA1c ≤6.5% (percent)	Comparison groups	Saxa 5 mg + Met vs Sita 100 mg + Met
		Difference from Sita 100 mg + Met	-2.8
		95% CI	(-9.0, 3.5)
		P-value	NC
Notes	Source: D1680C00002 CSR [+] Achieved the prespecified level for non-inferiority. Saxa + Met was considered non-inferior to Sita + Met if the upper confidence limit of the estimate of the between-group difference was <0.3%. [a] No *a priori* hypotheses were established for secondary endpoints. FPG and HbA1c ≤6.5% were included in a series of exploratory secondary endpoints and the results were presented without pre-specified statistical comparisons. CI Confidence interval; FPG Fasting plasma glucose; HbA1c Glycosylated hemoglobin; Met Metformin; NA Not applicable; NC Not calculated; Sita Sitagliptin; Saxa Saxagliptin		

Table 16. Summary of Efficacy for Study CV181066

Title: A 4-week, multicenter, randomized, double-blind, placebo-controlled phase 3 trial to evaluate the efficacy and safety of saxagliptin in comparison to placebo as add-on treatment to metformin XR in subjects with type 2 diabetes who have inadequate glycemic control with diet and exercise and a stable dose of metformin XR ≥1500 mg/day			
Study identifier	Study code: CV181066 ClinicalTrials.gov identifier: NCT00683657		
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group; metformin treatment failure subjects		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		4 weeks 4 weeks NA
Hypothesis	Superiority after 4 weeks		
Treatment groups	Saxa 5 mg QPM + Met XR		Saxagliptin 5 mg (administered with the evening meal) on a background therapy of open-label metformin XR (at pre-study dose, 1500-2000 mg), 4 weeks, 46 randomized
	Plac + Met XR		Placebo on a background therapy of open-label metformin XR (at pre-study dose, 1500-2000 mg), 4 weeks, 47 randomized
Endpoints and definitions	Primary endpoint	24-hour MWG	Adjusted mean change from baseline to Week 4 in 24-hour MWG (defined as 24-hour plasma glucose AUC ÷ 24 hours)
	Secondary endpoint	4-hour mean weighted PPG	Adjusted mean change from baseline to Week 4 in 4-hour mean weighted PPG (4 hours after the evening meal calculated as 4 hour PPG AUC ÷ 4 hours)
	Secondary endpoint	2-hour PPG	Adjusted mean change from baseline to Week 4 in 2-hour PPG (2 hours after the evening meal)
	Secondary endpoint	Mean daily glucose	Adjusted mean change from baseline to Week 4. Based on 7 daily fingerstick glucose measurements (pre-meal, 2-hour post-meal, and at bedtime) collected by subjects at home in a 3-day period, prior to collection of the 24-hour blood samples
	Secondary endpoint	2-day FPG	Adjusted mean change from baseline to Week 4 in 2-day average FPG.
Database lock	15 April 2009		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Randomized subjects dataset, consisting of all randomized subjects who took at least 1 dose of double-blind study medication during the 4-week double-blind period		
Descriptive statistics and estimate variability	Treatment group	Saxa 5 mg QPM + Met XR	Plac + Met XR
	Number of subjects (randomized subjects dataset)	46	47
	24-hour MWG (mg/dL) (adjusted mean change)	-13.8	3.0
	Standard error	2.99	2.89
	4-hour mean weighted PPG (mg/dL) (adjusted mean change)	-30.7	-0.4
	Standard error	5.14	4.90

	2-hour PPG (mg/dL) (adjusted mean change)	-38.2	-2.8
	Standard error	7.49	7.23
	Mean daily glucose (mg/dL) (adjusted mean change)	-11.7	7.0
	Standard error	3.02	2.94
	2-day FPG (mg/dL) (adjusted mean change)	-10.8	4.5
	Standard error	2.84	2.81

Effect estimate per comparison	Primary endpoint: 24-hour MWG (mg/dL)	Comparison groups	Saxa 5 mg QPM + Met XR vs Plac + Met XR
		Mean difference from Plac + Met XR	-16.8
		95% CI	(-25.1, -8.5)
		P-value	0.0001*
	Secondary endpoint: 4-hour mean weighted PPG (mg/dL)	Comparison groups	Saxa 5 mg QPM + Met XR vs Plac + Met XR
		Mean difference from Plac + Met XR	-30.2
		95% CI	(-44.4, -16.1)
		P-value	<0.0001*
	Secondary endpoint: 2-hour PPG (mg/dL)	Comparison groups	Saxa 5 mg QPM + Met XR vs Plac + Met XR
		Mean difference from Plac + Met XR	-35.4
		95% CI	(-56.2, -14.7)
		P-value	0.0010*
	Secondary endpoint: Mean daily glucose (mg/dL)	Comparison groups	Saxa 5 mg QPM + Met XR vs Plac + Met XR
		Mean difference from Plac + Met XR	-18.7
		95% CI	(-27.1, -10.3)
		P-value	<0.0001*
	Secondary endpoint: 2-day FPG (mg/dL)	Comparison groups	Saxa 5 mg QPM + Met XR vs Plac + Met XR
		Mean difference from Plac + Met XR	-15.3
		95% CI	(-23.3, -7.4)
		P-value	0.0002*
Analysis description	**Secondary analysis**		
NA	NA		
Notes	Source: CV181066 CSR * Between group comparison significant after controlling overall alpha of the study (∞ = 0.05). CI Confidence interval; FPG Fasting plasma glucose; HbA1c Glycosylated hemoglobin; Met Metformin; MWG Mean weighted glucose; NA Not applicable; Plac Placebo; PPG Postprandial glucose; Saxa Saxagliptin		

Table 17. Summary of Efficacy for Study CV181080

Title: A multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial to evaluate the efficacy and safety of 2.5-mg saxagliptin, PO, BID, in combination with metformin in subjects with type 2 diabetes mellitus who have inadequate glycemic control on metformin alone			
Study identifier	Study code: CV181080 ClinicalTrials.gov identifier: NCT00885378		
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group; metformin treatment failure subjects		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 2 weeks NA
Hypothesis	Superiority after 12 weeks		
Treatment groups	Saxa 2.5 mg BID + Met		Saxagliptin 2.5 mg administered twice daily on a background therapy of open-label metformin (at pre-study dose, 1500-3000 mg), 12 weeks, 74 randomized
	Plac + Met		Placebo on a background therapy of open-label metformin (at pre-study dose, 1500-3000 mg), 12 weeks, 86 randomized
Endpoints and definitions	Primary endpoint	HbA1c	Adjusted mean change from baseline to Week 12
	Secondary endpoint	FPG	Adjusted mean change from baseline to Week 12
	Secondary endpoint	HbA1c <7.0%	Therapeutic glycemic response, defined as the proportion of subjects achieving HbA1c <7.0% at Week 12
	Secondary endpoint	HbA1c ≤6.5%	Proportion of subjects achieving HbA1c ≤6.5% at Week 12
Database lock	22 March 2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Randomized subjects dataset, consisting of all randomized subjects who took at least 1 dose of double-blind study medication during the 12-week double-blind period		
Descriptive statistics and estimate variability	Treatment group	Saxa 2.5 mg BID + Met	Plac + Met
	Number of subjects (randomized subjects dataset)	74	86
	HbA1c (%) (adjusted mean change)	-0.56	-0.22
	Standard error	0.089	0.084
	FPG (mg/dL) (adjusted mean change)	-13.73	-4.22
	Standard error	4.506	4.200
	HbA1c <7.0% (adjusted percent)	37.5	24.2
	HbA1c ≤6.5% (adjusted percent)	24.6	10.7
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Saxa 2.5 mg BID + Met vs Plac + Met
		Mean difference from Plac + Met	-0.34
		95% CI	(-0.58, -0.10)
		P-value	0.0063*

	Secondary endpoint: FPG (mg/dL)	Comparison groups	Saxa 2.5 mg BID + Met vs Plac + Met
		Mean difference from Plac + Met	-9.51
		95% CI	(-21.68, 2.66)
		P-value	0.1248
	Secondary endpoint: HbA1c <7.0% (adjusted percent)	Comparison groups	Saxa 2.5 mg BID + Met vs Plac + Met
		Difference from Plac + Met	13.2
		95% CI	(1.1, 25.4)
		P-value	NC
	Secondary endpoint: HbA1c ≤6.5% (adjusted percent)	Comparison groups	Saxa 2.5 mg BID + Met vs Plac + Met
		Difference from Plac + Met	13.8
		95% CI	(3.0, 24.7)
		P-value	NC
Analysis description	**Secondary analysis**		
NA	NA		
Notes	Source: CV181080 CSR * Between group comparison significant after controlling overall alpha of the study (α = 0.05). CI Confidence interval; FPG Fasting plasma glucose; HbA1c Glycosylated hemoglobin; Met Metformin; NA Not applicable; NC Not calculated; Plac Placebo; Saxa Saxagliptin		

Table 18. Summary of Pharmacokinetics/Pharmacodynamics for Study CV181152

Title: A pharmacokinetics/pharmacodynamics study of saxagliptin following multiple dose administration of 2.5 mg twice-daily as compared to 5 mg once-daily when administered with standard meals to healthy subjects			
Study identifier	Study code: CV181152 ClinicalTrials.gov identifier: NA		
Design	Open-label, randomized, 2-period, 2 multiple-dose treatment, cross-over study; healthy subjects		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		41 days (including Screening) NA NA
Hypothesis	Equivalence of total daily exposure of saxagliptin after multiple dosing of 5 mg once-daily and 2.5 mg twice-daily in healthy subjects		
Treatment groups	Saxa 5 mg QD		Saxagliptin 5 mg administered once daily with a standard meal, 7 days, 16 subjects randomized[a]
	Saxa 2.5 mg BID		Saxagliptin 2.5 mg administered twice daily with a standard meal, 7 days, 16 subjects randomized[a]
Endpoints and definitions	Primary endpoint	AUC_{0-24h}	Total daily saxagliptin and BMS-510849 exposure, or AUC over the 24-hour period following the AM dose[b]
	Secondary endpoint	C_{max}	Maximum observed saxagliptin and BMS-510849 plasma concentration within a dosing interval
	Secondary endpoint	T_{max}	Time to saxagliptin and BMS-510849 C_{max} within a dosing interval
	Secondary endpoint	AUC_{tau}	Saxagliptin and BMS-510849 AUC over 1 dosing interval (TAU=24 for once daily, and TAU=12 for twice daily)
	Secondary endpoint	C_{min}	Trough (predose) saxagliptin and BMS-510849 plasma concentration
	Secondary endpoint	I_{max} (DPP-4)	Maximum plasma DPP4 percent inhibition
	Secondary endpoint	T_{max} (DPP-4)	Time to I_{max}
	Secondary endpoint	Trough (DPP-4)	DPP-4 percent inhibition of last collected plasma sample postdose within a dosing interval
	Secondary endpoint	$AUEC_{tau}$ (DPP-4)	Area under the DPP-4 percent inhibition (effect)-time curve over 1 dosing interval
	Secondary endpoint	$AUEC_{0-24h}$ (DPP-4)	Total daily DPP-4 percent inhibition, or area under the DPP-4 % inhibition (effect)-time curve over the 24-hour period following the AM dose[c]
	Secondary endpoint	C_{max} (iGLP-1)	Maximum observed postprandial iGLP-1plasma concentration
	Secondary endpoint	T_{max} (iGLP-1)	Time of C_{max}
	Secondary endpoint	$AUEC_{0-3h}$ (iGLP-1)	AUC of iGLP-1 over the 3-hour period after each meal (breakfast, lunch, or dinner)
	Secondary endpoint	Total $AUEC_{0-3h}$ (iGLP-1)	Sum of $AUEC_{0-3h}$ of iGLP-1 after every meal of the day (breakfast, lunch, and dinner)
Database lock	20 April 2011		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point	PK population dataset, consisting of all subjects who had valid PK parameters on Day 7 for at least 1 of the treatments		

description	PD population dataset (DPP-4 and iGLP-1), consisting of all subjects who had valid PD parameters for at least 1 of the treatments		
Descriptive statistics and estimate variability	Treatment group	Saxa 5 mg QD	Saxa 2.5 mg BID
	Number of subjects (PK/PD dataset)	16	16
	AUC_{0-24h} Geometric LS mean (ng•hr/mL) - Saxagliptin	99.27	103.32
	CV%	15	14
	AUC_{0-24h} Geometric LS mean (ng•hr/mL) - BMS-510849[d]	325.81	317.82
	CV%	19	16
	$AUEC_{0-24h}$ (DPP-4) Geometric LS mean (%•hr)	1740.00	1838.45
	CV%	6	4
	I_{max} (DPP-4) (%)	82.00	82.03 (for AM dose)
	CV%	2	3
	Total $AUEC_{0-3h}$ (iGLP-1) Geometric LS mean (pM•hr), Day -1	85.16	84.07
	CV%	31	30
	Total $AUEC_{0-3h}$ (iGLP-1) Geometric LS mean (pM•hr), Day 7	105.90	106.53
	CV%	23	27
Effect estimate per comparison	Primary endpoint: AUC_{0-24h} Geometric LS mean (ng•hr/mL) - Saxagliptin	Comparison groups	Saxa 2.5 mg BID vs Saxa 5 mg QD
		Ratio (%) (BID/QD) of Geometric LS Means	104.08
		95% CI	(101.03, 107.22)*
		P-value	NC
	AUC_{0-24h} Geometric LS mean (ng•hr/mL) - BMS-510849[d]	Comparison groups	Saxa 2.5 mg BID vs Saxa 5 mg QD
		Ratio (%) (BID/QD) of Geometric LS Means	97.55
		95% CI	(94.02, 101.21)*
		P-value	NC
	Secondary endpoint: $AUEC_{0-24h}$ (DPP-4) Geometric LS mean (%•hr)	Comparison groups	Saxa 2.5 mg BID vs Saxa 5 mg QD
		Ratio (%) (BID/QD) of Geometric LS Means	105.66
		95% CI	(102.23, 109.20)*
		P-value	NC
	Secondary endpoint: I_{max} (DPP-4) (%)	Comparison groups	Saxa 2.5 mg BID vs Saxa 5 mg QD
		Ratio (%) (BID/QD) of Geometric LS Means	100.03
		95% CI	(98.65, 101.43)*
		P-value	NC
	Secondary endpoint: Total $AUEC_{0-3h}$ (iGLP-1)	Comparison groups	Saxa 5 mg QD: Day 7 vs Day -1

	Geometric LS mean (pM•hr)	Ratio (%) (Day 7/-1) of Geometric LS Means	124.35
		95% CI	(114.13, 135.49)
		P-value	NC
		Comparison groups	Saxa 2.5 mg BID: Day 7 vs Day -1
		Ratio (%) (Day 7/-1) of Geometric LS Means	126.72
		95% CI	(116.30, 138.07)
		P-value	NC
		Comparison groups	Saxa 2.5 mg BID vs Saxa 5 mg QD (Day 7)
		Ratio (%) (BID/QD) of Geometric LS Means	100.60
		95% CI	(92.33, 109.61)**
		P-value	NC
Analysis description	**Secondary analysis**		
NA	NA		
Notes	Source: CV181152 CSR [a] A total of 16 subjects were randomized and received study medication. Subjects were randomly assigned to received either Saxa 5 mg QD or Saxa 2.5 mg BID during the first 7-day treatment period. After a washout interval of at least 6 days, subjects received the other Saxa dosing regimen during the second 7-day treatment period. [b] Total daily exposure (AUC_{0-24h}) is either: (1) the AUC_{tau} value following the daily (AM) dose of the Saxa 5 mg QD regimen, or (2) the sum of the AUC_{tau} values following the AM and PM doses of the Saxa 2.5 mg BID regimen. [c] Total daily DPP4 % inhibition ($AUEC_{0-24h}$ [DPP4]) is either: (1) the $AUEC_{tau}$ value following the AM dose of the Saxa 5 mg QD regimen, or (2) the sum of $AUEC_{tau}$ values following the AM and PM doses of the Saxa 2.5 mg BID regimen. [d] BMS-510849 is an active metabolite of saxagliptin and contributes to the efficacy of the parent molecule. * The 90% CI of the ratios (%) of geometric least squares (LS) means (Saxa 2.5 mg BID regimen vs Saxa 5 mg QD regiment) were entirely contained within the 80% to 125% criterion limits for concluding bioequivalence. ** Although there were no predefined criteria for equivalence, the Saxa 2.5 mg BID regimen appears to have an equivalent impact on iGLP-1 when compared with the Saxa 5 mg QD regimen with respect to the total $AUEC_{0-3h}$ of iGLP-1. AM Morning; AUC Area under the plasma concentration-time curve; BID Twice daily; CI Confidence interval; CV Coefficient of variation; DPP-4 Dipeptidyl peptidase 4; LS Least squares; NA Not applicable; NC Not calculated; QD Once daily; Saxa Saxagliptin		

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

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

N/A

2.5.3. Discussion on clinical efficacy

The clinical development program included data from 7 phase 3 studies with a total of 4326 subjects randomised and treated, of whom 2158 received saxagliptin plus metformin. Data included in this submission reflect up to 102 weeks total duration of treatment.

Saxagliptin added on to metformin has been evaluated in studies **CV181014** and **CV181080**. However, only the new pivotal study **CV181080** investigated the intended posology of 2.5 mg saxagliptin BID added to metformin versus placebo added to metformin. In study CV181080, there was a statistically significant reduction in adjusted mean change in HbA1C from baseline to Week 12 in the saxagliptin treatment group compared with placebo (-0.56% vs -0.22%), but the effect size was small (-0.34%), the predefined Δ of 0.6% was not reached, and the duration of 12 weeks is limited. The reduction in FPG was numerically greater, but this was without statistical significance. Additionally, in study **CV181080** there was no comparison with saxagliptin 5 mg once daily. Thus, there was no confirmation that saxagliptin 2.5 mg BID is as efficacious as saxagliptin 5 mg QD when added to metformin. This was pointed out in the day 120 list of questions during the procedure and also led to the submission of study CV181152 during the procedure.
The balance of evidence concerning the effect size of saxagliptin added to metformin, as previously evaluated in a study with saxagliptin 2.5 mg qD (CV181014) and in studies of longer duration (18 to 52 weeks duration: the studies CV181080, D1680C00001, and D1680C00002) indicated that the effect size of the FDC during longer than 12 weeks is acceptable for the add on indication.
Concerning study CV181080, the Applicant was asked in the day 120 list of questions to perform a true ITT analysis in which the observed values after rescue/discontinuation are imputed, instead of using LOCF data or exclusion of the missing data. Since the Applicant was not able to perform this analysis, alternative methods for handling missing data were used. The step-wise worse case sensitivity analyses showed that imputation of unfavorable values up to 9% for the intervention group patients still retained the statistical significance of the difference. The repeated measurements analysis and BOCF analysis showed statistically significant HbA1c changes from baseline for the intervention group, compared to the control group. Therefore, the conclusion that "the reduction of HbA1c by Komboglyze is statistically significantly better than by placebo", was reasonably robust against the missing data, and therefore the CHMP found the efficacy of Komboglyze as an "add-on" indication in patients treated with metformin to be sufficiently supported.
During the procedure the CHMP questioned whether the substantial percentage of patients (62%) on metformin on doses ≥2000 mg daily at baseline in study CV181080 limits the relevance of this study for the proposed posology of the FDC allowing a maximum of 2000 mg per day of metformin. The applicant argued that while the majority of patients received ≥2000 mg metformin per day, only 8.8% of subjects received in excess of 2000 mg per day, and that the change in HbA1c was similar in the subgroups with >2000 mg metformin per day compared with ≤2000 mg, respectively, consistent with that in the overall study population, which was found to be satisfactory by the CHMP. The proposed dosages of metformin in the FDC with saxagliptin cover the most commonly used dosages of metformin, which for most patients also represents a maximally effective dosage. The same results can be obtained when lower doses of metformin are given, like those that can be obtained with the FDC (maximally 2000 mg).

The claimed indication also consisted of a switch indication, for patients already on metformin BID + saxagliptin 5 mg QD switched to the FDC, which was ultimately found to be acceptable with regard to shown efficacy by the CHMP, because of the results of the newly submitted study PK study CV181152.

2.5.4. Conclusions on the clinical efficacy

For patients already on metformin BID + saxagliptin 5 mg QD switched to the FDC (switch indication), the balance of evidence showed therapeutic equivalence between saxagliptin 2.5 mg bid and 5 mg o.d.
For the add-on indication, demonstration of relevant add-on effects of the combination in non-responders to metformin alone were also found to be acceptable by the CHMP.

2.6. Clinical safety

Clinical safety

As there is no meaningful PK interaction between saxagliptin and metformin, as reported in the original saxagliptin (study CV181017) the safety and tolerability profile of co-administered metformin and saxagliptin is expected to be similar to those of the individual agents.

In the subsequent sections, information is provided in detail with regard to the newly submitted study **CV181080,** which is the only available study where saxagliptin was used as 2.5 mg BID.
A summary of clinical cafety concerning this application is mainly based on phase 3 studies that examined saxagliptin and metformin administered as combination therapy (separate tablets) in subjects with type 2 diabetes from previous phase 3 studies included in the initial MAA for Onglyza, and in some cases their extension. Because of design differences among these phase 3 studies, no pooling of data has been performed and the findings from these studies had been analyzed separately.

Patient exposure

Overall, 2158 patients were exposed to the combination of saxagliptin and metformin, including FDC product, in phase 3 and 72 patients in phase 1. Mean durations of exposure to saxagliptin in combination with metformin (including rescue) were greatest in the phase 3 studies **CV181014** and **CV181039**. Mean duration of exposure to saxagliptin as add-on therapy to metformin ranged from 75 weeks to 81 weeks in study **CV181014** at the cut-off date for the interim analysis (ST + LT). In study **CV181039**, mean duration of exposure to saxagliptin in combination with metformin as initial therapy was approximately 62 weeks for the ST + LT periods. In the saxagliptin monotherapy study (**CV181038**), mean duration of exposure to the 5-mg evening dose of saxagliptin was
60 weeks. Furthermore, mean duration of exposure to saxagliptin as add-on therapy to metformin in the ST period of study **D1680C00001** was 45 weeks. In studies **D1680C00002**, **CV181080** and **CV181066** the mean duration of exposure were 17 weeks, 11.5 and 4.1 weeks, respectively. A summary of these studies is provided in the efficacy section of this report.

In study **CV181080** in the saxagliptin 2.5 mg BID group 74 patients were included and 66 completed 12 weeks, in the placebo group 86 were included and 78 completed 12 weeks.

Adverse events

The safety assessment during the original MAA of saxagliptin given at doses of 2.5 and 5 mg was associated with an overall clinical AE profile that was comparable to placebo. Upper respiratory tract infections (URI), headache and UTI were the adverse events that were more frequent (≥5) among subjects treated with the recommended dose of saxagliptin (5 mg) as compared to placebo.

Adverse events of special interest for saxagliptin included hypoglycaemia, skin disorders, infections, lymphopenia, thrombocytopenia, localized edema and cardiovascular events.

Pancreatitis, gastrointestinal-related AEs, hypersensitivity reactions and fractures were identified as AEs of special interest after the original saxagliptin registration dossier was prepared.

The second component of Komboglyze, metformin, has a well-established safety profile that includes several common events (primarily gastrointestinal AEs such as nausea or diarrhoea) and as rare event lactic acidosis occurring in predisposed patients (particularly those with renal insufficiency).

In comparison to metformin monotherapy, the saxagliptin/metformin combination was associated with an increase in the adverse drug reactions nasopharyngitis, dyspepsia, myalgia, gastritis, arthralgia and erectile dysfunction. These events are included in the RMP and the AEs reflected in the SPC.

Previously assessed studies:

Once-daily, orally-administered saxagliptin was safe and well-tolerated at the doses studied. Saxagliptin given at doses of 2.5 and 5 mg was associated with an overall clinical AE profile that was comparable to placebo. The frequency of AEs leading to discontinuation was low, most frequently lymphopenia, increased blood CK, increased blood creatinine, nausea and eye pain.

In the placebo-controlled phase 3 studies, upper respiratory tract infections (URI), headache and UTI were the adverse events that were more frequent (≥5% and without any thresholds between treatment groups) among subjects treated with the recommended dose of saxagliptin (5 mg) as compared to placebo. The monotherapy study **CV181038** demonstrated that the AE profile of saxagliptin was not compromised by evening administration.

In the add-on to metformin combination study (**CV181014**), the overall frequency of AEs (excluding events of hypoglycaemia) during the ST period was higher for subjects receiving saxagliptin (73.2%) relative to placebo (64.8%). AEs were reported by 78.1%, 69.6%, and 71.8% of the subjects in the saxagliptin 2.5 mg, 5 mg, and 10 mg treatment groups, respectively. AEs were more frequent (>2%) in the pooled saxagliptin group than placebo group for the following SOCs: Infections and Infestations (38.3% vs. 35.8%); Investigations; Eye Disorders; Blood and Lymphatic Disorders. AEs that were more frequent (>1%) among saxagliptin- than placebo-treated subjects included: URI, abdominal pain, arthralgia, pharyngolaryngeal pain, and blood CK increased.
Adverse reactions with saxagliptin 5 mg were: upper respiratory tract infection, urinary tract infection, gastroenteritis, sinusitis, headache, and vomiting. Adverse events considered at least possibly related (investigator assessed) to saxagliptin 5 mg were dyspepsia and myalgia.
Long term extension of this study was assessed in variation EMEA/H/C/001039/II/07 and EMEA/H/C/001039/FUM011 for Onglyza. No new safety signals were detected compared with the analyses after 24 weeks treatment.

In the short term treatment period of the initial combination study (**CV181039**) with saxagliptin 10 mg plus metformin, diarrhoea was an AE in 10% of subjects. Overall, at a frequency of ≥ 5%, nasopharyngitis, and headache were more common for subjects receiving initial combination saxagliptin 5 mg plus metformin relative to metformin monotherapy. Severe nasopharyngitis was reported for 1 subject in the saxagliptin 5 mg plus metformin group. Headache of severe intensity was reported for 2 subjects in each of the control groups (saxagliptin 10 mg monotherapy and metformin monotherapy); otherwise,all of the events in the saxagliptin 5 mg plus metformin group were of mild or moderate intensity. The majority of these AEs were considered unrelated to treatment, and none resulted in discontinuation of treatment. Adverse events considered at least possibly related (investigator assessed) to saxagliptin5 mg plus metformin were: gastritis, arthralgia, myalgia, and erectile dysfunction. The overall safety of the initial combination use of saxagliptin 5mg plus metformin was similar to saxagliptin monotherapy or metformin monotherapy. Long-term results were assessed in variation EMEA/H/C/001039/II/07. Compared to the short term period no new and unexpected safety concerns were identified.

The following adverse events of special interest were identified:
Hypoglycaemia: Incidence of hypoglycaemia was low with saxagliptin treatment in the original MAA.
Skin disorders: Evaluation of clinical data did not revealed signals that correlate to the skin findings in the Cynomolgus monkey. Taking into consideration the fact that skin lesions are a concern for other DPP-4 inhibitors and the limited experience in patients with diabetic skin complications treated with saxagliptin, this issue is reflected in the SPC.
Infections: The frequency of infection-related AEs leading to discontinuation was low.
Lymphopenia and thrombocytopenia: At a saxagliptin dose of 5 mg, a small decrease in mean absolute lymphocyte count from baseline was observed; the decreases were not associated with clinically relevant adverse events. There is no evidence that there is an effect of saxagliptin treatment on platelet count that is of clinical importance
Localized edema: The frequency of localized edema adverse events was low.
Cardiovascular events: Overall, the frequency of cardiovascular AEs was low across the monotherapy studies and the add-on combination studies. In these studies, the frequency of cardiovascular deaths was 0.2% (4/2043) in subjects treated with saxagliptin and 0.8% (6/799) in subjects in the control group. The overall experience in patients with heart failure and other cardiac disorders is limited by the inclusion criteria in the studies. The limited experience heart failure is reflected in the SPC.
Hypersensitivity reactions: The frequency of hypersensitivity reaction adverse events was low. This is of importance as in other DDP4-inhibitors in the long-term an increased risk of hypersensitivity reaction adverse events has been reported. These events are included in the RMP and the AEs reflected in the SPC.

The frequency of serious adverse events (SAEs) was generally comparable between the saxagliptin and control groups throughout the main phase 3 studies. Serious adverse events were uncommon in all studies, and there was no predominance of any single, specific SAE associated with saxagliptin treatment. In the individual studies, SAEs considered to be related to study drug (≤0.9%) or leading to

discontinuation (≤1.6%) were infrequent in subjects who received saxagliptin and occurred at rates generally comparable to that of placebo.
The frequency of deaths in the phase 2b/3 studies was similar in subjects who received saxagliptin and placebo. One death in saxagliptin and one in the metformin group (CV181039) were considered possibly related to study medication.

The clinical adverse event profile of saxagliptin did not differ consistently within major subgroups, including by gender, age (<65 and ≥65 years), race, ethnicity, BMI, duration of diabetes, and degree of renal insufficiency. In an analysis of 5 pooled placebo-controlled monotherapy and combination studies, 71.3% of subjects <65 years of age treated with saxagliptin and 67.2% of subjects in the placebo group were reported to have AEs. AEs were reported in fewer subjects ≥ 65 years of age treated with saxagliptin compared with subjects treated with placebo (71.3% and 79.6%, respectively).

Actively controlled studies

D1680C00001 (saxagliptin plus metformin versus glipizide plus metformin).
This study was assessed in variation EMEA/H/C/001039/II/05 of Onglyza. It was concluded that saxagliptin added to metformin was safe and well tolerated**.**
There was no saxagliptin-associated pancreatitis. Saxagliptin resulted in a significantly lower proportion of patients with hypoglycaemia: 3% versus 36.3% for glipizide. Saxaglitpin treatment resulted in a decrease from baseline in body weight as compared with glipizide. Overall safety was acceptable without any unexpected events.

D1680C00002 (saxagliptin plus metformin to sitagliptin plus metformin).
This study was assessed in variation EMEA/H/C/001039/II/06 of Onglyza. Overall, the numbers of subjects experiencing any AE or SAE were similar between the treatment groups, and no new, unexpected adverse events were seen.
The number of hypoglycaemia was low in both groups, however, there were several incidents of hyperglycaemia. This happened more often in the saxagliptin group in comparison with the sitagliptin group. There was a modest mean decrease in body weight in both treatment groups.

Adverse events in the newly submitted study **CV181080**:

Table19: Overall Summary of Adverse Events During Double-Blind Treatment Period

-	Number (%) of Subjects	
	Saxa 2.5 mg (BID) N=74	Placebo N=86
AT LEAST ONE ADVERSE EVENT	19 (25.7)	34 (39.5)
AT LEAST ONE RELATED ADVERSE EVENT	1 (1.4)	3 (3.5)
DEATHS	0	0
AT LEAST ONE SAE	1 (1.4)	1 (1.2)
AT LEAST ONE RELATED SAES	0	0
DISCONTINUATIONS DUE TO SAES	0	0
DISCONTINUATIONS DUE TO AES	0	0

Data set: Treated subjects
AEs are included up to the last of 1) the last treatment day + 1 day or 2) the last visit day in the DB period.
SAEs are included up to the last of 1) the last treatment day + 30 days or 2) the last visit day + 30 days in the DB period.
Discontinuation due to AE is any AE with action taken (AEACTL) to be 5 (Discontinued).
Related AE or SAE includes events with a relationship to study drug of certain, probable, possible, and missing.
Events of hypoglycaemia are included in all categories.

Subjects experiencing at least one AE was 25.7% for saxa- treated subjects as compared with 39.5% of subjects in the placebo group. No subjects discontinued due to AEs or SAEs.

The overall incidence of most common AEs (incidence ≥2%) during the double-blind treatment period, excluding all events of hypoglycaemia, was 24.3% in subjects receiving saxagliptin compared with 39.5% in subjects receiving placebo (table 19). AEs occurring in ≥ 2 subjects receiving saxagliptin were: back pain, dizziness, hypertension, lymphadenopathy, and nasopharyngitis, (all in 2 subjects each, 2.7%). AEs occurring in ≥ 2 subjects receiving placebo were: back pain, diarrhea, headache, and

muscle spasms (all in 3 subjects each, 3.5%) and bronchitis, cholecystitis, hypertension, nasopharyngitis, and sinus congestion (all in 2 subjects each, 2.3%).
The only SOC for which there was a ≥ 5.0% difference in the incidence of AEs for saxagliptin overall versus placebo was Infections and Infestations: saxagliptin 5 subjects, 6.8%; placebo 11 subjects, 12.8%.

Table 20: Most Common Adverse Events (Incidence ≥ 2%) - Summary by System Organ Class and Preferred Term

System Organ Class (SOC) (%) Preferred Term (PT) (%)	Saxa 2.5 mg (BID) N=74	Placebo N=86
TOTAL SUBJECTS WITH AN EVENT	18 (24.3)	34 (39.5)
INFECTIONS AND INFESTATIONS	5 (6.8)	11 (12.8)
BRONCHITIS	1 (1.4)	2 (2.3)
NASOPHARYNGITIS	1 (1.4)	2 (2.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4 (5.4)	8 (9.3)
BACK PAIN	2 (2.7)	3 (3.5)
MUSCLE SPASMS	1 (1.4)	3 (3.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (4.1)	0
LYMPHADENOPATHY	2 (2.7)	0
GASTROINTESTINAL DISORDERS	3 (4.1)	6 (7.0)
DIARRHOEA	1 (1.4)	3 (3.5)
NERVOUS SYSTEM DISORDERS	2 (2.7)	5 (5.8)
DIZZINESS	2 (2.7)	0
HEADACHE	0	3 (3.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (2.7)	3 (3.5)
SINUS CONGESTION	1 (1.4)	2 (2.3)
VASCULAR DISORDERS	2 (2.7)	3 (3.5)
HYPERTENSION	2 (2.7)	2 (2.3)
HEPATOBILIARY DISORDERS	1 (1.4)	2 (2.3)
CHOLECYSTITIS	0	2 (2.3)
PSYCHIATRIC DISORDERS	0	2 (2.3)
INSOMNIA	0	2 (2.3)

The only subject with a confirmed hypoglycemic event (symptoms with finger stick glucose ≤ 50 mg/dL) was a placebo subject. Four (5.4%) subjects in the saxagliptin group and 1 (1.2%) subject in the placebo group experienced a hypoglycemic AE. All events were of mild or moderate intensity and no subjects required medical assistance.

There were no AEs of skin disorders, lymphopenia, localized edema, hypersensitivity, fractures, nor of pancreatitis. Percentage subjects who experienced at least 1 AE was lower in saxagliptin-treated subjects (25.7%) compared with subjects in the placebo group (39.5%). This difference was scattered over many SOCs, including Infections and Infestations (6.8% versus 12.8%), Musculoskeletal and Connective Tissue Disorders (5.4% versus 9.3%), and Gastrointestinal Disorders (4.1% versus 7.0%). There was 1 SAE in each arm, and no subjects discontinued due to AEs.

Summary

Based on information from trials performed at the time of the initial MAA for Onglyza, trials performed post marketing, and from spontaneous reports, the most common adverse reactions with the combined use of saxagliptin and metformin are upper respiratory infection, urinary tract infection, gastroenteritis, sinusitis, nasopharyngitis, headache, vomiting, nausea and rash. A common side effect of metformin use is metallic taste.

From post marketing trials and spontaneous reports of Onglyza, additional, uncommon adverse reactions emerged: pancreatitis (now mentioned in section 4.8 of the SPC, and also included as a warning in section 4.4 of the SPC to raise awareness), serious hypersensitivity reactions including anaphylactic reaction, anaphylactic shock and angioedema (included now in section 4.3, 4.4 and 4.8 of the SPC), dermatitis, pruritus, and urticaria.

Serious adverse event/deaths/other significant events

In study **CV181080** no deaths were reported. One subject in each treatment group reported at least 1 SAE during the double-blind treatment period, none of which was considered by the investigator to be related to study drug.

In previous studies, the frequency of serious adverse events (SAEs) was generally comparable between the saxagliptin and control groups throughout the main phase 3 studies. Serious adverse events were uncommon in all studies, and there was no predominance of any single, specific SAE associated with saxagliptin treatment. In the individual studies, SAEs considered to be related to study drug (≤0.9%) or leading to discontinuation (≤1.6%) were infrequent in subjects who received saxagliptin and occurred at rates generally comparable to that of placebo.
The frequency of deaths in the phase 2b/3 studies was similar in subjects who received saxagliptin and placebo. One death in saxagliptin and one in the metformin group (CV181039) were considered possibly related to study medication

Laboratory findings

In study **CV181080** mean absolute lymphocyte counts were generally stable across both treatment groups. No MA in platelet count was reported. There were no MAs in ALP or total bilirubin in either treatment group. One subject in the saxagliptin group had MAs in AST and ALT (>3 xULN but not >5 x ULN) and baseline levels of AST and ALT were elevated in this subject. Laboratory studies, vital signs and ECGs did not reveal a safety signal. No safety signal was detected for any of these types of events.

Safety in special populations

In study **CV181080** the AE profiles across the saxagliptin and comparator group were similar within subgroups by age (<65 and ≥65 years) and sex, as compared with the overall study population.

Because of the risk of metformin accumulation and lactic acidosis when renal function is impaired, the SPC states that Komboglyze is contraindicated in patients with moderate and severe renal impairment (creatinine clearance <60 mL/min).

Because of the elevated risk of lactic acidosis in patients with hepatic impairment the SPC states that Komboglyze is contraindicated in patients with hepatic impairment.

There are no adequate and well-controlled studies in pregnant and lactating women. Until April 2010, no reports of lactating women taking saxagliptin were revealed.

Safety related to drug-drug interactions and other interactions

There have been no formal interaction studies for Komboglyze. Based on the evaluation of study CV181017 in the original MAA of Onlgyza, there is no indication of a significant interaction between the individual components of Komboglyze, and this is therfore acceptable. No new and unexpected drug-drug interaction and other interactions have been reported.

Discontinuation due to adverse events

In study **CV181080** there was 1 SAE in each arm, and no subjects discontinued due to AEs.

Post marketing experience

Komboglyze is not marketed, therefore no postmarketing experience is available for the FDC product. The most recent review of the safety data for Onglyza (saxagliptin) did not reveal any new significant safety issues. Additional, uncommon adverse reactions emerging from spontaneous reports of Onglyza have been adressed as described above. The safety profile of saxagliptin remains similar to the profile established during clinical trials. Metformin is a widely available and an established treatment for T2DM that has proven to be safe at recommended doses.

2.6.1. Discussion on clinical safety

The safety and tolerability profile of co-administered saxagliptin and metformin is expected to be similar to those of the individual components, as there is no indication of a significant interaction between the individual components in the FDC (**CV181017**) and no new and unexpected drug-drug interaction or other interactions were reported.

Overall, 2158 patients were exposed to the combination of saxagliptin and metformin, including FDC product, in phase 3 and 72 patients in phase 1. The application did not contain a full summary of safety data due to differing study designs, but provided safety reports of the individual studies. The safety assessment during the original MAA of saxagliptin given at doses of 2.5 and 5 mg was associated with an overall clinical AE profile that was comparable to placebo. Upper respiratory tract infections (URI), headache and UTI were the adverse events that were more frequent (≥5) among subjects treated with the recommended dose of saxagliptin (5 mg) as compared to placebo.
Adverse events of special interest for saxagliptin included hypoglycaemia, skin disorders, infections, lymphopenia, thrombocytopenia, localized edema and cardiovascular events. Pancreatitis, gastrointestinal-related AEs, hypersensitivity reactions and fractures were identified as AEs of special interest after the original saxagliptin registration dossier was prepared.
In comparison to metformin monotherapy, the saxagliptin/metformin combination was associated with an increase in the adverse drug reactions nasopharyngitis, dyspepsia, myalgia, gastritis, arthralgia and erectile dysfunction. These events are included in the RMP and the AEs reflected in the SPC.

The overall profile of AEs associated with extended dosing of saxagliptin for up to 2 years was consistent with that seen at 24 weeks.
From the safety database all the adverse reactions reported in clinical trials have been included in the SPC.

2.6.2. Conclusions on the clinical safety

Once-daily, orally-administered saxagliptin was safe and well-tolerated at the doses studied, and the safty profile of metformin is well known. The safety of the combined use of saxagliptin and metformin therapy has been extensively characterized in the original saxagliptin registration dossier.
The safety findings from the recently submitted phase 3 studies presented in this application are generally consistent with the results of AE assessments in the original Onglyza registration dossier. There were no unexpected adverse events. In general, the observed adverse events profile of saxagliptin/metformin was acceptable and manageable.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

Table 21: Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Lactic acidosis	Routine PV	Product labeling is sufficient to address safety concern. Lactic acidosis is listed in the product labeling (SmPC): Section 4.2 Posology and method of administration Monitoring of renal function is necessary to prevent metformin- associated lactic acidosis, particularly in the elderly. Section 4.4 Special warnings and precautions for use Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin, a component of Komboglyze, accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately. The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure which has been associated with lactic acidosis in patients receiving metformin. As Komboglyze contains metformin, a patient with type 2 diabetes previously well controlled on Komboglyze who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Section 4.5 Interaction with other

		medicinal products and other forms of interaction There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to the metformin active substance of Komboglyze. Consumption of alcohol and medicinal products containing alcohol should be avoided. The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Therefore Komboglyze must should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re- evaluated and found to be normal. Section 4.8 Undesirable effects Lactic acidosis is listed as a very rare adverse reaction. Section 4.9 Overdose High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.
Hypersensitivity reactions	Routine PV	Product labeling is sufficient to address safety concern. Specific hypersensitivity reactions are listed in the product labeling (SmPC): Section 4.3 Contradindications hypersensitivity to the active substance(s) or to any of the excipients, or history of a serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock, and angioedema, to any dipeptidyl peptidase 4 (DPP4) inhibitor. Section 4.4 Special warnings and precautions for use; As Komboglyze contains saxagliptin, it should not be used in patients who have had any serious hypersensitivity reaction to a dipeptidyl peptidase 4 (DPP4) inhibitor. During postmarketing experience, including spontaneous reports and clinical trials, the following adverse reactions have been reported with the use of saxagliptin: serious hypersensitivity reactions, including anaphylactic reaction, anaphylactic shock, and angioedema. If a serious

		hypersensitivity reaction to saxagliptin is suspected, discontinue Komboglyze, assess for other potential causes for the event, and institute alternative treatment for diabetes. Section 4.8 Undesirable effects Hypersensitivity reactions are listed as an uncommon adverse reaction.
Pancreatitis	Routine PV Pancreatitis is a safety objective in a large cardiovascular outcomes trial for Onglyza	Product labeling is sufficient to address safety concern. Pancreatitis is listed in the product labeling (SmPC): Section 4.4 Special warnings and precautions for use In post-marketing experience with saxagliptin, there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of saxagliptin. If pancreatitis is suspected, Komboglyze and other potentially suspect medicinal products should be discontinued. Section 4.8 Undesirable effects Pancreatitis is listed as an uncommon adverse reaction.
Hepatitis	Routine PV	Product labeling is sufficient to address safety concern. Hepatitis is listed in the product labeling (SmPC): Section 4.8 Undesirable effects Hepatitis is listed as a very rare adverse reaction.
Infections	Routine PV	Product labeling is sufficient to address safety concern. Specific infections are listed in the product labeling (SmPC): Section 4.8 Undesirable effects Upper respiratory tract infection, urinary tract infection, gastroenteritis, sinusitis and nasopharyngitis are listed as common adverse reactions.
Gastrointestinal-related AEs	Routine PV	Product labeling is sufficient to address safety concern. Specific GI-related AEs are listed in the product labeling (SmPC): Section 4.8 Undesirable effects Vomiting is listed as a common adverse reaction.
Vitamin B12 deficiency	Routine PV	Product labeling is sufficient to address safety concern. Vitamin B12 deficiency is listed in the product labeling (SmPC): Section 4.8 Undesirable effects Vitamin B12 deficiency is listed as a very rare adverse reaction.

Important Potential Risks		
Skin lesions (ulcer, erosion, and necrosis)	Routine PV	Product labeling is sufficient to address safety concern. Skin lesions are described in the product labeling (SmPC): Section 4.4 Special warnings and precautions for use Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non clinical toxicology studies for saxagliptin. Although skin lesions were not observed at an increased incidence in clinical trials, there is limited experience in patients with diabetic skin complications. Postmarketing reports of rash have been described in the DPP4 inhibitor class. Rash is also noted as an adverse event (AE) for saxagliptin. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended. Section 5.3 Preclinical safety data In cynomolgus monkeys saxagliptin produced reversible skin lesions (scabs, ulcerations and necrosis) in extremities (tail, digits, scrotum and/or nose) at doses ≥ 3 mg/kg/day. The no effect level (NOEL) for the lesions is 1 and 2 times the human exposure of saxagliptin and the major metabolite respectively, at the recommended human dose of 5 mg/day (RHD). The clinical relevance of the skin lesions is not known, however clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.
Lymphopenia	Routine PV	Product labeling is sufficient to address safety concern. Effect on lymphocyte counts is described in the product labeling (SmPC): Section 4.8 Undesirable effects Across clinical studies, the incidence of laboratory adverse event was similar in patients treated with saxagliptin 5 mg compared to patients treated with placebo. A small decrease in absolute lymphocyte count was observed. From a baseline mean absolute lymphocyte count of approximately 2,200 cells/µl, a mean decrease of approximately 100 cells/µl relative to placebo was observed in the placebo controlled pooled analysis. Mean absolute lymphocyte counts remained stable with daily dosing up to 102 weeks in duration. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The clinical

		significance of this decrease in lymphocyte count relative to placebo is not known.
Thrombocytopenia	Routine PV	None
Hypoglycemia	Routine PV	Product labeling is sufficient to address safety concern. Hypoglycemia is described in the product labeling (SmPC): Section 4.8 Undesirable effects Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The incidence of reported hypoglycaemia for saxagliptin 5 mg versus placebo given as add on therapy to metformin was 5.8% versus 5%. The incidence of reported hypoglycaemia was 3.4% in treatment- naive patients given saxagliptin 5 mg plus metformin and 4.0% in patients given metformin alone.
Bone fracture	Routine PV	None
Severe cutaneous adverse Reactions	Routine PV	None
Opportunistic infections	Routine PV	None
Important Missing/Limited Information		
Safety in patient ≥ 75 years of age	Routine PV	Product labeling is sufficient to address safety concern. Specific information for the elderly population is described in the product labeling (SmPC): Section 4.2 Posology and method of administration As metformin and saxagliptin are excreted by the kidney, Komboglyze should be used with caution in the elderly. Monitoring of renal function is necessary to prevent metformin-associated lactic acidosis, particularly in the elderly. Section 4.4 Special warnings and precautions for use Experience in patients aged 75 years and older is very limited with saxagliptin and caution should be exercised when treating this population. Section 5.2 Pharmacokinetic properties Elderly patients (65-80 years) had about 60% higher saxagliptin AUC than young patients (18-40 years). This is not considered clinically meaningful, therefore, no dose adjustment for Komboglyze is recommended on the basis of age alone.

Safety in paediatric population < 18 years of age	Routine PV A paediatric plan (eg, PIP) for saxagliptin has been approved by EMA	Safety not established in this population. Specific information for the paediatric population is described in the product labeling (SmPC): Section 4.2 Posology and method of administration The safety and efficacy of Komboglyze in children from birth to < 18 years of age have not been established. No data are available.
Patients with cardiovascular disease (defined as significant cardiovascular history within 6 months) and patients with compromised cardiac function (CHF) III and IV	Routine PV A large cardiovascular outcomes trial for Onglyza is being conducted to evaluate the effect of saxagliptin on the incidence of CV death, myocardial infarction, or ischaemic stroke in patients with Type 2 diabetes Ongoing CV adjudication in saxagliptin clinical trial program Saxagliptin epidemiology program for further risk evaluation of major adverse cardiovascular events.	Product labeling is sufficient to address safety concern. Specific information for this population is described in the product labeling (SmPC): Section 4.3 Contraindication Komboglyze is contraindicated in patients with: acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock
Safety in immunocompromised Patients	Routine PV	Product labeling is sufficient to address safety concern. Warning and precaution information for immunocompromised patients is described in the product labeling (SmPC): Section 4.4 Special warnings and precautions for use Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome, have not been studied in the saxagliptin clinical program. Therefore, the efficacy and safety profile of saxagliptin in these patients has not been established.
Safety in pregnancy/breast feeding	Routine PV	Product labeling is sufficient to address safety concern. Specific information (warnings and precautions) regarding the use of saxagliptin metformin FDC in pregnancy and nursing women is described in the product labeling (SmPC): Section 4.6 Fertility, pregnancy and lactation The use of Komboglyze or saxagliptin has not been studied in pregnant women. Studies in animals have shown reproductive toxicity at high doses of saxagliptin alone or in combination with metformin. The potential risk for humans is unknown. A limited amount of data suggest the use of metformin in

		pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development. Komboglyze should not be used during pregnancy. If the patient wishes to become pregnant, or if a pregnancy occurs, treatment with Komboglyze should be discontinued and switched to insulin treatment as soon as possible. Studies in animals have shown excretion of both saxagliptin and/or metabolite and metformin in milk. It is unknown whether saxagliptin is excreted in human milk, but metformin is excreted in human milk in small amounts. Komboglyze must therefore not be used in women who are breast-feeding.
Malignancy/neoplasm	Routine PV Assessment in cardiovascular outcomes study for Onglyza	None

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

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The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The benefits with Komboglyze are: 1) its reduction of blood glucose levels in patients inadequately controlled by metformin alone as "add-on" to an existing metformin monotherapy and 2) as being equivalent in its glucose-lowering effect compared to the combined use of saxagliptin 5mg once daily and metformin twice daily as an alternative option for patients being treated with these 2 medicines as separate tablets already ("switch indication").
With regard to 1) the use of Komboglyze following a monotherapy with metformin it was shown in study CV181080, that after 12 weeks saxagliptin 2.5 mg BID resulted in a statistically significant greater reduction in HbA1c from baseline than placebo, when added to metformin. The difference in the adjusted mean change from baseline versus placebo was -0.34% (95% CI [-0.58, -0.10]). In addition, effects on FPG were numerically greater in the saxagliptin 2.5 mg group, although the difference was not statistically significant.
With regard to 2) the "switch indication" the criteria for bioequivalence of saxagliptin and metformin from the 2.5 mg saxagliptin/850 mg metformin FDC tablets compared to co-administered 2.5 mg

saxagliptin and 850 mg EU-sourced metformin as separate tablets under both fed and fasted conditions were met for Cmax, AUC(INF) and AUC(0-T) (study CV181121). Furthermore, the applicant demonstrated in a newly submitted PK/PD study (CV181152) that saxagliptin 2.5 mg BID is equivalent to saxagliptin 5 mg QD in terms of PK/PD. This study showed that over 24 hours, AUC(0-24 h), one 5 mg saxagliptin tablet and 2 combination tablets containing 2.5 mg saxagliptin is bioequivalent in terms of exposure. The inhibition of DPP-IV activity and elevation in iGLP-1 activity by saxagliptin 2.5 mg BID were also equivalent to the 5 mg QD regimen. This, together with clinical data, allowed the conclusion that a difference seen in C_{max}, within this dose range, does not result in differences in glucose lowering activity.Komboglyze was thus shown to be equivalent in its glucose-lowering effect compared to the combined use of saxagliptin 5mg once daily and metformin in its corresponding dose given twice daily. It can be assumed, that the use of only one type of tablet instead of two may improve patient compliance.

Uncertainty in the knowledge about the beneficial effects.

The effect size in study CV181080 was small and its clinical relevance with regard to HbA1c lowering effect debatable (-0.34%) and the 95% confidence interval (CI) was wide (-0.58, -0.10). Furthermore, the predefined Δ of 0.6% was not reached, but nevertheless a significant effect on HbA1c was demonstrated and thus acceptable (see Discussion section below).

Risks

Unfavourable effects

Saxagliptin 2.5 mg BID added to metformin BID was well tolerated and there were no unexpected adverse events.
Based on information from trials performed at the time of the initial MAA for Onglyza, trials performed post marketing, and from spontaneous reports, the most common adverse reactions with the combined use of saxagliptin and metformin are upper respiratory infection, urinary tract infection, gastroenteritis, sinusitis, nasopharyngitis, headache, vomiting, nausea and rash. A common side effect of metformin use is metallic taste.
From post marketing trials and spontaneous reports of Onglyza, additional, uncommon adverse reactions emerged: pancreatitis (mentioned in section 4.8 of the SPC, and also included as a warning in section 4.4 of the SPC to raise awareness), serious hypersensitivity reactions including anaphylactic reaction, anaphylactic shock and angioedema (included in section 4.3, 4.4 and 4.8 of the SPC), dermatitis, pruritus, and urticaria.

Uncertainty in the knowledge about the unfavourable effects

Elderly patients and patients with co-morbidities were excluded. This exclusion makes an assessment of the efficacy and safety in such subjects impossible. These uncertainties are reflected in the SmPC.

Benefit Risk Balance

Importance of favourable and unfavourable effects

The single benefit with regard to the "switch indication" is the assumption of a benefitial effect on patient compliance in the long term treatment. The benefit of the "add on" indication is improved glycaemic control. The combination of saxagliptin and metformin is well tolerated and has not resulted in unexpected unfavourable effects.

Benefit-risk balance

The overall B/R of Komboglyze is positive.

Discussion on the Benefit Risk Balance

The indication consists of a switch indication, for patients already on metformin BID + saxagliptin 5 mg QD switched to the FDC, and an add-on indication for patients insufficiently controlled on metformin BID alone.
For the **switch indication**, it was shown that saxagliptin 2.5 mg BID was equivalent to saxagliptin 5 mg QD in terms of exposure and PD. The lower C_{max}, within this dose range does not impact its glucose lowering activity. The use of Komboglyze, compared to the use of saxagliptin and metformin as individual tablets, is to be equally efficacious with the assumed benefit of improved compliance.
For the **add-on indication**, demonstration of add-on effects of the combination in non-responders to metformin alone was acceptable. Study CV181080 demonstrated efficacy, but the effect size was small and its clinical relevance debatable (-0.34% reduction in HbA1c). As equivalence between saxagliptin 2.5 mg BID and saxagliptin 5 mg QD has been demonstrated, the assessment took also into account the larger effect size seen in larger, previous clinical studies where saxagliptin 5 mg was added to metformin and for which and add-on indication has been approved, and therefore in analogy this indication was also acceptable for the FDC with regard to demonstrated efficacy. As no unexpected adverse side effects occurred, these indications were considered acceptable by the CHMP.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Kombogyze in the treatment of type 2 diabetes is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).
In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow the standard requirements.

Conditions or restrictions with regard to the safe and effective use of the medicinal product
Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.
Not applicable.