European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Onglyza

International Nonproprietary Name: saxagliptin

Procedure No. EMEA/H/C/001039

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Bristol-Myers Squibb/AstraZeneca EEIG submitted on 1 July 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Onglyza, 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 EMEA/CHMP on 24 January 2008.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The applicant applied for the following indication:

Add-on combination therapy:
Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin, when the single agent alone, with diet and exercise, does not provide adequate glycaemic control.

Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with a sulfonylurea, when the single agent alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate.

Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with a PPARγ agonist (i.e., a thiazolidinedione, TZD) when the single agent alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a PPARγ agonist is considered appropriate.

Initial combination therapy:
Onglyza is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control in patients with type 2 diabetes mellitus when treatment with both Onglyza and metformin therapy is appropriate.

Scientific Advice:
The applicant received Scientific Advice 20 March 2007. The Scientific Advice pertained to clinical aspects of the dossier, specifically relating to the design of an add-on active-controlled study.

Licensing status:
A new application was filed in the following countries: United States of America
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Pieter de Graeff Co-Rapporteur: Liv Mathiesen

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 1 July 2008.
- The procedure started on 23 July 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 October 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2008.
- During the meeting on 20 November 2008, 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 21 November 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 April 2009 and an updated version on 17 April 2009.
- During the CHMP meeting on 23 April 2009, 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 consolidated List of Outstanding Issues on 15 May 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 08 June 2009.
- During the meeting on 22-25 June 2009, 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 Onglyza on 25 June 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 June 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Type 2 Diabetes Mellitus (T2DM) is a common chronic metabolic disorder, which can lead to substantial morbidity and increased mortality rates. Data from the Diabetes Control and Complications Trial, the Stockholm Diabetes Intervention Study in type 1 diabetes, and the United Kingdom Prospective Diabetes Study in T2DM, compared intensive with standard glucose management and showed a reduced risk of complications with improved glucose control as measured by HbA1c. Three key defects underlie the pathogenesis of the disease: insulin resistance, reduced insulin secretion, and hepatic glucose overproduction. Limitations of current therapies include a range of safety and tolerability issues, limited extent and/or durability of efficacy, and inconvenience in dosing. The most common adverse events associated with current agents are hypoglycaemia (with sulphonylureas, meglitinides, insulin), weight gain (with sulphonylureas, meglitinides, insulin, thiazolidinediones [TZDs]), and gastrointestinal intolerance (with metformin, alpha-glucosidase inhibitors). DPP4 (dipeptidyl peptidase 4) inhibitors, such as saxagliptin, have distinct mechanisms of action and might offer an improved safety and tolerability profile with good efficacy and durability. Already authorised are sitagliptin (Januvia®) and vildagliptin (Galvus®).

This application concerns the centralised procedure (Regulation (EC) No 726/2004, article 3(1) indent 3). It is submitted in accordance with Article 8(3) in Directive 2001/83/EC for a new active substance. Conditional approval, an approval under exceptional circumstances or an accelerated review were not requested.

The claimed indication was:

Add-on combination therapy:
Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin, when the single agent alone, with diet and exercise, does not provide adequate glycaemic control.

Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with a sulfonylurea, when the single agent alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate.

Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with a PPARγ agonist (i.e., a thiazolidinedione, TZD) when the single agent alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a PPARγ agonist is considered appropriate.

Initial combination therapy:
Onglyza is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control in patients with type 2 diabetes mellitus when treatment with both Onglyza and metformin therapy is appropriate.

The approved indication is:

Add-on combination therapy
Onglyza is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control:

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

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

2.2 Quality aspects

Introduction
Onglyza contains saxagliptin as active substance which is a highly potent, selective, reversible, and competitive dipeptidyl peptidase 4 (DPP4) inhibitor. DPP4 is the enzyme responsible for the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).
Incretin hormones are gastrointestinal hormones that increase insulin secretion in response to enteral stimulation. In humans, incretins such as GLP-1, regulate blood glucose via multiple mechanisms; these include stimulation of glucose-dependent insulin secretion, delaying of gastric emptying, and inhibition of hepatic glucose production. However, incretins such as GLP-1 are rapidly inactivated by DPP4. Therefore, DPP4 inhibitors should extend the effects of incretins.

Onglyza is an immediate release, film-coated tablet. Tablets contain 5 mg saxagliptin and are commercially supplied in Alu/Alu blister packaging.

Active Substance
The INN name of the active substance is saxagliptin and the chemical name (IUPAC) (1*S*,3*S*,5*S*)-2-((2*S*)-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.
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 1.2 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. Reproccessing steps have been laid down for cases when they are required; 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) and Key Process Parameters (KPP) were identified based on the risk assessments of the manufacturing process. Uni- and multivariate experiments were utilized to define the design space within the studied ranges.
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.
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. The process is considered to be sufficently under control.

- **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 (methylene chloride (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.

Results for 9 batches manufactured by the commercial process D, 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 manufactured by the process C and manufactured at a different site which were provided are considered supportive, as the two processes are essentially equivalent.

- **Stability**

A stability study on two batches manufactured by the commercial process, Process D at the commercial site covers 12 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 12 months). The results were within specifications at the long-term condition.
Results from another stability study for three batches of saxagliptin manufactured by the Phase III process 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 batches manufactured by the commercial process is lower than or similar to the level seen in batches used to support the Phase III studies.
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.

Medicinal Product

- **Pharmaceutical Development**

Saxagliptin is prone to undergo an intra-molecular cyclisation reaction in solution and solid states to form a cyclic amidine. The tablet formulation was developed using active an active coating process to minimize this formation. Saxagliptin was embedded within a film coat of Opadry spray coated onto inert core tablets. During the coating process, saxagliptin free base is converted in-situ into hydrochloride salt.
A specification limit for particle size of the drug substance is not relevant, considering that it is dissolved in a coating suspension during manufacturing of the drug product and is converted into the HCl salt.
There are no unusual excipients included. The selection of excipients was based upon the results of excipient compatibility studies to minimize the formation of the cyclic amidine.
During formulation development, several prototype formulations were investigated to arrive at the commercial formulation. Full excipient compatibility studies were performed.
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. Proven acceptable ranges have been established for several of the unit processes at three specified scales.

The risks to the commercial manufacturing of drug product and the factors potentially affecting manufacture were assessed during the development program to develop appropriate control strategies, and assess whether any factor or parameter was critical. A cause and effect diagram has been developed. 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, in-process controls, etc. for all manufacturing steps. Multiple batches of drug product manufactured at each scale over the Proven Acceptable Ranges met all CQAs and demonstrates control of the manufacturing process.

A mechanistic model has been constructed which predicts the performance of the coating process, and has been shown to closely match the experimental data. The model captures the process knowledge and relates typical operating parameters to operating conditions. The correspondence of the model predictions with experimental values was demonstrated.

- **Adventitious Agents**

Magnesium stearate is of vegetable origin. The applicant has confirmed that lactose monohydrate is the only material of animal origin and that it is sourced from healthy animals in the same way as for human use complying with regulations to ensure patient safety.

- **Manufacture of the Product**

The manufacturing process for Onglyza tablets involves active coating of saxagliptin onto an inert core tablet, followed by standard unit operations such film-coating and printing. The manufacturing equipment and the process controls were adequately described. Proven acceptable ranges (PAR) for each unit operation have been established.

The process validation was performed in a conventional manner, according to the NfG on process validation. At least three production batches were validated, and results were well within the criteria.

- **Product Specification**

The specifications of the drug product include tests for description (visual), identification (HPLC, UV, only at release), assay (HPLC), uniformity of dosage units (Ph.Eur. only at release), impurities/ degradants (HPLC), dissolution (Ph.Eur. HPLC, not routinely), microbial limits (Ph. Eur. only at

release). Drug dissolution results have been presented for six commercial scale batches of drug product. All batches display fast dissolution: 86 % or more after 10 minutes. Moreover, saxagliptin can be classified as a BCS Class III (high solubility, low permeability) compound meaning the absorption rate is the rate limiting step in vivo. It is therefore justified not to test dissolution routinely. Instead, dissolution will be tested in the 10 first commercial batches and thereafter one batch per year. The periodical dissolution test is included in the product specification.
Batch analysis results have been provided for eleven batches of 5 mg tablets from the proposed manufacturing site.
Also five 5 mg batches from another site have been submitted as supportive data. All results were well within specification.

- **Stability of the Product**

Stability data were presented for three batches. The tablets were made from drug substance manufactured by Process C. The data cover 24 months at 25°C/60%RH, 30°C/65%RH and 30°C/75%RH, and 6 months at 40°C/75%RH. The tablets were stable at all storage conditions tested, and statistical analysis was performed to support extrapolation of the data.
A matrix approach was applied to the long term conditions and the study was conducted as per ICH guidelines. For one batch the hold time of active suspension was the maximum proposed. The results for these batches were not significantly different from the results from the other batches.
Microbial quality was tested initially on tablets in HDPE bottles and on samples stored at the two 30°C storage conditions for tablets in PVC/Aclar blister packs, which was regarded as worst case in water and oxygen permeation. No change from initial was observed.
At 25°C/60%RH no significant change in assay or dissolution was seen after 24 months. The level of total degradation products increased after 24 months at 25°C/60%RH but the level was well within specifications. At 40°C/75%RH the level of total impurities increased more compared to normal condition as expected.
For photo-stability studies in accordance with ICH Q1B, no change was observed for directly exposed tablets in any parameter tested.

In conclusion the proposed shelf life and storage conditions are acceptable.

Discussion on chemical, pharmaceutical and biological aspects
The quality of Onglyza film-coated tablet is adequately established. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product including Quality by Design principles has been presented. 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.
Stability tests under ICH guidelines conditions indicate that the product is chemically stable for the proposed shelf life and storage conditions.

2.3 Non-clinical aspects

Introduction
The non-clinical profile of saxagliptin was established in a comprehensive investigational program that included studies of *in vitro* and *in vivo* pharmacodynamics, safety pharmacology, pharmacokinetics and metabolism, and toxicity and toxicokinetics. The non-clinical data from saxagliptin were also compared (where possible and appropriate) to currently available DPP4 inhibitors (vildagliptin [Galvus®] and sitagliptin [Januvia®]) developed for the treatment of type 2 diabetes mellitus.

All pivotal toxicity studies supporting the safety of saxagliptin were designed and conducted in compliance with ICH guidelines. Pivotal safety pharmacology and toxicology studies were performed

in compliance with GLP regulations. Non-pivotal and investigational studies were non-GLP; this is considered acceptable.

Pharmacology

- Primary pharmacodynamics

Saxagliptin is a selective DPP4 inhibitor which results in increased concentration of plasma GLP-1, which subsequently leads to lower plasma glucose levels. The *in vitro* affinity for the DPP4 enzyme has been shown and maximal enzyme inhibition measured *ex vivo* in plasma is evident at low doses. The affinity for other DPPs is lower with a ratio of 75 for DPP9 and 391 for DPP8. *In vivo* efficacy has been demonstrated in SD and Zucker rats, and Zucker fa/fa rats, a model for type 2 diabetes by several pharmacodynamic endpoints: plasma GLP-1, insulin and glucose levels post-glucose challenge, and fasting glucose levels. Although all endpoints were affected by treatment, long-term efficacy has not been demonstrated in an animal model.

The main metabolite, BMS-510849, also has high affinity for the DPP4 enzyme, but shows less pharmacodynamic effect in terms of lowering glucose levels than the parent compound. Only at doses in excess of those required to produce maximal DPP4 inhibition, a significant *in vivo* effect was shown. This might be due to the decreased volume of distribution of the metabolite as compared to the parent. The contribution of the metabolite to the overall efficacy of saxagliptin is probably modest.

- Secondary pharmacodynamics

Saxagliptin was evaluated *in vitro* for the potential to antagonize the binding of appropriate radioligands to 42 receptors and ion-channels or to inhibit 14 different proteases. No significant effects were observed (<25% inhibition at 10 μM) on the receptors, ion-channels, or enzymes evaluated. Cell surface DPP4 (also known as CD26) has been reported to function as a co-stimulatory signalling molecule in T lymphocyte activation. Inhibition of T-lymphocytes was shown at much higher concentrations of saxagliptin than is needed for DDP4 inhibition. Moreover, these concentrations exceed the C_{max} that is measured in humans after therapeutic doses. However, due to the large volume of distribution it cannot be excluded that the concentration required to inhibit T cell activation is reached within the T cells. No other secondary pharmacodynamic studies were performed.

- Safety pharmacology programme

No significant findings were reported from safety pharmacology studies, and therefore no adverse effects on the cardiovascular, respiratory and central nervous system are anticipated in humans.

- Pharmacodynamic drug interactions

Drug interaction studies were not conducted in non-clinical animal models. This is acceptable, considering that the issue has been adequately addressed with the clinical data.

Pharmacokinetics

The pharmacokinetics of saxagliptin and BMS-510849 the active metabolite, have been studied adequately. Plasma samples collected from mouse, rat, rabbit, dog and monkey were analysed with a validated LC/MS/MS method. For BMS-510849, this validated method was found to have co-eluting peaks of other mono-hydroxylated metabolites of saxagliptin with the same mass spectral characteristics. Subsequently, a new bioanalytical assay was developed and validated for both saxagliptin and BMS-510849 in plasma from mouse, rat, rabbit, dog and monkey. Both the original and the new validated analytical procedures used are sensitive, accurate and precise for the measurement of saxagliptin. Only the new method is sensitive, accurate and precise for the measurement of BMS-510849. Comparison of both methods showed an overestimation of the plasma concentrations of BMS-510849 by the original assay (up to 42.7%).

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 and monkey (2.1-4.4 hr). When considering the toxicokinetic

studies the AUC increase is linear with doses between 30 and 600 mg/kg for mouse, between 2 and 600 mg/kg for rat, between 0.2 and 25 mg/kg for dog, and for all doses investigated for monkey. No substantial accumulation of saxagliptin and BMS-510849 was observed after once-daily repeated dosing of saxagliptin.

The intrinsic membrane permeability of saxagliptin is very low. Both saxagliptin and BMS-510849 were not prominent substrates for P-glycoprotein (P-gp) or for cellular uptake transporters.
Protein binding of saxagliptin was not observed in dog and human, and low in mouse (27%), rat (18%) and monkey (20%). Protein binding of BMS-510849 was also very low in all species tested (up to 10%).

The highest concentrations (1-12 h) of saxagliptin related material were found in gastrointestinal tissues, liver, urinary bladder and kidney. Since radioactivity was below 1% of the dose at 24 h post-dose, accumulation is not expected. Saxagliptin and BMS-510849 levels were lowest in the brain. After oral dosing, concentrations in whole blood were lower than in plasma (blood to plasma ratio 0.71-0.88). However, 12 hours post-dose, mean concentrations in whole blood exceeded those in plasma (blood to plasma ratio 1.55), indicating binding of radioactive material to erythrocytes at later times. Saxagliptin-derived radioactivity was widely distributed in both maternal and foetal tissues. This demonstrates that saxagliptin-derived components cross the placenta in rats; therefore, Onglyza should not be used during pregnancy unless clearly necessary.

The pathways for *in vivo* metabolism of saxagliptin in humans were qualitatively similar to those in mice, rats, dogs, and cynomolgus monkeys. BMS-510849 was the major metabolite identified in plasma, urine and/or faeces in all species. The metabolic profiles from *in vitro* studies in liver microsomes and hepatocytes from various species were also similar. A large difference is observed in the number of metabolites between *in vivo* and *in vitro* metabolism. In the *in vivo* studies 46 metabolites were detected, while 3-6 metabolites were observed in *in vitro* studies. Co-administration with ketoconazole and diltiazem, CYP3A4/5 inhibitors, resulted in a 2.5 and 2.1 fold increase of the AUC of saxagliptin. No animal studies have been conducted on the effects of CYP3A4 inducers on the exposure of saxagliptin.

Following an oral dose of [^{14}C] saxagliptin, almost all the radioactivity administered was recovered in the urine and faeces of rats, dogs and monkeys. Approximately 75% of the dose in human was excreted in the urine. In humans, saxagliptin and BMS-510849 accounted for 33.6% and 28.2% of the dose in urine suggesting that both elimination of unchanged saxagliptin and metabolism to BMS-510849 plays a major role in the disposition of saxagliptin. [^{14}C] saxagliptin-derived radioactivity was excreted in milk, with radioactivity detected at all time points through 24 hours post-dose; in view of this a decision must be made whether to discontinue breastfeeding or therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy to the woman (see section 4.6 of the SPC).

Interactions with other drugs via protein binding are not expected, since saxagliptin and BMS-510849 are poorly bound to plasma proteins. Saxagliptin is unlikely to cause clinically relevant drug-drug interactions through either inhibition or induction of the major CYP isozymes.

As a consequence of toxic effects related to cyanide release seen in male rats, a series of *in vitro* experiments were conducted to measure the cyanide released during biotransformation of saxagliptin and BMS-510849. Results from these experiments showed that cyanide formation was most abundant in the incubations of saxagliptin with expressed rat CYP2C11. A study on rats pre-treated with cimetidine, a known CYP2C11 inhibitor, was performed. Cimetidine inhibited, but did not block entirely, the CYP2C11-mediated metabolism of saxagliptin to M4 in male rats. Cyanide formation from saxagliptin was observed in the liver microsomes from male rat, and small amounts in male and female monkeys, but not from female rat, mouse, dog and human. De-cyanated metabolites were detected in the brains of both male and female rats, but significantly lower in female than male rat brains. Small amounts of cyanide were detected in incubations of saxagliptin with CYPs -2C8, -2C19, and -2C21. In humans, the gene encoding CYP2C19 shows polymorphism, and as a consequence, individuals can be categorised as poor or extensive metabolisers (EM). The cDNA used in the *in vitro*

experiments corresponded to extensive metabolisers. Additionally, the main proportion of CYP2C19 enzymes in the pooled human liver microsomes comes from EM. The applicant has calculated the blood cyanide concentration in the unlikely event of complete release of cyanide from saxagliptin in humans, with a resulting cyanide blood level sufficiently below that considered to elicit clinical signs and symptoms. Bearing in mind the low level of metabolization involving CYP2C19 enzymes, it seems unlikely that metabolization of saxagliptin by CYP2C19 EM could cause any significant toxicological effects.

Toxicology

- Single dose toxicity

All but one single dose toxicity study (DN01106) were conducted in compliance with GLP. Saxagliptin was administered orally in mice, rats and monkeys as benzoate salt in 1.25% Avicel, and the control groups received equivalent volumes of 1.25% Avicel. All animals were monitored for two weeks after dosing. Main evaluations included mortality/moribund conditions, changes in behaviour and appearance. Gross examination at necropsy was performed on selected dose groups in the GLP studies. Saxagliptin-related toxicity and mortality was observed in mice, rats and monkeys. In mice and rats saxagliptin was well tolerated up to 2000 mg/kg, while overt toxicity leading to death occurred in monkeys at 50 mg/kg (monkey NOEL 25 mg/kg).

- Repeat dose toxicity (with toxicokinetics)

The repeat dose toxicity of saxagliptin was evaluated in mice, rats, dogs and cynomolgus monkeys at exposures comparable to or markedly higher than the therapeutic exposure in a number of GLP-compliant non-clinical toxicology studies. In rats, the observed target organ changes were generally minimal splenic lymphoid hyperplasia, pulmonary histiocytosis, and mononuclear-cell infiltrates/inflammation in the ocular accessory gland and liver in short and long-term studies, and after 104 weeks of dosing, the lung, urinary bladder, and epididymis, but only at high doses.

Dose- and time-related skin lesions have been observed in monkeys, with low margins of safety. The mechanism for these lesions is not known. Skin lesions have been considered as a potential class related effect of DPP4 inhibitors, and were also seen after vildagliptin treatment. However, no skin lesions have been observed with sitagliptin. The clinical relevance of these lesions is not known. Existing clinical data have not revealed skin lesions in humans following up to two years treatment of saxagliptin. However, in view of the limited number of patients with long-term treatment with saxagliptin, and most importantly the limited experience in patients with diabetic complications including peripheral artery disease and ulcer formations, a clinical relevance cannot be dismissed.

Saxagliptin-related reduction in plasma lymphocyte levels has been reported in clinical studies, but were not observed in non-clinical studies. In the non-clinical dossier, saxagliptin-related effects were seen on several immune-related organs, including thymus (mouse, rat, dog: decreased organ weight, multifocal atrophy, lymphoid depletion and necrosis), spleen (mouse, rat, monkey: increased organ weight, lymphoid hyperplasia), mesenteric and/or mandibular lymph nodes (rat, monkey: lymphoid hyperplasia, dog: lymphoid depletion/necrosis) and bone marrow (monkey: hyperplasia), with low margins of safety. Furthermore, mononuclear cell infiltrates are seen in several species. While the infiltrates only were observed in liver and footpads in dogs, the infiltrates were apparent in multiple organs in mice and in numerous rat studies (including ocular accessory gland, liver, lung and genitourinary tract). The infiltrates were most extensive in monkeys (including skin, salivary, mammary and thyroid glands, pancreas, reproductive organs, brain, kidney, and urinary bladder), and with a NOAEL of 0.3 mg/kg/day (1 and 3 times the human exposure for females and males respectively).
Several potential explanations for the multiple immune-related effects have been proposed by the applicant, including stress, excessive pharmacological effects, and non-DPP4 related mechanisms. At present, the mechanism(s) is unknown, and a clinical relevance can not be excluded.

Transient hind leg lameness, tremor and laboured respiration were observed in several monkey studies, following single and repeated dosings. Due to the transient nature of these findings, they are unlikely to be drug-related.

With regard to glomerulopathy, no such effect was observed in the pivotal repeat-dose study where monkeys were dosed with up to 3 mg/kg day for 3 months. Therefore, a sufficient safety margin (21) exists, and a risk for human safety is unlikely. Numerous studies have been conducted to investigate the mechanism for induction of brain lesion in male rats. However, these lesions have only been observed in a single range finding study, at doses with an exposure multiple of >2600-fold the human exposure. Nevertheless, the investigational studies indicate that this finding is male rat specific, and is due to the release of cyanide by CYP2C11.

- Genotoxicity

Saxagliptin did not show mutagenicity (Ames test) and clastogenicity below cytotoxic concentrations (human lymphocytes). No genotoxic potential was demonstrated *in vivo* by saxagliptin in the DNA repair, oral micronucleus, or in vivo/in vitro cytogenetics assays in rats.

Impurities BMS-537679 and BMS-554083 have been adequately qualified, and no concern regarding genotoxicity or other toxicity remains.

- Carcinogenicity

The carcinogenic potential of saxagliptin was evaluated in 104-week oral carcinogenicity studies in CD-1 mice and Harlan SD rats. These rodent strains were selected based on the relevant historical control tumor databases for these strains at the facility that conducted the studies and their use in previous toxicity studies with saxagliptin. Doses were selected based on 3-month range-finding studies. These studies were adequately designed, included measurements of systemic exposure, and were conducted in conformance with ICH guidelines and in compliance with GLP regulations. With respect to tumor analysis, appropriate statistical analyses (i.e. 1-sided Peto-Pike trend tests, sensitive to tumor rates that increase with dose) were utilized.
In both two-year carcinogenicity studies, there were no treatment-related increases in tumor incidence in any organ at all tested doses. CNS-related neurodegenerative brain lesions were seen in rats and were the likely cause of increased mortality in the 300 mg/kg/day male group. This CNS toxicity is not considered relevant for it is only shown at high doses. In the repeat-dose studies it was seen that rodents are less sensitive to saxagliptin than other species.. However, the studies are in line with the guidelines and no further studies regarding carcinogenicity are considered necessary.

- Reproduction Toxicity

A complete battery of reproductive and developmental toxicity studies was conducted with saxagliptin to assess potential effects on fertility, reproductive performance, gestation, parturition, and lactation of the parental generation in rats; on embryonic and foetal development in rats and rabbits; and on growth, development, and reproductive performance of progeny in rats. Range-finding embryo-foetal development studies in pregnant rats and rabbits and 2-week and 3-month oral toxicity studies in non-pregnant rats were used to assist in the dose selection for subsequent pivotal reproductive toxicity studies. Systemic exposure data were collected in supporting toxicokinetic studies (fertility and embryo foetal development) or within the primary study (peri- and postnatal development). All pivotal studies were conducted in compliance with GLP regulations, were adequately designed, and met the ICH guidelines.

In the fertility and early embryonic development studies effects on fertility were only seen at doses far in excess of the recommended human dose. It is therefore unlikely that saxagliptin will have an effect on human male or female fertility at therapeutic doses.

The embryo-foetal development studies in rats showed only minor effects on ossification of the pubes at the mid-dose, which is far in excess of the human recommended dose. These effects are likely to be treatment-related, since no maternal toxicity was evident at the mid-dose. The high dose was sufficiently high enough to induce maternal toxicity. Likewise, in rabbits, only minor effects were observed. Four foetuses of one litter in the high dose had an absent gall bladder. This could be a treatment-related effect, but due to the high safety margin of 158 it is unlikely to be of clinical relevance.

The prenatal and postnatal development studies (including maternal function) showed that at all doses fertility rates of the F1 generation (no. pregnant/no. mated) were reduced (68% at low dose versus 84% in controls). However, this reduction was not dose dependent and within historical control range and is therefore not likely to be treatment-related.
A reduction in epididymis and testes weight was seen in the F1 generation in the high dose group. Due to the high safety margin (3870) for this effect and the absence of any other related effects, this is unlikely to be of human concern.

No studies in which juvenile animals were performed. This is acceptable as Onglyza is not recommended for use in children and adolescents.

- Local tolerance

The applicant has provided dermal and ocular irritation tests. Saxagliptin produced no ocular irritation to isolated bovine corneas and non dermal irritation to rabbit skin. In the local lymph node assay, saxagliptin was considered a skin sensitizer, able to induce allergic contact dermatitis. The applicant proposes that this mechanism is not relevant for the skin lesion observed in cynomolgus monkeys, since these are not consistent with allergic contact dermatitis. Because it is unlikely that the observed skin lesions are due to direct contact with saxagliptin, it is agreed that the positive result for saxagliptin as a skin sensitizer is not a plausible explanation for the skin lesion in cynomolgus monkeys. Therefore, potential skin sensitization properties of saxagliptin are not relevant for the intended population.

- Other toxicity studies

Immunotoxicity
The applicant states that no changes in T-cell-dependent humoral response could be detected at any dose level. However, in male rats, the mean antibody titres were 2356, 3552, 1162 and 1045 for the control, 10, 50, and 200 mg/kg/day groups respectively. These figures suggest that a decreased response is evident from 50 mg/kg/day. As the variation between the animals in one dose group is very large no conclusions can be drawn from this experiment. Although the positive control is significantly reduced, a more than 50% reduction in mean antibody titre does not reach significance due to individual variation.
Similarly, a substantial decrease in CD45RA cells (B cells), is seen in males and females at all doses (except males at 200 mg/kg/day). These decreases are also not significant due to large intra-group variation and no conclusions can be drawn with regard to these values.
Other findings in the 1-month study in rats were decreases in mean platelet counts in the high and mid-dose males and high-dose females, and leukopenia in one female in the high dose group. Although all these findings either lack statistical significance, or reflect minor changes, or are evident in individual animals, taken together they are suggestive of a potential for immunotoxicity of saxagliptin.
To conclude, due to large within-group variations, no definite conclusions can be drawn regarding the immunotoxicity of saxagliptin in rats.

Studies on impurities
Qualifying studies have been performed for the process-related impurities BMS-537679 and BMS-554083. In addition, studies have been performed with BMS-481146 and BMS-590102, potential impurities below LLOQ under current manufacturing processes.

The intended maximum human intake of saxagliptin is 5 mg/day. According to ICHQ3A and ICHQ3B, qualification limits for impurities in the drug substance and the drug product is 0.15% and 0.5%, respectively. While the proposed specification limits for three impurities (BMS-481146, BMS-590102 and BMS-554083) all are below the qualification limits, the proposed specifications for BMS-537679 in the product at release (0.2%) and at end of shelf life (0.1%) are above the qualification limit. Further, BMS-537679 has a structure-based alert for mutagenicity and carcinogenicity, and has therefore been extensively studied.

The submitted qualifying studies for BMS-537679 are in accordance with current regulations. Although structure-based alert for mutagenicity and carcinogenicity has been identified, BMS-537679 was considered non-genotoxic in the Ames test and a chromosomal aberration test *in vitro* and in a

bone marrow micronucleus test *in vivo*. Furthermore, no differences in toxicity were identified between saxagliptin and saxagliptin spiked with BMS-537679 in a three month repeat dose toxicity study. Based on these studies, BMS 537679 is considered qualified up to a level of 1.36%.

Ecotoxicity/environmental risk assessment
A phase II environmental risk assessment was conducted for saxagliptin as the trigger value was exceeded. Saxagliptin is neither persistent, bioaccumulating or toxic (PBT) nor very persistent, very bioaccumulating (vPvB). Risk to the surface water, groundwater, soil, sediment and sewage treatment plant is acceptable.

2.4 Clinical aspects

Introduction
The Clinical Pharmacology program consisted of 24 studies in 673 subjects, 620 of who were dosed with saxagliptin (see table below). Ascending dose studies, biopharmaceutical studies, a thorough corrected QT interval (QTc) study, and studies to investigate various clinical findings were conducted. Drug-drug interactions with saxagliptin and other antihyperglycaemic agents, drug metabolizing enzyme inhibitors and probe drugs, as well as with other drugs commonly used in this patient population were evaluated. The pharmacokinetics of saxagliptin was assessed in relation to age, gender, hepatic impairment, and renal impairment, and several studies have investigated the pharmacokinetics of saxagliptin delivered in various formulations. In addition, a population pharmacokinetic analysis was performed.

Outline of Saxagliptin Clinical Pharmacology studies

Study no.	Type of study	Dose [mg]	Formulation utilized	Subjects exposed to Saxagliptin [n]
	Basic Phase I			
CV181001	Ascending-dose, single dose	1-100	Capsule and oral solution	54
CV181034	Food effect with final formulation, single dose	10	Clinical tablet **	14
CV181010	Ascending-dose, multiple dose	40-400	Capsule	40
	Special Populations (effect of intrinsic factors)			
CV181018	Age and gender single dose	10	Early clinical tablet *	56
CV181002	Ascending dose, in T2DM subjects, single dose	2.5-50	Capsule	30
CV181019	Renal impairment, single dose	10	Early clinical tablet *	40
CV181020	Hepatic impairment, single dose	10	Early clinical tablet *	36
	Interaction Studies (effect of extrinsic factors)			
CV181005	Ketoconazole 200 mg bid, multiple dose single dose, saxagliptin	100	Early clinical tablet *	16
CV181052	Digoxin 0.25 mg, multiple dose single dose, saxagliptin	10	Early clinical tablet *	14
CV181053	diltiazem, multiple dose single dose, saxagliptin	10	Clinical tablet **	14
CV181017	metformin, single dose 1000mg saxagliptin, single dose.	100	Early clinical tablet *	18
CV181026	glyburide, single dose 5mg saxagliptin, single dose	10	Early clinical tablet *	30
CV181028	Pioglitazone , multiple dose 45 mg QD saxagliptin, multiple dose	10	Early clinical tablet *	30
CV181035	Aluminum hydroxide/magnesium	10	Clinical tablet **	15

Study no.	Type of study	Dose [mg]	Formulation utilized	Subjects exposed to Saxagliptin [n]
	hydroxide/simethicone (Maalox®), single dose famotidine, single dose omeprazole, multiple dose single dose, saxagliptin			
CV181033	simvastatine, multiple dose single dose, saxagliptin	10	Early clinical tablet *	24
	Specific Purpose Studies			
CV181004	[^{14}C]-saxagliptin mass balance, single dose	50	Oral solution	6
CV181003	Relative bioavailability, single dose	40	Capsule *vs.* Early clinical tablet *	16
CV181021	Relative bioavailability, single dose	5	Capsule *vs.* Early clinical tablet *	16
CV181036	Relative bioavailability, single dose	10	Clinical tablet ** *vs.* Early clinical tablet *	12
CV181037	Relative bioavailability, single dose	5	Capsule *vs.* Clinical tablet **	16

* These studies utilized a prototype film coated formulation (*early clinical tablet*)

** *Clinical tablets* are an optimized film coated tablet formulation (in 3 strengths: 2.5, 5, and 10 mg) differing from the *early clinical tablet* in the amount and color of coating material used. The tablets proposed for marketing are not different from the clinical tablets except in color and imprinting.

In the Phase 3 program, saxagliptin doses of 2.5, 5, and 10 mg administered once daily were evaluated to fully characterize the efficacy, safety, and benefit/risk profile of saxagliptin within the dose-response range established in Phase 2. In addition, the potential usefulness of titration of saxagliptin as monotherapy, using a starting dose of 2.5 mg, was examined. The rationale for selecting the dose range and dosing interval for Phase 3 was based on an integrated assessment of efficacy, pharmacodynamic, and safety data generated from subjects exposed to saxagliptin in Phase 1 and 2b studies.

The Phase 2b and Phase 3 worldwide clinical development program in T2DM included 8 studies in which 4607 subjects were randomized and treated. Of these, 3356 subjects received double-blind saxagliptin; an additional 66 subjects received open-label saxagliptin 10 mg in Study CV181011. A total of 1459 subjects received saxagliptin for more than 48 weeks, including 344 who received saxagliptin 10 mg, twice the recommended usual clinical dose. The 8 Phase 2b/3 studies included one 12-week Phase 2b dose-finding study (CV181008), one 12-week Phase 3 mechanism of action study (CV181041), and 6 Phase 3 studies with final data from the 24-week short-term treatment period. In the 6 Phase 3 studies (referred to as the Core Phase 3 studies), 4148 subjects with T2DM were randomized and received study drug, 3021 of who were treated with saxagliptin. All controlled studies in subjects with T2DM used a randomized, double blind design. Interim long-term data from the Phase 3 studies are also included in the submission.

Topline results from study D1680C0002 comparing saxagliptin+metformin with sitagliptin+metformin were submitted. These preliminary data are suggestive that saxagliptin is non-inferior to sitagliptin. However, a definitive assessment is only possible after submission of the full study report, which will be submitted as a post-authorisation follow-up measure.

The claimed indication was:

Add-on combination therapy
Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin, when the single agent alone, with diet and exercise, does not provide adequate glycaemic control.

Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with a sulfonylurea, when the single agent alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate.

Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with a PPARγ agonist (i.e., a thiazolidinedione, TZD) when the single agent alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a PPARγ agonist is considered appropriate.

Initial combination therapy
Onglyza is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control in patients with type 2 diabetes mellitus when treatment with both Onglyza and metformin therapy is appropriate.

The approved indication is:

Add-on combination therapy
Onglyza is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control:
- in combination with metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control;
- in combination with a sulphonylurea, when the sulphonylurea alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate.
- in combination with a thiazolidinedione, when the thiazolidinedione alone with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a thiazolidinedione is considered appropriate.

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

Formal scientific advice (EMEA/CHMP/SAWP/110905/2007) regarding pharmacokinetics has been given by CHMP.

There is no paediatric development program.

GCP

The CHMP requested a GCP inspection of the clinical study CV181-013. Two investigator sites were inspected in this routine GCP inspection. Although there was one critical finding the Inspectors did not find evidence that the deficiencies found had impact on the overall validity and credibility of the data reported in this clinical trial and therefore deemed the inspected clinical trial as valid for use in the assessment of the marketing authorisation application for Onglyza.

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.

Pharmacokinetics
The pharmacokinetics of saxagliptin has been investigated in 30 PK studies with 497 subjects exposed to saxagliptin doses up to 400 mg. Studies designed to explore drug-drug interactions, the effect of food, or pharmacokinetics in special populations conducted during the Phase 3 program applied the dose of 10 mg, as this dose represents the highest dose that could potentially be commercialized. Two drug-drug interaction studies (metformin and ketoconazole) conducted early in the saxagliptin development program utilized saxagliptin doses of 100 mg as this dose was the highest dose being studied in the Phase 2b program and represented the highest dose that could potentially be commercialized at that time.

Various laboratories and several versions of the analytical method (LC-MS) have been applied for the determination of saxagliptin and BMS-510849. The methods were not cross-validated between the involved laboratories. Two (for plasma analyses) and three laboratories (for urine analyses), and different versions of an LC-MS/MS method were involved at different stages during the study periods. The comparability of the analyses from the two methods (discriminating and non-discriminating) in the involved laboratories are considered justified.

Drug formulation
For the initial clinical studies (up to the end of Phase 2b), drug substance in the benzoate salt form (designated as BMS 477118-08) (tablets and capsules) was employed. Subsequently, the free base monohydrate (designated as BMS 477118-11) was selected for further development.
The applicant has utilized the following formulations in the clinical pharmacology studies: capsule, 'early clinical tablet', an adjusted 'clinical tablet' formulation, and an oral solution.
In order to provide a link between the various formulations, four relative bioavailability studies were conducted. Results from these studies indicate bioequivalence of the different formulations used.
Since the formulation of the tablet used in Phase 3 studies differs only in colour and imprinting from the proposed market formulation, no pivotal bioequivalence studies have been conducted. This is acceptable. Therefore, based on similarity in systemic exposure, saxagliptin administered with the commercially proposed formulation is expected to demonstrate similar safety, efficacy and tolerability profiles to that seen with equivalent doses of the capsule and (early) clinical tablet formulations.

- Absorption

The aqueous solubility of saxagliptin in the proposed clinical dose (5 mg) is relatively high across a broad range of pH values (≥16.9 mg/mL for pH 0.7-8.7).
Oral absorption of saxagliptin in humans is high (≥ 75%) as demonstrated in a mass balance study using 50mg [^{14}C]-saxagliptin (CV181004). Absorption is not affected by alterations in gastric pH (CV181035) and is not affected by food (CV181034)**,** since co-administration of saxagliptin with Maalox Max®, omeprazole, famotidine or a high fat breakfast did not affect the pharmacokinetics of saxagliptin.

Bioavailability
The applicant did not conduct an absolute bioavailability study. However, since the bioavailability is at least 75% (CV181004), and since the oral pharmacokinetics and mass-balance studies have satisfactorily characterized the pharmacokinetics of saxagliptin following oral administration, this is acceptable.

Influence of food
Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with a high-fat meal resulted in no change in saxagliptin C_{max} and a 27% increase in AUC compared with the fasted state. Therefore, saxagliptin may be administered with or without food.

- Distribution

Saxagliptin and its major metabolite BMS-510849 do not bind to plasma proteins in *in vitro* serum, which has also been confirmed by the mass balance study that also suggests that saxagliptin and its related compounds are not retained in the body to a substantial extent.
Population PK analyses suggest that the apparent volume of distribution of saxagliptin is much higher than that of BMS-510849.

- Elimination

Metabolism
The biotransformation of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). BMS-510849 is saxagliptin's major metabolite. BMS-510849 is pharmacologically active (also a selective, reversible, competitive DPP-4 inhibitor). However, the contribution of BMS-510849 metabolite to glucose lowering effect is unclear. The applicant defines active moiety based on plasma exposure and difference in DPP-4 inhibition potency *in vitro* (sum of saxagliptin AUC and 50% of the active metabolite AUC).

The Applicant discussed the contribution of BMS-510849 to the glucose-lowering effect of saxagliptin *in vivo* in humans based on a saxagliptin-rifampicin drug-drug interaction study (CV181059) and an *in vivo* study in rats (Study 930008283). Study CV181059 suggests that BMS-510849 plays a significant role in plasma DPP4 inhibition in humans, where exposures to BMS-510849 are relatively high compared to parent drug. The rat study suggested that although the effect on plasma DPP was similar for parent and metabolite, approximate equimolar systemic exposures of saxagliptin and BMS-510849 resulted in between 5- and 20-fold lower glucose-lowering activity for BMS-510849 compared to parent. This is postulated to be due to differences in distribution of parent and metabolite, resulting in much lower metabolite exposure at site of action. In conclusion, the studies show that BMS-510849 contributes to the glucose-lowering effect of saxagliptin; however, as stated above, it is difficult to elaborate the precise contribution of the parent compound compared to the main metabolite to the overall efficacy/safety of saxagliptin.

Excretion
Renal excretion is an important route of clearance for saxagliptin with a total radioactivity of 75%, being recovered in urine within 24 hours (saxagliptin and BMS-510849 accounted for 24 and 36% of the radio-activity, respectively). In addition, 22% of the radioactivity was recovered in faeces mainly as oxidative metabolites with only trace amounts of parent saxagliptin detected (~0.5 % of dose) (CV181004). The majority of total radioactivity (85.3%) was excreted in urine or faeces within 24h of dosing (0-24 h urinary [71.4%] and faecal recovery [13.9%]).
Following a single oral dose of 5 mg saxagliptin in the fasted state the mean terminal half-life values for saxagliptin and BMS-510849 were 2.5 and 3.1 h, respectively (CV181037).
Renal elimination for saxagliptin occurs via a combination of glomerular filtration and active renal secretion, whereas BMS-510849 appears to be only filtered. Saxagliptin is not a substrate for organic anion transporter-1 (OAT1), OAT3, organic anion transporting polypeptide-A (OATPA), OATPC, OATP8, organic cation transporter-1 (OCT-1), OCT-2, sodium taurocholate co-transporting peptide (NTCP), and peptide transporters (PepT1 and PepT2).

Inter-conversion
Inter-conversion has not been assessed as all centres have the ***S*** configuration.

Pharmacokinetics of metabolites
The systemic exposure to BMS-510849 is about 3.3-times higher than the systemic exposure to parent saxagliptin (CV181002). The systemic exposure to saxagliptin related compounds was almost entirely (mean 97.8%) due to parent saxagliptin (mean 21.8%) and BMS-510849 plus other unidentified minor monohydroxylated metabolites (mean 76.0%). The renal clearance of BMS-510849 (51 to 103 mL/min) was similar to or less than the estimated creatinine clearance, suggesting glomerular filtration. No appreciable accumulation was observed for either saxagliptin or BMS-510849 at any of the doses investigated following up to 2 weeks of QD dosing (CV181002; CV181010).

Consequences of possible genetic polymorphism
Given the metabolic profile of saxagliptin, genetic polymorphisms are not expected to be of relevance to saxagliptin PK.

- Dose proportionality and time dependencies

Saxagliptin exhibits dose proportional pharmacokinetics in dose ranges up to 50 mg. There is no evidence for non-linear pharmacokinetics.
There was no clinically significant accumulation observed and there was no evidence of saxagliptin inducing or inhibiting its own metabolism following once daily dosing of 40 to 400 mg for 14 days.
Saxagliptin does not exhibit time dependent PK.

Intra- and inter-individual variability
According to the Applicant saxagliptin pharmacokinetics displays moderate intra- and inter-individual variability in healthy volunteer populations, although no formal evaluation in the form of a replicate-design study of within-subject variability has been performed. The observed inter- and intra-individual variability is however not expected to be of clinical relevance.

- Special populations

Impaired renal function

In mild renal impairment, saxagliptin's AUC(INF) values were less than 2-fold higher than the mean values in subjects with normal renal function. Therefore, no dose adjustment has been recommended for patients with mild renal impairment.

The mean AUC (INF) values for BMS-510849 were however ~3-fold higher in subjects with moderate renal impairment than in subjects with normal renal function. The applicant initially proposed a dose of 2.5 mg in subjects with moderate renal impairment. Based on the efficacy, safety and PK-data, the proposed dose reduction to 2.5 mg saxagliptin in patients with moderate renal impairment, might seem reasonable. The modelling and simulation analysis showed that patients with moderate renal impairment dosed with 2.5 mg saxagliptin have BMS-510849 and total active moieties within the exposures expected and observed in patients with normal renal function/mild renal impairment dosed with 10 mg saxagliptin in the pivotal monotherapy study (CV181011).
However, the importance of renal excretion of saxagliptin and its metabolites, the target disease population and the limited number of subjects with moderate renal impairment, must also be taken into account. An ongoing study on saxagliptin in subjects with moderate or severe renal impairment will provide more data in this patient group. It was therefore considered unjustified to put this patient group at unnecessary risk and recommend use in such subjects, before results from this study are known; in particular as other treatment options are also available for use in diabetic patients with renal impairment. Therefore, at this moment, saxagliptin is not recommended in patients with moderate renal impairment, and this is reflected in the SPC sections 4.2 and 4.4.

The applicant proposed similar dose recommendations for severe renal impairment; the AUC(INF) values in subjects with severe renal impairment are 1.6 fold higher than in subjects with moderate renal impairment (4.5 folds versus 2.9 fold higher exposure). In patients with creatinine clearance at the lower end of severe renal impairment and not on dialysis (CLcr about 10-15 ml/min) exposure of BMS-510849 is probably substantially higher than that observed in the severe renal impairment group. In these patients exposure after administration of a proposed daily dose 2.5 mg will exceed the exposure obtained at 10 mg in patients with normal renal function. Furthermore, the exposure to saxagliptin and BMS-510849 in end stage renal disease (ESRD) subjects was evaluated after administration of saxagliptin before dialysis, with a resulting saxagliptin exposure lower than that in subjects with normal renal function and BMS-510849 exposure similar to subjects with severe renal impairment. Approximately 4% of the dose was recovered as saxagliptin and 19% of the dose as BMS-510849 in the dialysate following a 4 h dialysis session. Given that BMS-510849 seems to be almost completely excreted unchanged in urine, the initial proposal to administer saxagliptin after dialysis may result in very high BMS-510849 exposure. Therefore, the proposed recommendations in case of severe renal impairment and haemodialysis are not acceptable.

Impaired hepatic function

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. The applicant has compared AUC and C_{max} in patients with moderate hepatic impairment for saxagliptin and sitagliptin. This comparison is not ideal as hepatic elimination has a larger influence on saxagliptin than on sitagliptin, and the fact that saxagliptin also has an active metabolite, BMS-510849.
BMS-510849 was shown to be approximately 2-fold less potent than parent saxagliptin with respect to DPP-4, but is considered to contribute to the DPP-4 inhibitory effect due to higher plasma concentrations than the mother substance. Clinical study experience with saxagliptin in patients with moderate to severe hepatic impairment is very limited. Therefore, saxagliptin should be used with caution in patients with moderate hepatic impairment, and not recommended used in severe hepatic impairment. No dose adjustment is necessary for patients with mild or moderate hepatic impairment. Accordingly, this is to be reflected in the SPC.

Effect of age and gender
Elderly subjects (65 to 80 years) had 23% and 59% higher C_{max} and AUC(INF) values of saxagliptin, respectively, than young subjects (18 to 40 years). Because of the <2-fold magnitude of the differences between the young and elderly subjects and the Phase 3 experience with saxagliptin with enrolment open to subjects up to 77 years, no dose adjustment on the basis of age is proposed. However, experience in patients aged 75 years and older is very limited, so caution should be exercised when treating this population.
Compared to males, females had approximately 25% higher exposure values for BMS-510849, but this difference is not considered to be of clinical relevance. No dosage adjustment on basis of gender is therefore proposed.

Race
The Applicant did not provide data on studies specifically designed to characterize saxagliptin pharmacokinetics in a specific racial group. A population-based exposure modelling analysis compared the pharmacokinetics of saxagliptin and BMS-510849 in 309 white subjects with 105 non-white subjects (consisting of 6 race groups). No significant difference in the pharmacokinetics of saxagliptin and BMS-510849 were detected between these 2 populations. This is plausible, since saxagliptin is not known to be metabolized by polymorphic enzymes.

Weight
The Applicant has conducted an analysis on the effect of body weight with a large dataset (699 subjects with a weight range of 49.5 to 116.9 kg) from the Clinical Pharmacology studies. Body weight did influence the pharmacokinetics of saxagliptin and BMS-510849, the impact was small and not considered clinically meaningful.

Children
There are no PK data in children.

- Pharmacokinetic interaction studies

Interactions in vitro
Saxagliptin and BMS-510849 neither inhibited CYP1A2, 2A6, 2B6, 2C9, 2C8, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4 *in vitro*. Therefore, saxagliptin and its major metabolite are unlikely to alter the metabolic clearance of co-administered drugs that are metabolized by these enzymes.
While the potential induction effect of these 2 compounds on CYP2C19 activity was not evaluated directly, it may be inferred from the experimental observations. In these experiments, the activities and mRNA expression levels of CYP1A2, 2B6, 2C9, and 3A4 were measured and utilized as sensitive markers for evaluating activation of the hAhR (CYP1A2), hCAR (CYP2B6 and CYP2C9), and hPXR (CYP3A4 and CYP2C9) nuclear receptors by the 2 compounds. Since CYP2C enzymes, including CYP2C19, are known to be regulated by PXR or CAR receptors, any induction of CYP2B6, 2C9, or CYP3A4 enzymes would also indicate the possibility of CYP2C19 induction. Furthermore, literature reports suggest that CYP2C19 is comparable or less sensitive to induction effects than CYP2C9 when treated with known PXR and CAR inducers, such as rifampicin and phenobarbital. The actual experimental results showed no increases in the activities of CYP2B6, CYP2C9, or CYP3A4, nor were there significant dose-related increases in the mRNA content of these enzymes after exposure to saxagliptin at concentrations up to 25 μM or to BMS-510849 at concentrations up to 100 μM. These *in vitro* test concentrations were ~300- and ~700-fold higher, for each analyte, respectively, than the plasma C_{max} values following a 5 mg dose of saxagliptin to humans (Study CV181037 - C_{max} values for saxagliptin and BMS-510849 were 0.08 μM and 0.14 μM, respectively). In contrast, the positive control inducers, rifampicin (for CP3A4, CYP2C9) and phenobarbital (for CYP2B6), showed substantial increases in the enzyme activities and mRNA content of the corresponding enzymes. Based on these results, saxagliptin and its metabolite did not activate either CAR or PXR, and are therefore unlikely to induce CYP2C19. It is not considered necessary to further evaluate the induction potential of CYP2C19 by saxagliptin or other potential CYP2C inducers.

The biotransformation of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). Furthermore, saxagliptin, but not BMS-510849, has been shown to be a substrate for P-gp with basolateral to apical polarization ratios in P-gp expressing cells approximately 3-fold higher than in control cells. On basis of the *in vitro* findings drug-drug interactions mediated through CYP3A4 and/or P-gp are possible.

Interactions in vivo

Interactions with oral Antidiabetic agents

Metformin

Co-administration of 1000 mg metformin with 100 mg saxagliptin results did not affect the overall systemic exposure to saxagliptin, but has resulted in a modest decrease in the C_{max} of saxagliptin and BMS-510849. This reduction is possibly due to reduction of gastrointestinal motility and is unlikely to be of clinical consequence.

Glyburide

Glyburide is a CYP2C9 substrate. Even at supra-therapeutic concentrations, neither saxagliptin nor BMS-510849 inhibit the activity of CYP2C9. Results from CV181026 suggest indeed that saxagliptin and glyburide do not affect the pharmacokinetics of each other.

Pioglitazone

Pioglitazone is a CYP3A4 and CYP2C8 substrate. Even at supra-therapeutic concentrations, neither saxagliptin nor BMS-510849 inhibit or induce the *in vitro* activity of CYP3A4 or inhibit the *in vitro* activity of CYP2C8. Saxagliptin is metabolized by CYP3A4/3A5. There is no evidence to date implicating pioglitazone in altering the activity of CYP3A4/3A5. Saxagliptin C_{max} and AUC(TAU) values were 20% higher and 18% higher, respectively, when pioglitazone was co-administered with saxagliptin compared to when saxagliptin was administered alone. There was a 14% increase in the steady state C_{max} of pioglitazone when co-administered with saxagliptin, whereas the overall exposure [AUC(INF)] remained unchanged. The data suggests a small effect on the absorption rate of pioglitazone, which is unlikely to be of clinical consequence.

Interactions with Gastric Acid Controllers

Co-administration of saxagliptin with Maalox Max®, omeprazole and famotidine do not profoundly affect saxagliptin and BMS-510849 pharmacokinetics. Alterations in gastric pH are therefore unlikely to cause clinically meaningful alterations in the pharmacokinetic, safety, tolerability and efficacy profile of saxagliptin.

Interactions with CYP3A4/5 substrates/inhibitors

Simvastatin

Co-administration of simvastatin with saxagliptin, increased the steady state C_{max} and overall systemic exposure AUC(TAU) of saxagliptin by 21 and 12% , respectively. However, co-administration did not significantly affect AUC(TAU) and steady state C_{max} of BMS-510849, and did not significantly alter the steady state C_{max} and AUC(TAU) of simvastatin or simvastatin acid. The changes in C_{max} and AUC(TAU) of saxagliptin are not considered to be clinically relevant.

Omeprazole

Since saxagliptin and omeprazole share common metabolic pathways (CYP3A4), the potential for a drug-drug interaction between these 2 agents theoretically existed. However, saxagliptin pharmacokinetics is not altered by omeprazole.

Ketoconazole

The effects of saxagliptin on ketoconazole pharmacokinetics are limited and clinically irrelevant. However, ketoconazole had a pronounced effect on saxagliptin pharmacokinetics. Compared to when saxagliptin was administered alone, the geometric mean C_{max} and AUC(INF) values for saxagliptin were 62% and 2.5-fold (95% CI: 2.30-2.60) higher, respectively, when saxagliptin was co-administered with steady-state ketoconazole. The corresponding values for BMS-510849 were 95% (95% CI: 0.05-0.06) and 88% (95% CI: 0.10, 0.13) lower, respectively. Since the increase in

saxagliptin overall exposure was accompanied by a substantial decrease in BMS-510849 exposure and since the AUC(INF) values of the total active moiety (saxagliptin+BMS-510849) increased by less than 2-fold (mean of 13% increase, range of 4% decrease to 28% increase) compared to when saxagliptin was administered alone, no dose adjustments are required. However, monitoring of the adverse events related to saxagliptin should be recommended by the SPC when both drugs, ketoconazole and saxagliptin, are combined.

Diltiazem
Co-administration of the moderate inhibitor of CYP3A4/5 diltiazem with saxagliptin increases the C_{max} and AUC(INF)values of saxagliptin by 63% and 2.1-fold, respectively, and the corresponding values for the active metabolite were decreased by 44 and 34%, respectively. As the increase in saxagliptin overall exposure was accompanied by a decrease in BMS-510849 exposure, the effects of diltiazem on saxagliptin are not expected to lead significant clinical effects. Therefore, no dose adjustment for saxagliptin is recommended when co-administered with diltiazem or other moderate CYP3A4 inhibitors.

Interactions with CYP3A4 inducers
An interaction study with rifampicin, a potent inducer of CYP3A4, (CV180159) has been conducted. While there were substantial effects of rifampicin co-administration on parent saxagliptin pharmacokinetics (53% and 76% decrease in the maximum observed concentration [C_{max}] and the area under the concentration time curve from time zero to infinity [AUC(INF)] values, respectively), there were smaller and opposite effects of rifampicin on BMS-510849 pharmacokinetics (39% and 3% increase, respectively), These pharmacokinetic effects caused by rifampicin resulted in no substantial impact on plasma DPP4 inhibition over a dose interval. Overall, a 5 mg dose of saxagliptin administered with rifampicin inhibits plasma DPP-4 to an extent slightly less than 5 mg saxagliptin administered alone.
The co-administration of saxagliptin and CYP3A4/5 inducers, other than rifampicin (such as carbamazepine, dexamethasone, phenobarbital and phenytoin) has not been studied and may result in decreased plasma concentration of saxagliptin. Therefore the full glycaemic benefit of Onglyza 5 mg may not be provided in patients also using potent CYP 3A4 inducers. It is recommended that glucose monitoring be conducted during the combination of saxagliptin with a potent CYP3A4 inducer.

Interactions with P-gp substrates
Digoxin
Digoxin when co-administered with saxagliptin did not significantly alter the steady state exposure of saxagliptin and BMS-510849. Saxagliptin co-administered with digoxin dosed to steady-state did not significantly alter the pharmacokinetics of digoxin.

Interactions with CYP2C19 substrates/inhibitors
Omeprazole
Co-administration of omeprazole (CYP2C19 substrate) to steady-state did not meaningfully alter the pharmacokinetics of saxagliptin or BMS-510849.

- Pharmacokinetics using human biomaterials

Incubation of saxagliptin and BMS-510849 in human hepatic microsomal suspensions at concentrations ≤ 50 μM did not result in concentration- or time-dependent inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4.

Pharmacodynamics
Pharmacodynamics were studied in eight trials, all in healthy volunteers except one multiple ascending dose trial that was performed in T2DM subjects. In order to characterize the effects of saxagliptin on DPP4 inhibition, plasma DPP4 activity and the plasma concentrations of its substrate of primary interest, active GLP-1, were measured in the ascending dose studies CV181001, CV181002, and CV181010. In addition, the multiple ascending-dose studies in subjects with T2DM (CV181002) and in healthy subjects (CV181010) examined the effect of saxagliptin on various markers of glucose regulation at selected times during the course of the study.

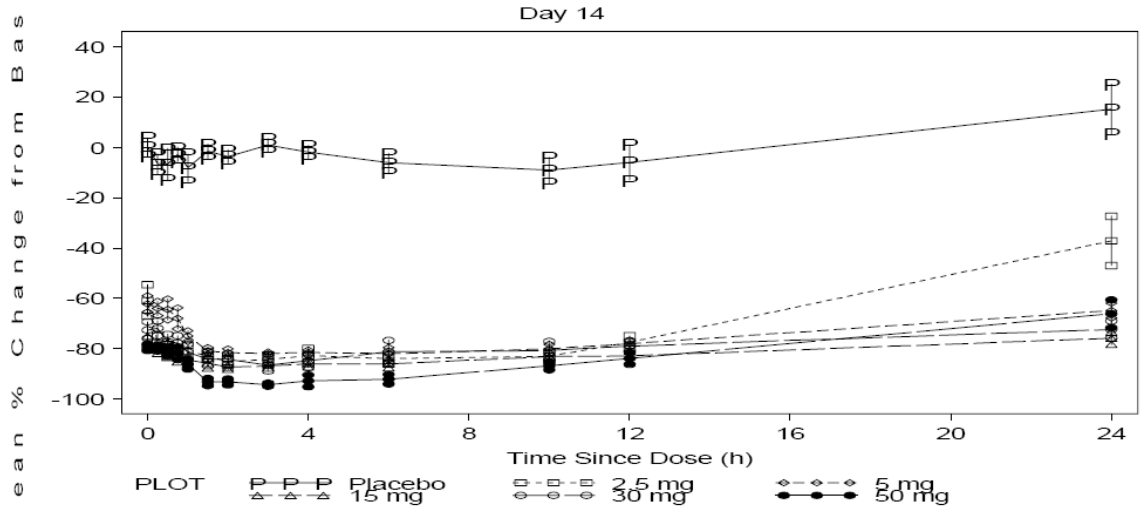
- Mechanism of action

Saxagliptin is a potent, selective, reversible, competitive, dipeptidyl peptidase-4 (DPP4) inhibitor. Dipeptidyl peptidase-4 is an enzyme that selectively cleaves dipeptides from the N-terminus of oligopeptides with proline or alanine in the penultimate position. DPP4 actively converts the key insulinotropic hormone glucagon like peptide-1 (GLP 1) from the active to inactive form, and is responsible for the short half-life of intact GLP-1 *in vivo*. Inhibitors of DPP-4 increase endogenous intact GLP-1 concentrations and potentiate its physiological actions, augmenting postprandial insulin secretion and improving the glycaemic profile in subjects with type 2 diabetes mellitus. Because DPP4 inhibitors stimulate insulin secretion in a glucose-dependent manner, this mechanism of action is expected to present low risk of hypoglycaemia and may not lead to weight gain.

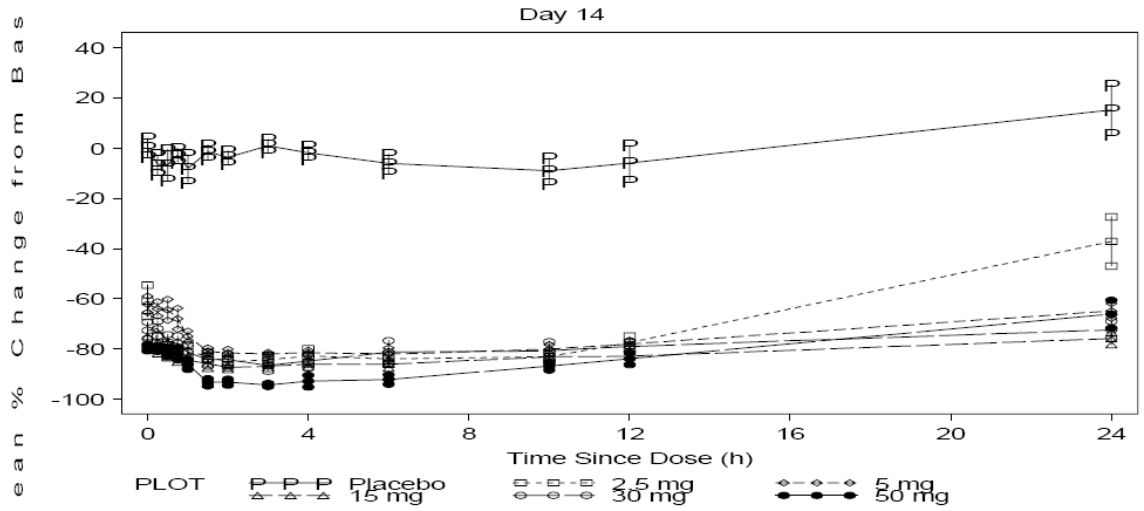
- Primary and Secondary pharmacology

Pharmacodynamics were studied in eight trials, all in healthy volunteers except one multiple ascending dose trial that was performed in T2DM subjects. In order to characterize the effects of saxagliptin on DPP4 inhibition, plasma DPP4 activity and the plasma concentrations of its substrate of primary interest, active GLP-1, were measured in the ascending dose studies CV181001, CV181002, and CV181010. In addition, the multiple ascending-dose studies in subjects with T2DM (CV181002) and in healthy subjects (CV181010) examined the effect of saxagliptin on various markers of glucose regulation at selected times during the course of the study. Inhibition of plasma DPP4 activity appeared to be dose-dependent (see figures below). Doses of 5 mg and higher did not have a similar inhibition at steady-state: in T2DM subjects maximal effect was higher with 50 mg dose. In general, plasma active GLP-1 concentrations were higher in saxagliptin-exposed subjects, but no dose related saxagliptin effect was discernable. No clinically meaningful change was observed in any of the glycaemic parameters studied in subjects with T2DM or healthy subjects.

Mean Plasma DPP-4 Activity (%Change from Baseline) vs. Time Profiles Over a Dose Interval (24 hr) on Day 14 in Studies CV181002 (Subjects with Type 2 Diabetes)



Mean Plasma DPP-4 Activity (%Change from Baseline) vs. Time Profiles Over a Dose Interval (24 hr) on Day 14 in Studies CV181010 (Healthy Subjects)



A mechanism of action study indicated an effect of saxagliptin on insulin release by pancreatic beta-cells.
Two studies investigated the effect of saxagliptin dosing on lymphocyte count. Only at the highest dose of exposures studied in CV181022 and CV181031 (20 mg + ketoconazole and 40 mg saxagliptin, respectively), a modest and transient decrease in lymphocyte count occurred when dosing was interrupted by 7 or 8 days. The mechanism for the lymphocyte decreases remains unknown.
Results of a thorough QTc study indicated that saxagliptin and its main metabolite are not associated with prolongation of the QTc interval at 40 mg dose.

Clinical efficacy

- Dose response study

Study **CV181008** was a randomized, double-blind, dose-ranging, placebo-controlled parallel group study comparing 5 doses of saxagliptin (2.5, 5, 10, 20, and 40 mg) with placebo (0-40 mg cohort) and comparing a higher dose of saxagliptin (100 mg once daily) with placebo (0,100 mg cohort) in treatment-naïve subjects with T2DM. The 0-40 mg cohort was treated for 12 weeks, whereas subjects in the 0,100 mg cohort were treated for 6 weeks. The treatment groups were well balanced with respect to the baseline characteristics with the exception of gender where the proportion of males/females varied between the groups. Titration of study medication was not permitted during double-blind period.
Results on HbA1c are shown in the table below. All doses resulted in statistically and clinically relevant reductions in HbA1c, although 5 mg led to the numerically largest reduction. As also seen in the mechanistic studies, there was no dose-effect relationship. This might reflect the close to « all-or-none» effect on DPP-4 inhibition as also seen for a recently approved DPP-4 inhibitor. The choice of the doses for the phase 3 trials (2.5, 5 and 10 mg) is acceptable.

Changes in HbA1c Randomised Subjects Data Set

	n/N	Baseline HbA_{1c} (%) mean (SD)	Change in HbA_{1c} (%) adj. mean (SE)	Change in HbA_{1c} (%) adj. mean (SE) versus placebo	95% CI	p-value
Dose selection studies						
Study CV181008 (12 weeks, placebo-controlled dose finding)						
Saxa 2.5 mg qd	51/55	7.63 (0.81)	-0.72 (0.12)	-0.45 (0.17)	(-0.78, -0.13)	0.0068
Saxa 5 mg qd	42/47	8.05 (1.10)	-0.90 (0.14)	-0.63 (0.18)	(-0.97,- 0.29)	0.0004
Saxa 10 mg qd	60/63	7.83 (0.96)	-0.81 (0.11)	-0.54 (0.16)	(-0.85, -0.23)	0.0008
Saxa 20 mg qd	51/54	7.85 (0.98)	-0.74 (0.12)	-0.47 (0.17)	(-0.80 , -0.14)	0.0049
Saxa 40 mg qd	50/52	7.77 (0.97)	-0.80 (0.12)	-0.53 (0.17)	(-0.86, -0.20)	0.0016
Placebo	62/67	7.92 (0.97)	-0.27 (0.11)			

- Main studies

The main studies of this application were six phase 3 studies (see table below):

- 2 monotherapy trials (CV181011 and CV181038),
- 3 add-on trials (CV181013, CV181040 and CV181014) and
- 1 initial combination study (CV181039).

In addition to these, a summary of the topline results from Study D1680C0002, a study assessing the efficacy and safety of saxagliptin in comparison with sitagliptin when added to a stable dose of metformin, was provided during the procedure. The full clinical study report will be provided as a post-authorisation follow-up measure.

Summary of Controlled Phase 2-3 Clinical Trials

Study No.	Study objectives (Population)	Randomized and treated subjects (All/Saxa)	Duration short-term (total)	Saxagliptin (mg) dosage
Monotherapy placebo-controlled				
CV181008	Dose-ranging safety and efficacy (A1C 6.8%-9.7%)	423/315	12 weeks or 6 weeks	2.5, 5, 10, 20, or 40 QD or 100 QD
CV181011	Safety and efficacy (A1C 7%-10%)	401/306*	24 weeks (206 weeks)	2.5, 5, or 10 QD
CV181038	Safety and efficacy (A1C 7%-10%)	365/291	24 weeks (76 weeks)	2.5, 5, or 2.5/5 QAM, or 5 QPM
CV181041	Mechanism of action (A1C 6%-8%)	36/20	12 weeks (116 weeks)	5 QD
Add-on combination placebo-controlled				
CV181013	Safety and efficacy (A1C 7%-10.5%)	565/381	24 weeks (76 weeks)	2.5 or 5 QD (+ TZD)
CV181014	Safety and efficacy (A1C 7%-10%)	743/564	24 weeks (206 weeks)	2.5, 5, or 10 QD (+metformin)
CV181040	Safety and efficacy (A1C 7.5%-10%)	768/501	24 weeks (76 weeks)	2.5 or 5 QD (+glibenclamide)
Initial combination active-controlled				
CV181039	Safety and efficacy (A1C 8%-12%)	1306/978	24 weeks (76 weeks)	5 or 10 QD (+metformin) or 10 mg QD

* An additional 66 subjects received open-label saxagliptin in Study CV181011.
QD = once daily, QAM = once daily in the morning, QPM = once daily in the evening

CV181011

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin (BMS-477118) as Monotherapy in Subjects with Type 2 Diabetes Who have Inadequate Glycemic Control with Diet and Exercise.
Conducted at 137 sites in the US, Puerto Rico, Canada, Mexico, Australia, and Taiwan.
Study period: 29 Jul 2005 - 27 Aug 2006.

CV181038

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.
Conducted at 72 sites in the US, Russia, India, and Taiwan.
Study period: 19 Jun 2006 – 01 Nov 2007.

CV181041
Mechanism of Action and Efficacy of Saxagliptin (BMS-477118) in the Treatment of Type 2 Diabetic Patients.
Conducted at 3 US sites.
Study period: 15 Sep 2006 - 23 Feb 2008.

CV181013
A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin (BMS-477118) in Combination with Thiazolidinedione Therapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Thiazolidinedione Therapy Alone.
Conducted at 172 sites the US, India, Canada, Argentina, Peru, Mexico, Puerto Rico, and the Philippines.
Study period: 13 Mar 2006 - 15 Oct 2007.

CV181014
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.
Conducted at 152 sites the US, Canada, Mexico, Argentina, Brazil, Puerto Rico, Australia, Taiwan, and Chile.
Study period: 29 Jul 05 – 14 Aug 06.

CV181040
A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Glyburide in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Glyburide Alone.
Conducted at 132 sites in the US, Brazil, Mexico, Israel, South Africa, Korea, Argentina, Taiwan, Peru, Philippines, Puerto Rico, Hong Kong, and Singapore.
Study period: 17 Apr 2006 – 14 Sept 2007.

CV181039
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.
Conducted at 196 sites in the Russian Federation, the US, Argentina, India, Mexico, Germany, Ukraine, Brazil, Poland, Philippines, Puerto Rico, Hungary, and Italy.
Study period: 30 May 2006 – 27 Nov 2007.

D1680C00002
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.
Conducted at 99 sites in Argentina, Belgium, Denmark, France, Italy, Mexico, Norway, South Africa, and Sweden.
Study period: 08 April 2008 - 13 March 2009.

METHODS

Study Participants
Monotherapy studies (CV181011 and CV181038):

- Main inclusion criteria
  - Male and female age ≥18 and ≤ 77 with T2DM
  - Drug-naïve.

- HbA1c in the range 7.0-10% (CV181011 had open label treatment of HbA1c >10 and ≤12)
- Body mass index (BMI)≤ 40 kg/m^2
- Fasting C-peptide ≥1ng/ml

- Main exclusion criteria included
  - Symptoms of poorly controlled diabetes.
  - History of diabetic ketoacidosis or hyperosmolar non-ketotic coma
  - Cardiovascular history of myocardial infarction, coronary angioplasty or bypass graft(s), valvular disease or repair, unstable angina, transient ischemic attack, or cerebrovascular accidents within 6 months before study entry.
  - Congestive heart failure, NYHA class III and IV.

Add-on studies - add-on to metformin, (CV181014), thiazolidinedione (CV181013) and glyburide (CV181040).

- Main inclusion criteria

CV181014 : Subjects with type 2 diabetes requiring treatment with at least 1500 mg but not greater than 2500 mg of a stable dose of metformin therapy for at least 8 weeks prior to screening and HbA1c ≥ 7.0% and ≤ 10.0% obtained at the screening visit
CV181013: Men and women with type 2 diabetes with inadequate glycaemic control (HbA1c ≥ 7.0% and ≤ 10.5%) and were currently receiving a stable dose of TZD therapy (pioglitazone 30 mg or 45 mg, once daily, or rosiglitazone 4 mg, once daily, or 8 mg, either once daily or in 2 divided doses of 4 mg) for at least 12 weeks prior to screening.
CV181040: Subjects with type 2 diabetes mellitus with inadequate glycaemic control (HbA1c ≥ 7.5% and ≤ 10.0%) requiring treatment with a submaximal dose of a sulfonylurea for ≥ 2 months.

- Fasting C-peptide concentration ≥ 1.0 ng/mL
- BMI ≤ 40 kg/m2 (≤ 45 kg/m2 in CV181013)
- Age between 18 and 77.

- Main exclusion criteria were similar to those mentioned for monotherapy.

Initial combination therapy (CV181039).

- Main inclusion criteria

CV181039: Drug-naïve subjects with T2DM HbA1c ≥ 8% but ≤ 12% or have received medical treatment for diabetes for less than a total of 1 month since original diagnosis. In addition, subjects should not have received any antihyperglycaemic therapy for more than 3 consecutive days or a total of 7 non-consecutive days during the 8 weeks prior to screening.

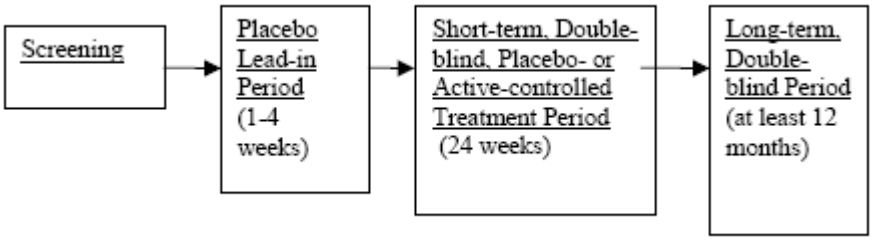
- Fasting C-peptide concentration ≥ 1.0 ng/mL
- Body mass index (BMI) ≤ 40 kg/m2 (≤ 45 kg/m2 in CV181013)
- Age between 18 and 77.

- Main exclusion criteria were similar to those mentioned for monotherapy.

- **D1680C00002**

Males and females with T2DM, ≥18 years old, who had inadequate glycaemic control defined as HbA1c >6.5 % and ≤10%, currently on a stable dose (1500 mg or higher) of metformin therapy for at least 8 weeks prior to screening were eligible for enrolment into the placebo lead-in period.

Treatments
The design of the core phase 3 trials was as follows:



- Monotherapy trials

Treatment naïve patients were randomised to receive saxagliptin 2.5, 5, 10 mg (CV181011) or placebo once daily in the morning. In **CV181011** 66 subjects were enrolled into a saxagliptin 10 mg open-label cohort study.
In **CV181038** also a 5 mg saxagliptin group was studied with evening (PM) dosing and a saxagliptin titration group (2.5 to 5 mg). Double-blind metformin was administered in the LT periods to placebo-randomized subjects completing the ST period without requiring rescue therapy.

- Add-on combination studies

In **CV181040** subjects with inadequate glycaemic control despite submaximal **SU** were randomized to saxagliptin 2.5 mg, 5 mg, or placebo in combination with an intermediate dose of glibenclamide. Saxagliptin with a fixed intermediate dose of glibenclamide was compared with titration to a higher dose of glibenclamide plus placebo. Subjects were treated with a sub-maximal dose of glyburide (glibenclamide).
In **CV181014** subjects with inadequate glycaemic control despite **metformin** were randomized to saxagliptin 2.5, 5, 10 mg, or placebo in combination with metformin. During the lead-in period subjects received open-label metformin at their pre-study dose, up to 2500 mg daily. Subjects who had been receiving a metformin dose > 2500 mg daily had their dose adjusted to 2500 mg.
In **CV181013** subjects with inadequate glycaemic control despite **TZD** were randomized to saxagliptin 2.5 or 5 mg in combination with a TZD. In the lead-in period subjects received open-label TZD at their pre-study dose. No titration of study medication was allowed, and open-label metformin (500 – 2500 mg) was given as rescue medication.

- Initial Combination Study

In study **CV181039** subjects were randomized to saxagliptin 5 or 10 mg in combination with metformin 500 mg, to saxagliptin 10 mg monotherapy, or to metformin 500 mg monotherapy.

- D1680C00002

Following the enrolment phase (Period A), subjects entered a 2-week, single-blind lead-in phase (Period B) with counselling on dietary and lifestyle modifications, after which eligible subjects were randomized to a double-blind, active-controlled 18-week treatment phase (Period C). Subjects maintained their dose of open-label metformin therapy and were randomized (1:1) to one of the following 2 treatment groups: saxagliptin 5 mg once daily or sitagliptin 100 mg once daily.

Objectives
All core phase 3 trials except D1680C0002 were designed to demonstrate superiority of investigational treatments over placebo/control treatments, with regards to change in HbA1c.

The primary efficacy objective of this study **D1680C00002** was to compare that, after 18 weeks of oral administration of double-blind treatment, the change from baseline in HbA1c achieved with saxagliptin 5 mg per day added onto metformin is non-inferior to sitagliptin 100 mg per day added onto metformin in subjects with type 2 diabetes who had inadequate glycaemic control on 1500 mg or higher doses of metformin therapy alone.

Outcomes/endpoints
In all studies change from baseline to week 24 in HbA1c, except the mechanism of action study and DC1680C0002 in which change from baseline was noted at week 18, was the primary efficacy endpoint. Secondary endpoints included change from baseline to week 24 in FPG and Post-Prandial

Glucose Area Under the Concentration curve (PPG AUC), as well as the proportion of subjects achieving a glycaemic response of HbA1c<7% at week 24.

Sample size
For monotherapy studies sample sizes were calculated to detect a true difference of 0.7% in mean change from baseline HbA1c between saxagliptin and placebo for a two tailed test at $\alpha = 0.05$ with a power of 90%.

In study D1680C00002 with a total of 710 subjects randomized and treated (or 355 per treatment group), there was 90% power to establish the non-inferiority comparison on change from baseline to Week 18 in HbA1c at the 5% level, assuming that the standard deviation of change from baseline in HbA1c is 1.1%, with a non-inferiority limit set at 0.3% and an assumed zero true difference between the 2 randomized treatments. The sample size also assumed that 20% of the randomized subjects would be excluded from the Per Protocol (PP) analysis set.

Randomisation
Subjects were randomly assigned to different treatment groups using a block randomisation schedule (permuted blocks stratified by site).

Blinding (masking)
For blinding purposes all dose forms of saxagliptin were identical in design and there was a single placebo tablet to match all dose forms of saxagliptin. Clinical supplies were packaged with unblinding information concealed by a tear-off label to permit unblinding in emergency situations or pregnancy. After the database was locked, the data were unblinded for reporting purposes.

Statistical methods
The primary efficacy endpoint of each core phase 3 study is the change in HbA1c from baseline to Week 24, or the last pre-rescue post-baseline measurement prior to Week 24, if no Week 24 assessment is available. This includes subjects in the Randomised Subjects data set who have a baseline and at least one post-baseline HbA1c assessment.

The primary efficacy analysis was an ANCOVA model of the primary endpoint (LOCF), with treatment group as a fixed effect and baseline value as a covariate in the model. Within the framework of this ANCOVA model, point estimates and 95% confidence interval for the mean change from baseline within each treatment group as well as for the difference in mean change from baseline between each investigative treatment group and the placebo or active comparator treatment group were calculated. The treatment-by-baseline interaction was also tested and distributional assumptions assessed. The treatment comparison was performed using a t-test with pre-specified value of α.

A repeated measure analysis (using MIXED model) was used to analyse the response variable change from baseline in HbA1c to each time point. In addition to the results presented for each study, the primary efficacy endpoint was analysed with the Pooled Mono data for the 2.5 mg, 5 mg (AM and PM), and placebo arms with an Analysis of Covariance model.

Secondary analyses common to all 6 pivotal phase 3 studies include change from baseline to week 24 LOCF in FPG, change from baseline to Week 24 (LOCF) in 3 hour post-prandial glucose AUC and proportion of subjects achieving a therapeutic glycaemic response at week 24 (defined as HbA1c<7%).
Mean changes from baseline at Week 24 (LOCF) in FPG, PPG AUC and during the short-term treatment period were compared between each investigative treatment group and the control group, based on adjusted means generated by ANCOVA. The percents of subjects achieving therapeutic glycaemic response at Week 24 (LOCF) were compared between each of the investigative treatment groups and the control group, using Fisher's exact test. Therapeutic glycaemic response (HbA1c<7.0%) analysis at Week 24 was also performed using the Pooled Monotherapy group for the 2.5 mg, 5 mg (AM and PM), and placebo doses. Overall association between treatment group and therapeutic glycaemic response adjusted for study was analyzed using the Mantel-Haenszel test. The Breslow-Day test was used to test for homogeneity of effect across studies.

Time to study discontinuation for lack of glycaemic control or rescue for failing to achieve glycaemic targets during the long-term treatment period was summarized by treatment arm using Kaplan-Meier estimates of the cumulative proportion (with 95% CI).
The Short-term Completers data set was used for Completers analysis.
Standard error and within group 95% confidence interval were calculated using Fieller's theorem for % of efficacy maintained between Week 24 and long-term Week t.

The following data sets were defined:
Lead-in subjects were defined as all subjects who took at least one dose of placebo lead-in study-drug.
Randomised subjects were defined as all randomised subjects who took at least one dose of double-blind treatment
Treated Subjects defined as all subjects who received at least one dose of double-blind study medication during the short-term period.
Evaluable subjects is a subset of randomised subjects, defined as all randomised subjects without protocol deviation that may significantly interfere with the assessment of the primary endpoint.

Since less than 10% of subjects in all treatment groups had significant protocol deviations, no analyses were performed in the Evaluable Subjects Data Set.
Due the large number of sites in the study and the small number of subjects enrolled at most sites, site was not included as a factor in the ANCOVA model.

In study D1680C00002 the PP analysis set, excluding non-completers and subjects with significant protocol deviations, was the analysis set used for the primary efficacy analysis to establish non-inferiority of saxagliptin plus metformin vs. sitagliptin plus metformin with a 0.3% non-inferiority limit on the change in HbA1c from baseline to Week 18. The primary efficacy variable was also analyzed using the Full analysis set. All other efficacy variables were analyzed using the Full analysis set only. In last observation carried forward (LOCF) analyses at Week 18, the measurement designated as the Week 18 measurement was used. If no Week 18 measurement was available, the last available earlier post-baseline measurement was used.
The primary efficacy analysis to establish non-inferiority with 0.3% non-inferiority limit on the change in HbA1c from baseline to Week 18 was performed on the PP analysis set using an analysis of covariance model (ANCOVA). The model used treatment group as a fixed effect and baseline value as a covariate. Within the framework of the ANCOVA model, point estimates and the 2-sided 95% confidence intervals (CIs) for the mean change within each treatment group were performed. These analyses were also performed for the differences in mean change between the saxagliptin plus metformin treatment arm and the sitagliptin plus metformin treatment group. Saxagliptin plus metformin would be considered not inferior to sitagliptin plus metformin if the upper limit of the 2-sided 95% CI of the difference in change in HbA1c from baseline to Week 18 between saxagliptin plus metformin and sitagliptin plus metformin was less than 0.3%.
For secondary continuous glycaemic outcome variables, such as change from baseline in FPG at Week 18, a similar ANCOVA model was used: point estimates and the 2-sided 95% CIs for the mean change within each treatment group as well as for the differences in mean change between the two treatment groups were reported.
Summaries of categorical endpoints (such as achieving HbA1c $\leq$6.5% at specific visits) provided frequencies and percents for each treatment group. In addition, the percent difference from sitagliptin + metformin and 95% CIs were estimated. No a priori hypotheses for secondary objectives were proposed.
The change in PPG from baseline to Week 18 of randomized treatment was evaluated for a subset of subjects within the Full analysis set for whom an extended OGTT was conducted. The target was to include 50 subjects in the subgroup. A total of 51 subjects underwent OGTT at 8 different South African sites, of whom 49 had glucose values measured at each required time point.

RESULTS

Participant flow

Across all Core Phase 3 studies, 74% of subjects in all treatment groups completed the ST period. A higher proportion of subjects in the control groups were rescued or discontinued from the study due to lack of efficacy compared with subjects treated with saxagliptin. A summary of the disposition of subjects in the randomized and open label data sets is given in the table below. There are expected differences between studies such as duration of diabetes. The number of patients > 65 years is adequate. The number of patients >75 was low (<1%).

Disposition of Subjects in the Short-Term Treatment Period of the Core Phase 3 Studies Tabulated according to Dose

Study	Treatment Group	No. Randomized and Treated	Completed n (%)	D/C for lack of efficacy (excluding rescue) n (%)	Rescued n (%)
CV181011	Saxa 2.5 mg	102	73 (71.6)	9 (8.8)	14 (13.7)
	Saxa 5 mg	106	68 (64.2)	8 (7.5)	21 (19.8)
	Saxa 10 mg	98	69 (70.4)	9 (9.2)	14 (14.3)
	Placebo	95	55 (57.9)	15 (15.8)	25 (26.3)
	Open Label	66 (OL)	25 (37.9)	--	--
CV181038	Saxa 2.5 mg	74	55 (74.3)	1 (1.4)	8 (10.8)
	Saxa 5 mg	74	57 (77.0)	0 (0)	10 (13.5)
	Saxa 2.5/5 mg	71	52 (73.2)	1 (1.4)	9 (12.7)
	Saxa 5 mg QPM	72	55 (76.4)	0 (0)	8 (11.1)
	Placebo	74	53 (71.6)	1 (1.4)	11 (14.9)
CV181013	Saxa 2.5+TZD	195	159 (81.5)	1 (0.5)	18 (9.2)
	Saxa 5 mg+TZD	186	140 (75.3)	0 (0)	12 (6.5)
	Placebo+TZD	184	138 (75.0)	5 (2.7)	14 (7.6)
CV181040	Saxa 2.5+Gly	248	192 (77.4)	3 (1.2)	42 (16.9)
	Saxa 5 mg+Gly	253	195 (77.1)	1 (0.4)	41 (16.2)
	Placebo+Gly	267	176 (65.9)	1 (0.4)	78 (29.2)
CV181014	Saxa 2.5 mg + Met	192	148 (77.1)	9 (4.7)	25 (13.0)
	Saxa 5 mg + Met	191	143 (74.9)	12 (6.3)	22 (11.5)
	Saxa 10 mg + Met	181	140 (77.3)	11 (6.1)	25 (13.8)
	Placebo+Met	179	112 (62.6)	20 (11.2)	45 (25.1)
CV181039	Saxa 5 mg +Met	320	262 (81.9)	1 (0.3)	23 (7.2)
	Saxa 10 mg +Met	323	261 (80.8)	0 (0)	18 (5.6)
	Saxa 10 mg	335	225 (67.2)	2 (0.6)	69 (20.6)
	Metformin	328	243 (74.1)	6 (1.8)	27 (8.2)

In study DC1680C00002 all randomized subjects received at least 1 dose of study medication and 92.3% of subjects completed the 18-week, double-blind, randomized treatment period. The percentage of subjects discontinuing study treatment during double-blind treatment was similar overall between the 2 treatment groups. More subjects discontinued from the saxagliptin + metformin group than the sitagliptin + metformin group due to the development of study-specific discontinuation criteria (3.5% and 1.8%, respectively).

Conduct of the study

In CV181038, the only significant protocol deviation was non-compliance with study medication, which involved 6 subjects in the saxagliptin treatment groups and 3 subjects in the placebo group. Protocol deviations in testing of the OGTT were identified. Due to an incorrect amount of glucose solution administered at some sites in Europe, the OGTT parameters for 50 subjects were excluded from all analyses. In CV181011, four subjects (1%) had at least 1 significant protocol deviation during

the treatment period; 3 subjects (1 in each saxagliptin treatment group) were non-compliant with study drug and 1 subject in the placebo group received another antihyperglycaemic medication for ≥ 14 days.

Overall the protocol amendments are considered to not have any significant impact on the conduct of the study.

Baseline data
The demographic and baseline characteristics of the patients included in the six core Phase 3 studies (*age, gender, weight, geographic region*) are given in the table below:

Demographic and baseline characteristics of patients in the Core Phase 3 studies.

Category		CV181011 Randomized N=401	CV181011 Open Label N=66	CV181038 N=365	CV181013 N=565	CV181040 N=768	CV181014 N=743	CV181039 N=1306
Male (%)		51	49	46	50	45	51	49
Race (%):	White	85	92	70	55	59	81.6	76
	Black/Afr. Amer.	5.5	4.5	6.6	3.9	2.5	5.4	1.8
	Asian	4.5	1.5	23.3	34.7	18.1	2.7	16.3
	Other	5	1.5	0.5	6.7	20.7	10.4	5.7
Mean Age (yr) (SD)		53.5 (11.29)	49.09 (8.63)	55 (10.31)	54 (10.13)	55 (10.09)	54.6 (9.98)	52 (10.73)
Age ≥65 (%)		16	3	17.5	15	18	15.7	11
Mean weight (kg) (SD)		89.78 (17.86)	91.41 (20.65)	85.43 (17.7)	81.2 (21)	75.6 (16.55)	87.04 (17.79)	82.60 (16.89)
Mean Duration of Diabetes (yr) (SD)		2.6 (3.2)	3.1 (3.7)	1.7 (3.2)	5.2 (5.2)	6.9 (5.8)	6.5 (5.1)	1.7 (3.1)
Mean Baseline A1C (%) (SD)		7.9 (1.0)	10.7 (0.8)	7.9 (0.9)	8.3 (1.1)	8.4 (0.9)	8 (0.9)	9.5 (1.3)
Mean Baseline FPG (mg/dL) (SD)		175 (43.5)	241.3 (49.2)	162 (42.71)	161.8 (46.96)	173.3 (42.99)	175.8 (46.4)	200.6 (57.44)
Mean Baseline BMI (mg/kg2) (SD)		31.71 (4.59)	31.73 (4.73)	30.54 (4.95)	30 (5.62)	29.04 (4.60)	31.4 (4.85)	30.18 (4.81)
Geographic region (%)								
	North America	78.1	80.3	44.7	45.1	15.4	55.5	16.5
	Latin America	16.5	15.2	0	22.1	63.7	42.7	28.3
	Europe	0	0	34.0	0	4.3	0	39.4
	Asia/Pacific	5.5	4.5	21.4	32.7	16.7	1.9	15.8

In study D1680C00002, of the 801 randomized subjects, approximately 51% were female, 66% were White, and 51% were from Europe. The mean age was 58 years, and 71% were <65 years of age. Mean weight was 86 kg, and 54% had BMI ≥30 kg/m2 (i.e., overweight/obese population). Mean duration of T2DM was 6.3 years, mean baseline value HbA1c was 7.7%, and mean FPG level was 8.9 mmol/L (160.2 mg/dL). The mean baseline dose of metformin was 1829 mg/day.
The demographic and baseline characteristics of the PP analysis set were similar to those of the Randomized analysis set.

Numbers analysed
In the monotherapy studies the Randomised Subjects Data Set, which included all randomised subjects who took at least 1 dose of active double-blind study medication, includes a total of 401 (CV181011) and 365 (CV181038) subjects. These are also the subjects included in the efficacy analysis.

In the add-on and initial combination therapy studies the Randomised Subjects Data Set, which included all randomised subjects who took at least 1 dose of active double-blind study medication, includes a total of 743 (CV181014), 565 (CV181013), 768 (CV181040) and 1306 (CV181039) subjects. These are also the subjects included in the efficacy analysis.

In study DC1680C00002 a total of 801 subjects were assigned to randomized treatment with either saxagliptin + metformin (n=403) or sitagliptin + metformin (n=398).

Outcomes and estimation

HbA1c

In the **monotherapy trials**, all doses of saxagliptin induced a reduction in HbA1c, and the difference with placebo was statistically significant. However, the magnitude of the difference was questioned by the CHMP. Only saxagliptin 10 mg dose in study CV181011 reached delta of -0.7%. In addition, there is no difference in response between the 5 mg and 2.5 mg. Therefore, the choice of 5 mg as optimal dose is not justified by these studies. Furthermore, the placebo response differs between both studies, suggesting a difference in study population. In response to this issue a post hoc analysis was performed for HbA1c reduction from baseline to 12 weeks for the saxagliptin 5 mg and 2.5 mg groups. At 12 weeks a greater HbA1c reduction was observed in the 5 mg group vs. the 2.5 mg group. However, over a longer time period (50-102 weeks) the difference disappears and no difference was found at the end of this period between both doses. Therefore, it cannot be concluded with certainty that saxagliptin 5 mg per day is the optimal dose. The Applicant did not apply for Onglyza as monotherapy.

HbA1c changes from baseline at week 24 (LOCF)- Phase 3 monotherapy studies

Study / Treatment	n /N	Baseline Mean (SE)	Week 24 Mean (SE)	Adj. Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95% CI]
CV181011[a]					
Saxa 2.5 mg	100/102	7.91 (0.09)	7.48 (0.11)	-0.43 (0.10)	-0.62 [-0.90, 0.33][*+]
Saxa 5 mg	103/106	7.98 (0.11)	7.51 (0.13)	-0.46 (0.10)	-0.64 [-0.93, -0.36][*+]
Saxa 10 mg	95/98	7.85 (0.09)	7.32 (0.10)	-0.54 (0.10)	-0.73 [-1.02, -0.44][*+]
Placebo	92/95	7.88 (0.10)	8.07 (0.17)	0.19 (0.10)	--
CV181038[a]					
Saxa 2.5 mg	67/74	8.04 (0.11)	7.30 (0.11)	-0.71 (0.10)	-0.45 [-0.74, -0.16][**+]
Saxa 5 mg	69/74	7.93 (0.11)	7.27 (0.13)	-0.66 (0.10)	-0.40 [-0.69, -0.12][***+]
Saxa 2.5 / 5 mg	69/71	8.02 (0.13)	7.37 (0.14)	-0.63 (0.10)	-0.37 [-0.65, -0.08][****+]
Saxa 5 mg QPM[b]	70/72	7.88 (0.11)	7.29 (0.12)	-0.61 (0.10)	-0.35 [-0.63, -0.07][@+]
Placebo	68/74	7.79 (0.11)	7.57 (0.14)	-0.26 (0.10)	--
Pooled Studies[c]					
Pooled Saxa 2.5 mg	167/176	7.96 (0.07)	7.40 (0.08)	-0.58 (0.08)	-0.56 [-0.76, -0.35][#]
Pooled Saxa 5 mg	242/252	7.94 (0.06)	7.38 (0.08)	-0.54 (0.06)	-0.52 [-0.71, -0.32][#]
Pooled Placebo	160/169	7.84 (0.07)	7.86 (0.11)	-0.02 (0.08)	--

n=number of subjects with assessment at baseline and at week 24; N=number of subjects randomized.
All secondary endpoints tested (sequentially) at the 0.05 significance level and only for groups where primary endpoint showed statistical significance.
*p <0.0001 (Between group comparisons significant at a=0.019, applying Dunnetts adjustment)
**p=0.0023
***p=0.0059 (test performed at the 0.027 significance level, applying Dunnetts adjustment)
****p=0.0119 Significance test performed at the 0.027 level if 2.5 or 5 QAM showed statistical significance and at 0.05 if both 2.5 and 5 QAM groups showed statistical significance)
[@]p=0.0157
[#]p<0.0001 (calculation based on model: Change from baseline=Baseline treatment study treatment*study)
+=statistically significant at pre-specified level
[a]=ANCOVA model:post-pre=pre treatment
[b]=The Saxa 5 mg QPM group results were a secondary efficacy endpoint
[c]=ANCOVA model: Change from baseline=Baseline treatment study

In the **add-on trials**, all doses of saxagliptin, except saxagliptin 2.5 mg + TZD, induced a reduction in HbA1c that was superior to placebo (see table below).

HbA1c Changes from Baseline at Week 24 (LOCF). Phase 3 Add-on Combination Therapy Studies

Study/ Treatment	n / N	Baseline Mean (SE)	Week 24 Mean (SE)	Adj. Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95% CI]
CV181013					
Saxa 2.5 mg + TZD	192/195	8.25 (0.080)	7.59 (0.098)	-0.66 (0.074)	-0.36 [-0.57, -0.15]* +
Saxa 5 mg + TZD	183/186	8.35 (0.080)	7.39 (0.086)	-0.94 (0.075)	-0.63 [-0.84, -0.42]* +
Pla + TZD	180/184	8.19 (0.080)	7.91 (0.100)	-0.30 (0.076)	--
CV181040					
Saxa 2.5 mg + Gly	246/248	8.36 (0.057)	7.83 (0.074)	-0.54 (0.059)	-0.62 [-0.78, -0.45]** +
Saxa 5 mg + Gly	250/253	8.48 (0.056)	7.83 (0.074)	-0.64 (0.059)	-0.72 [-0.88, -0.56]** +
Pla + uptitrated Gly	264/267	8.44 (0.055)	8.52 (0.077)	0.08 (0.057)	--
CV181014					
Saxa 2.5 mg + Met	186/192	8.08 (0.07)	7.48 (0.08)	-0.59 (0.07)	-0.73 [-0.92, -0.53]*** +
Saxa 5 mg + Met	186/191	8.07 (0.06)	7.37 (0.08)	-0.69 (0.07)	-0.83 [-1.02, -0.63]*** +
Saxa 10 mg + Met	180/181	7.98 (0.08)	7.42 (0.09)	-0.58 (0.07)	-0.72 [-0.91, -0.52]*** +
Pla + Met	175/179	8.06 (0.07)	8.19 (0.09)	0.13 (0.07)	--

Data Set: Randomized Subjects
n = number of subjects with assessments at baseline and at Week 24; N = number of subjects randomized
+ = statistically significant at pre-specified level
ANCOVA model: post-pre = pretreatment
*p-values: for 2.5 mg=0.0007; for 5 mg=<0.0001 (Between group comparisons significant at alpha=0.027, applying Dunnetts adjustment)
**p-value <0.0001 (Between group comparisons significant at alpha = 0.027, applying Dunnetts adjustment)
***p-value <0.0001 (Between group comparisons significant at alpha = 0.019, applying Dunnetts adjustment)
Unit: Percent

Data over time during ST+LT Treatment Period of CV181013, CV181040 and CV181014 shows that not only at 24 weeks but also over time the 5 mg dose is better as compared with saxagliptin 2.5 mg in the add-on combination placebo-controlled studies.
With respect to the add-on to TZD trial, a relatively large effect was seen in the placebo group. The majority of patients were on mid-dose TZD and median duration of TZD treatment previous to the trial was 0.6 years. The data suggest that patients in this trial were not real TZD failures and part of the effect seen in the combination treatment arm might be due to ongoing TZD effect. However, addition of saxagliptin to TZD was superior to placebo and the results of the study can still be accepted.

In the **initial combination study**, a reduction in HbA1c was also observed for all doses. The difference in change in HbA1c was statistically significant compared to metformin, but the 95% CI is wide [-0.73, -0.35] and the clinical relevance debatable (see table below).

Changes from Baseline at Week 24 (LOCF)- Phase 3 Initial Combination Study CV181039

Treatment	n / N	Baseline Mean (SE)	Week 24 Mean (SE)	Adj. Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95% CI]
Saxa 5 mg + Met	306/320	9.41 (0.072)	6.93 (0.066)	-2.53 (0.070) [-2.66, -2.39]	
vs Saxa 10 mg[a,b]					-0.84 [-1.03, -0.65]*+
vs Met[a,b]					-0.54 [-0.73, -0.35]*+
Saxa 10 mg + Met	315/323	9.53 (0.069)	7.02 (0.067)	-2.49 (0.069) [-2.62, -2.35]	
vs Saxa 10 mg[a,b]					-0.80 [-0.99, -0.61]*+
vs Met[a,b]					-0.50 [-0.70, -0.31]*+
Saxa 10 mg	317/335	9.61 (0.075)	7.86 (0.085)	-1.69 (0.069) [-1.82, -1.55]	--
Metformin	313/328	9.43 (0.073)	7.48 (0.084)	-1.99 (0.069) [-2.12, -1.85]	--

Data Set: Randomized Subjects
n = number of subjects with assessments at baseline and at Week 24; N = number of subjects randomized
For each of the 2 combination treatment groups, the treatment comparison of the primary efficacy endpoint was considered significant only if comparison of the respective combination treatment group versus each monotherapy, active-control groups was significant.
+ = statistically significant at pre-specified level
[a] Difference in adjusted change from baseline vs monotherapy group
[b] Estimate = adjusted mean change for combination group - adjusted mean change for monotherapy group
*p <0.0001 (Between group comparisons significant at alpha = 0.027, applying Dunnetts adjustment)
Unit: Percent

It has not been shown in this nor in any other study that an initial combination treatment would be a better option than adding a second glucose-lowering agent (i.e. OAD) (=add-on) when the first does not show the intended effect. Moreover, in a number of subjects included in this initial combination study one glucose-lowering agent (metformin) would be sufficient to reach the glycaemic target. In addition to this, initial combination therapy with saxagliptin and metformin, as studied in CV181039, is not in accordance with current European and US therapeutic guidelines (Diabetes Care, vol. 32, no.1, January 2009) that recommends starting with monotherapy.
The Applicant argued that patients with a high baseline HbA1c need highly effective treatment with rapid onset of action and good tolerability, and suggested restricting the initial combination therapy to the subgroup of patients with high baseline HbA1c levels (>10%). A post hoc analysis was performed in subjects with HbA1c ≥10 %. The CHMP had concerns on whether the population with HbA1c >10% at baseline is representative for the European situation. Newly diagnosed patients with T2DM seldom have HbA1c >10%: in most cases HbA1c is ≤ 8%. As could be expected, the response in this subgroup was higher compared to subjects with baseline HbA1c<10%, but this was true for all treatment groups. In the metformin monotherapy group 27% reached HbA1c <7% and would not need combination treatment. In addition the number of subjects needing rescue for metformin (8.2%) is in the same order of magnitude as for saxagliptin 5 mg + metformin (7.2%). Furthermore, claims in the SPC should have been pre-specified and the statistical analysis plan should have been adjusted for multiplicity. Taking into account all these considerations the claim for initial combination therapy was not granted.

In a comparative study with sitagliptin added to metformin a total of 801 subjects were randomized and treated, 403 to saxagliptin and 398 to sitagliptin. Only preliminary results were submitted. 739 subjects (365 [90.6 %] in the saxagliptin + metformin group and 374 [94.0 %] in the sitagliptin + metformin group, respectively) completed the study.
Of the 801 randomized subjects, 795 (99.3%) were included in the full analysis set, 677 (84.5%) were included in the PP analysis set, and 801 (100%) were included in the safety analysis set.

Mean baseline HbA1c values were similar in the 2 treatment groups. Both treatments resulted in a reduction from baseline to Week 18 in HbA1c values: adjusted mean change from baseline -0.52% for saxagliptin + metformin and -0.62% for sitagliptin + metformin. Based on the difference in adjusted mean changes from baseline, treatment with saxagliptin + metformin group was non-inferior to treatment with sitagliptin + metformin in the PP analysis set (difference vs sitagliptin + metformin 0.09; 95% 2-sided confidence interval [CI] -0.01 to 0.20). The upper limit of the 95% CI was below the predefined criterion for non-inferiority, an upper confidence limit of the estimate <0.3%. In the full analysis set the adjusted mean changes from baseline were -0.42% for saxagliptin + metformin and -0.59 % for saxagliptin + metformin (95% CI: 0.06 to 0.28), with the upper limit of the 95% CI still within the pre-defined non-inferiority margin.
The proportions of subjects achieving a therapeutic response (defined as HbA1c ≤6.5%) were similar in the 2 treatment groups (26.3% and 29.1% for the saxagliptin + metformin and sitagliptin + metformin groups, respectively, (95% 2-sided CI -9.0% to 3.5% for the between group difference). These preliminary results will be assessed further when the final results are submitted as a Follow Up Measure.

Long-term efficacy

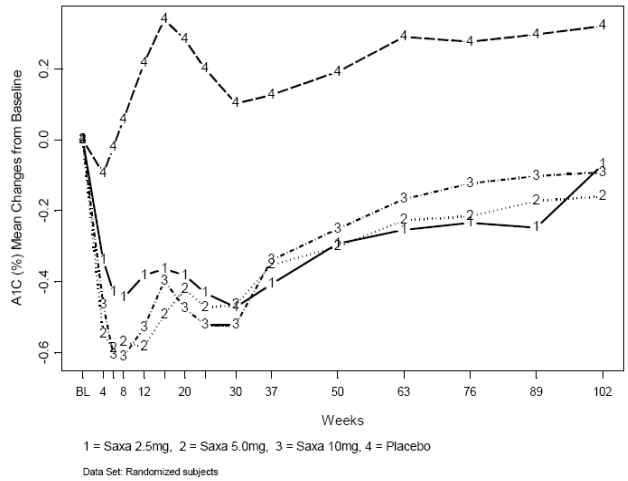
The Core Phase 3 studies all included an extension phase of at least 12 months after the 24 weeks short-term period. Subjects on placebo in the monotherapy trials were treated with metformin 500 mg in this phase. Long-term efficacy was measured by the percentage of patients discontinued due to lack of efficacy or requiring rescue treatment, and by HbA1c. Long-term phases are still ongoing and data presented are based on interim analyses. Therefore, analyses of the long-term interim data have their limitations.
In the monotherapy trials the Kaplan-Meier curves showed no clear difference between saxagliptin treated patients and placebo/metformin treated patients in number and percentage discontinuing or requiring rescue.

In the add-on trials saxagliptin patients had better control than the placebo group.

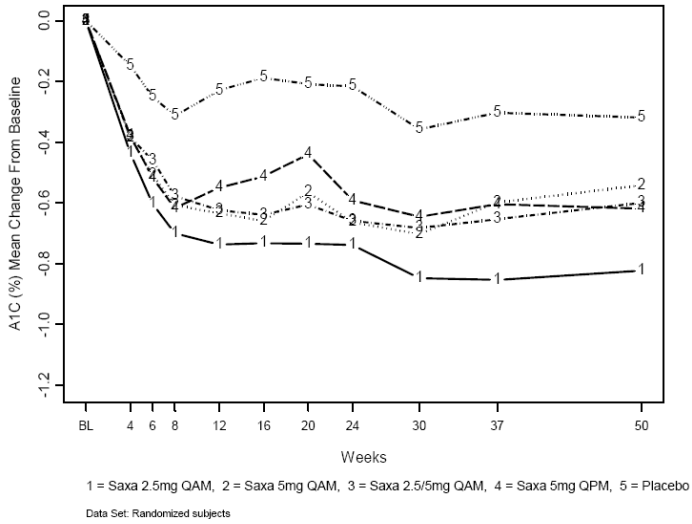
For the initial combination study, data curves seem too preliminary for a definitive assessment.
Interpretation of all Kaplan-Meier curves however is hampered by the fact that after 37 weeks only a relative low amount of subjects at risk is included.

The change in HbA1c over time in the monotherapy, add-on and initial combination therapy studies in can be seen in the following figures:

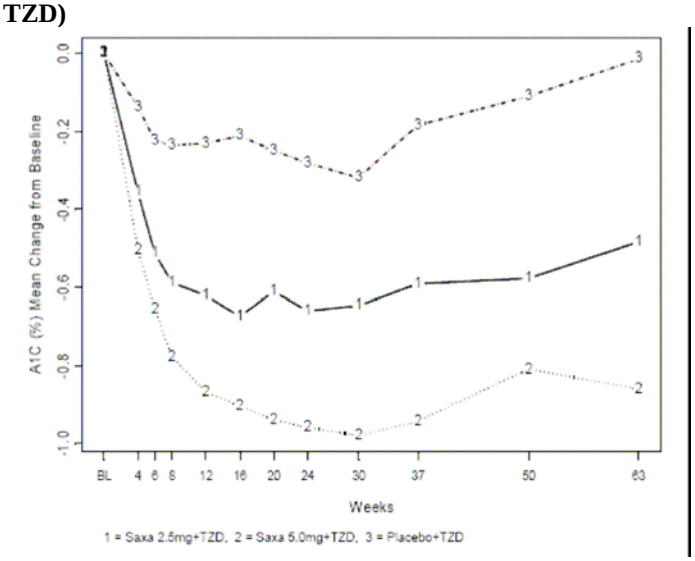
HbA1c over time, study CV181011 (Monotherapy)



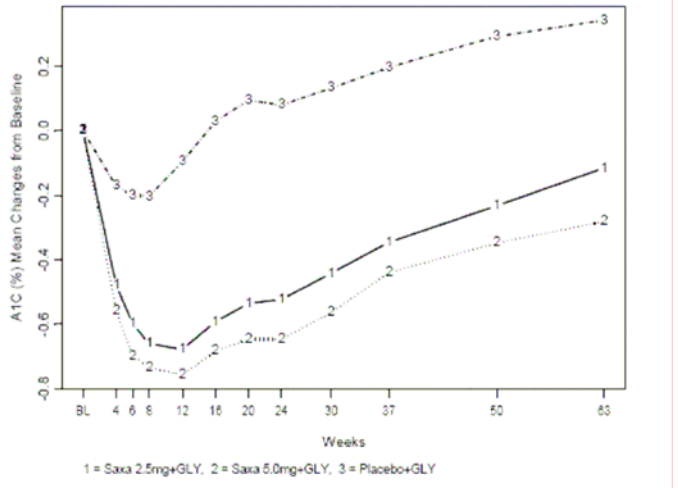
HbA1c over time, study CV181038 (Monotherapy)



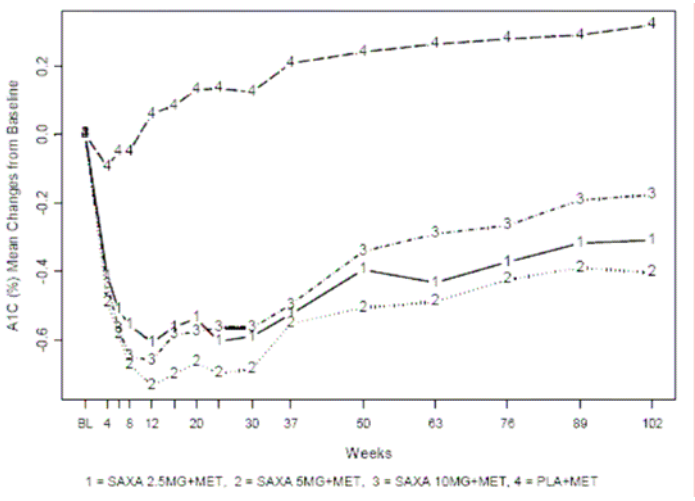
HbA1c Mean Changes from Baseline (LOCF) During ST + LT Treatment Period - CV181013 (add-on to TZD)



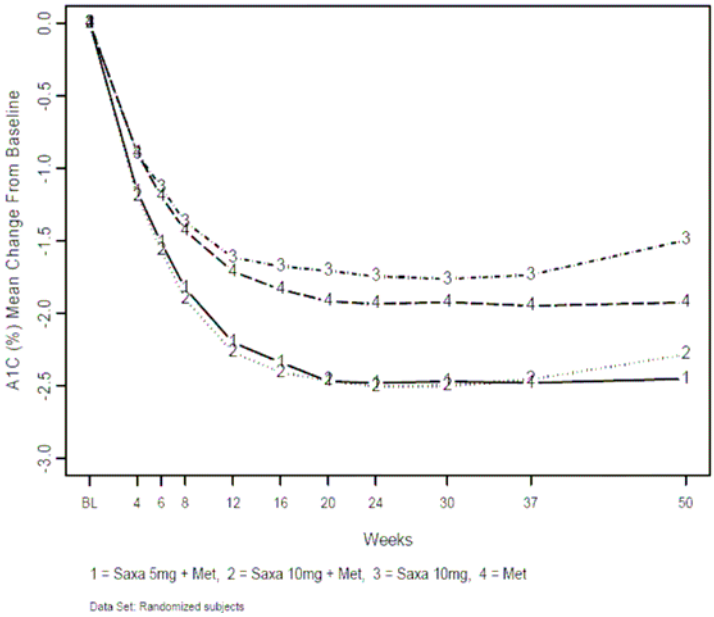
HbA1c Mean Changes from Baseline (LOCF) During ST + LT Treatment Period - CV181040 (add-on to SU)



HbA1c Mean Changes from Baseline (LOCF) During ST + LT Treatment Period - CV181014 (add-on to MET)



HbA1c Mean Changes from Baseline (LOCF) During ST+LT Treatment- CV181039



For the long-term data on HbA1c there is always a "better than placebo" response. However, in CV181011 the shape of the curve suggests typical continued diabetic progression as the HbA1c curves are not flat. Also in CV181040 and in CV181014 there is a suggestion of diabetic progression. In CV181038, CV181013 and CV18039 maximal HbA1c effect is relatively preserved.
Thus the long-term data in two of the three add-on combination studies and in one of the two monotherapy studies are consistent with progression of the disease in the long-term. In the initial combination study maximal HbA1c effect seems to be preserved in the long-term. However, data are based on interim results. Full study reports are awaited as a post-authorisation follow up measure.

Secondary and other efficacy endpoints

Secondary endpoints as FPG, percentage of patients reaching HbA1c<7%, and PPG confirmed the results obtained for HbA1c.
Other efficacy endpoints, such as post-prandial insulin and glucagon, β-cell function (calculated using the HOMA-2B method) were consistent with results obtained for HbA1c. The 10 mg dose did not provide increased efficacy as compared with the 5 mg dose.
Weight, BMI and waist circumference were measured in all of the Core Phase 3 studies. It appeared that saxagliptin has no clear effect on either of these parameters.

Ancillary analyses

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

The effect of saxagliptin on the adjusted mean change from baseline in HbA1c was assessed in 12 additional clinical subgroup categories of potential interest: baseline HbA1c, race, baseline HOMA-2B, baseline creatinine clearance, gender, geographic region, duration of T2DM, ethnicity, age, age in women only, baseline BMI, and baseline HOMA 2-IR. The effect of saxagliptin was analyzed across all 12 subgroup categories by study to assess whether there were subgroups where saxagliptin was ineffective.

There was no subgroup where saxagliptin was found consistently ineffective. There were 4 subgroup categories with an interaction p-value < 0.1 in more than 1 study: baseline HbA1c, race, baseline HOMA-2B, and baseline creatinine clearance.

Saxagliptin produced greater reductions from baseline for those with higher baseline HbA1c. This is frequently seen with antidiabetic drugs.

Saxagliptin treatment resulted in reduced HbA1c in all race subgroups. The data did not suggest that variability in saxagliptin response by race should influence clinical treatment decisions. Furthermore, results of the analyses performed to date have not revealed any differential treatment effects in different ethnic groups. Trials in China and the Southeast Asian region are ongoing; a placebo-controlled monotherapy trial is planned in India.

Saxagliptin treatment consistently resulted in reduced HbA1c from baseline to Week 24 for all subgroups by baseline HOMA-2B (reflecting pancreatic β-cell function). The variation in subgroup response identified by the interaction p-values <0.1 derived primarily from the variation in the control response by baseline HOMA-2B subgroup.

The basis for the interaction between baseline creatinine clearance and treatment appeared to be a greater dose-response separation in subjects in the subgroup with baseline creatinine clearance ≤80 mL/min in the add-on combination studies.

The apparent lack of a statistically significant effect vs. placebo in subjects ≥ 65 years of age in study CV181013 (add-on to TZD) might be due to the relatively large placebo effect in this study and the wide confidence intervals. An additional pooled analysis for subjects ≥ 65 years revealed similar efficacy for these patients as compared to younger subjects. This is also true for patients ≥ 75 year, but their number was small (36 in total).

- Clinical studies in special populations

No studies in special populations have been performed. Information on renally impaired and hepatically impaired patients can be found in the Pharmacokinetics section.

- Supportive studies

All main phase 3 studies included an extension phase of at least 12 additional months (see Outcomes and Estimations section).

Clinical safety

Safety and tolerability problems in members of the DPP4-inhibitor class are skin-related lesions (observed in monkey studies), gastrointestinal toxicity (in dogs), hypersensitivity reactions, abnormal liver function tests, increased incidence of infections and increased concentration of serum creatinine, as well as skin lesions, selected infections (e.g., related to herpes simplex virus or Mycobacterium tuberculosis), decreased lymphocyte counts, decreased platelet counts and events of localized oedema (symptomatic oedema of the hands and feet).

Recently (April 2008) in a Cochrane Systematic Review on DPP-4 inhibitors it was suggested that the new DPP-4 inhibitors, such as sitagliptin, may influence the immune system.

- Patient exposure

A total of 5346 subjects were studied in the saxagliptin Phase 1-3 clinical program (excluding study D1680C00002), of which 4042 subjects received saxagliptin. In the Phase 2b/3 program, which included eight studies in total, 3422 subjects received saxagliptin, including 66 subjects who received open-label saxagliptin 10 mg in study CV181011, and 1251 received placebo or control treatment.

Overall, 937, 1269, and 1066 subjects received saxagliptin at doses of 2.5 mg, 5 mg, and 10 mg, once daily.
There is exposure beyond the 24-week short-term treatment period. The total number of subjects exposed to saxagliptin (2.5 mg, 5 mg, or 10 mg) for >48 weeks included 303 subjects in monotherapy studies, 451 subjects in the add-on combination study with metformin, 369 subjects in the add-on combination study with SU, 195 subjects in the add-on combination study with TZD, and 141 subjects in the initial combination therapy with metformin. Unless specified, the safety findings described are based on exposure up to 24 weeks in duration.

The clinical safety database in number of 5346 treated subjects is extensive. However, as treatment with saxagliptin may be long-term, the time of exposure up to 24 weeks in most studies for assessing clinical safety is a limited period. The number of subjects exposed >48 weeks is very limited: the total number of subjects exposed to saxagliptin (2.5 mg, 5 mg, or 10 mg) for >48 weeks is: 303 subjects in monotherapy studies, 451 subjects in the add-on combination study with metformin, 369 subjects in the add-on combination study with SU, 195 subjects in the add-on combination study with TZD, and 141 subjects in the initial combination therapy with metformin. Further long-term data will be submitted post-authorisation, however to further address this point the Applicant submitted safety data from the 4 monthly safety update (MSU) (data cut-off dates of 20 June 2008 to 01 July 2008). The assessment of this data did not reveal any new safety issues.

- Adverse events

In the placebo-controlled Core Phase 3 studies, upper respiratory tract infections (URI) and headache and UTI were the adverse events (AEs) 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.
At a higher dose of saxagliptin (10 mg), the additional AEs of URI, nasopharyngitis, nausea, arthralgia, headache, and anxiety were more common in subjects receiving saxagliptin 10 mg, based on criteria of >1% difference relative to placebo.

In the add-on combination therapy studies the following findings were observed:

Add-on to Metformin (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 All saxagliptin 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 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.

Add-on to SU (CV181040): The overall frequency of AEs (excluding events of hypoglycaemia) during the ST period was lower in subjects receiving saxagliptin (70.9%) than in subjects receiving placebo (74.2%). AEs were reported by 71.4% and 70.4% of the subjects in the saxagliptin 2.5 and 5 mg groups, respectively. AEs were more frequent (>2%) in the All saxagliptin than placebo group for the following SOCs: Gastrointestinal Disorders and Vascular Disorders. AEs that were more frequent (>1%) among saxagliptin- than placebo-treated subjects included: gastroenteritis, abdominal pain, headache, and hypertension. The difference in the SOC Infections and Infestations between All saxagliptin and placebo was minimal.
Adverse reactions with saxagliptin 5 mg were: upper respiratory infection, urinary tract infection, gastroenteritis, sinusitis, hypoglycaemia, headache, and vomiting. Adverse events considered at least possibly related (investigator assessed) to saxagliptin 5 mg were: fatigue, dyslipidaemia, and hypertriglyceridaemia.

Add-on to TZD (CV181013): The overall frequency of AEs (excluding events of hypoglycaemia) during the ST period was comparable for subjects in the All Saxa and placebo groups (67.7% vs. 66.3%). AEs were more frequent for subjects treated with saxagliptin 5 mg (74.2%) than 2.5 mg (61.5%). AEs were more frequent (>2%) for saxagliptin- than placebo-treated subjects in the following SOCs: Blood and Lymphatic Disorders and Ear and Labyrinth Disorders. AEs that were more frequent (>1%) among saxagliptin- than placebo-treated subjects included: URI, sinusitis, arthralgia, musculoskeletal pain, headache, anaemia, peripheral oedema, and blood creatine phosphokinase increased. The difference in the SOC Infections and Infestations was 32.2% for All saxagliptin vs. 30.4% in placebo.
Adverse reactions with saxagliptin 5 mg were: upper respiratory infection, urinary tract infection, gastroenteritis, sinusitis, headache, vomiting, and peripheral oedema.

For the add-on combination studies it is difficult to state any definite dose-related AEs. However, peripheral oedema in subjects receiving concomitant TZD therapy may be an AE that is uniquely associated with this specific treated patient population. There was an increased frequency of peripheral oedema in the add-on combination study with TZD in the saxagliptin 5 mg group 15/186 (8.1%), but not in the saxagliptin 2.5 mg 6/195 (3.1%) and placebo 8/184 (4.3%) groups. All AEs of peripheral oedema in the add-on combination study with TZD were of mild to moderate intensity, and none resulted in study drug discontinuation.
In the LT period of each of the studies CV181014 and CV181039, subjects were eligible to receive pioglitazone as rescue treatment for hyperglycaemia. The addition of pioglitazone as rescue treatment did not substantially increase the frequency of peripheral oedema.

In a pooled analysis of the 2 monotherapy studies, the add-on to metformin study, and the add-on to SU study, the overall frequency of AEs of peripheral oedema observed in subjects treated with saxagliptin 5 mg was similar to placebo (1.7% *vs*. 2.4%).

In the short term treatment period of the initial combination study with metformin saxagliptin 10 mg + 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 + metformin relative to metformin monotherapy. Severe nasopharyngitis was reported for 1 subject in the saxagliptin 5 mg + 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 + metformin group were of mild or moderate in 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 saxagliptin 5 mg + metformin were: gastritis, arthralgia, myalgia, and erectile dysfunction. The overall safety of the initial combination use of saxagliptin 5mg + metformin is similar to saxagliptin monotherapy or metformin monotherapy; this indication however has been withdrawn by the Applicant.

In the comparative study with sitagliptin preliminary results showed that the incidence of AEs (including events of hypoglycaemia) during the 18-week, randomized treatment period was 47.1% among saxagliptin + metformin-treated subjects and 47.2% in sitagliptin + metformin-treated subjects. Nine subjects in each treatment group discontinued treatment due to AEs (2.2% in the saxagliptin + metformin group and 2.3% in the sitagliptin + metformin group).

The most frequent AEs for saxagliptin-treated subjects during the LT period seem to be consistent with those observed for the short term period. However, due to the large difference in exposure for the saxagliptin group compared with the control group (351.60 vs. 100.71 subject-years for the all saxagliptin and control groups, respectively), and since subjects that were randomized to placebo received metformin after week 24, no comparisons are possible between the saxagliptin and control groups, in pooled monotherapy studies including subjects with >= 24 weeks of treatment.
'Long-term' safety data cannot be considered sufficient thus far. This is a point of concern and is addressed in the risk management plan.

The frequency of AEs (excluding events of hypoglycaemia) was similar across the 2 treatment groups (46.7% in the saxagliptin + metformin group and 46.5% in the sitagliptin + metformin group). The

most common System Organ Class (SOC) in both groups was Infections and infestations (25.1% of subjects in each group).
The most common AEs considered by the investigator to be treatment-related were in the SOC Nervous System Disorders (5 [1.2%] subjects in the saxagliptin + metformin group and 3 [0.8%] in the sitagliptin + metformin group), in the SOC Gastrointestinal Disorders (4 [1.0%] subjects in the saxagliptin + metformin group and 13 [3.3%] subjects in the sitagliptin + metformin group), and in the SOC Skin and Subcutaneous Tissue Disorders (3 [0.7%] subjects in the saxagliptin + metformin group and 6 [1.5%] subjects in the sitagliptin + metformin group). A higher percentage of subjects in the sitagliptin + metformin group experienced treatment-related Gastrointestinal Disorders and Skin and Subcutaneous Tissue Disorders than did subjects in the saxagliptin + metformin group.
Adverse events in the categories of special interest were generally infrequent and balanced across the treatment groups. The numbers of subjects with skin disorders, based on either total AEs in the SOC Skin and Subcutaneous Disorders, or AEs considered by the investigator to be related to treatment, were higher in the sitagliptin + metformin group compared with the saxagliptin + metformin group.
Laboratory abnormalities classified as marked abnormalities (MAs) were few and balanced across the treatment groups. There was a small mean decrease in body weight in both treatment groups.

- Serious adverse event/deaths/other significant events

The frequency of deaths in the Phase 2b/3 studies was similar in subjects who received saxagliptin and placebo. In the Phase 2b and 3 studies, a total of 16 deaths were reported; 2 subjects (0.2%) each in the saxagliptin 2.5 and 5 mg groups, 3 subjects (0.3%) in the saxagliptin 10 mg group, 5 subjects (0.5%) treated with placebo and 4 subjects (1.2%) treated with metformin. There was 1 death of a subject with a history of hepatic impairment who received saxagliptin in clinical pharmacology study CV181020 and 1 death possibly related to study medication.
At the time of the 4 MSU, a total of 22 deaths had occurred in the ST + LT period of the clinical program.
There were no deaths during study D1680C00002.

The frequency of serious adverse events (SAEs) was generally comparable between the saxagliptin and control groups throughout the six Core Phase 3 studies. In the 5 pooled placebo-controlled monotherapy and combination studies, the proportion of subjects with SAEs was 3.4% in subjects who received saxagliptin 5 mg and 3.4% in subjects who received placebo.
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.
In the comparative study with saxagliptin a total of 12 subjects with SAEs were reported, 7 (1.7%) in the saxagliptin + metformin group and 5 (1.3%) in the sitagliptin + metformin group. One subject (0.2%) in the saxagliptin + metformin group and 2 subjects (0.5%) in the sitagliptin + metformin group had SAEs that were considered by the investigator to be treatment-related. Two subjects (0.5%) in the saxagliptin + metformin group and none in the sitagliptin + metformin group discontinued due to an SAE.

However ‘long-term’ safety data cannot be considered sufficient until now, these data should be updated. As stated previously this point is addressed in the risk management plan.

Incidence of hypoglycaemia was low with saxagliptin treatment. A higher incidence in hypoglycaemia was seen when saxagliptin was added to SU. This is a known phenomenon for antidiabetic drugs that are themselves not associated with hypoglycaemia. However, the incidence in the combination therapy group was not different from that in the SU monotherapy group, despite greater reductions in glycaemic control in the combination treatment group. No dose reduction of saxagliptin will be required when it is added to an SU. A lower dose of SU may be required to reduce the risk of hypoglycaemia. This is reflected in section 4.4 of the SPC.

Until now evaluation of clinical data has not revealed signals that correlate to the skin findings in the Cynomolgus monkey; however, the conclusion that there is no evidence that the findings in the

monkey are applicable to humans cannot be drawn with certainty as long as there are no long-term observations.
In the pooled monotherapy analysis rash was more frequent in the All saxagliptin group relative to the placebo group (2.5% vs. 0.6%). The pooled placebo-controlled safety analysis displayed smaller differences between the treatment groups, but confirmed the trend of highest frequency in the 2.5 mg and 10 mg saxagliptin groups. The increases in skin-related AEs do not seem to be dose-dependent.
In the pooled monotherapy analysis contact dermatitis was more frequent in the All saxagliptin group relative to the placebo group (1.2% vs. 0%). However, none of these cases were related to study drug.
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, section 4.4 includes recommendations for monitoring for skin disorders, such as blistering, ulceration or rash in diabetic patients. Section 4.8 of the SPC also includes rash.

The frequency of infection-related AEs leading to discontinuation was low. However, there are no long-term observations. In connection to this it is of importance to mention that in other DDP4-inhibitors in the long-term serious allergic reactions, such as anaphylaxis, angioedema and exfoliative skin reactions as Stevens-Johnson syndrome have been reported. This concern has been taken into account in the risk management plan.

Saxagliptin was not associated with prolongation of the QTc interval at 40 mg. The measurement of blood pressure (BP) during the ST period for the pooled monotherapy studies showed a small, not clinically relevant, mean reduction in systolic and diastolic BP. Mean BP declined in all core phase 3 studies and specific safety signals were not detected.

Overall, the frequency of cardiovascular AEs was low across the monotherapy studies and the add-on combination studies. In these studies, the frequency of CV deaths was 0.2% (4/2043) in subjects treated with saxagliptin and 0.8% (6/799) in subjects in the control group. In a metaanalysis of Phase 2/3 clinical trials, saxagliptin was not associated with an increased risk of cardiovascular events. The overall experience in patients with heart failure and other cardiac disorders is limited by the inclusion criteria in the studies. Information about the very limited experience in NYHA class I-II, and lack of experience in class III-IV is reflected in the SPC section 4.4.

The frequency of localized oedema adverse events was low. However, there are no long-term observations. In relation to this it is of importance that in other DDP4-inhibitors in the long-term an increased risk of localized oedema has been reported. This concern is addressed in the risk management plan as a potential risk.
The frequency of oedema increased when saxagliptin 5 mg was added to TZD. This is probably due to increased fluid retention mainly because of increase in insulin secretion.

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. For saxaglitpin however there are no further long-term observations, this lack of information is reflected in the risk management plan. In relation to the frequency of hypersensitivity AEs, although these had a low frequency, they occurred more frequently in the saxagliptin groups than in the placebo groups. These findings are reflected in section 4.8 of the SPC.

- Laboratory findings

The clinical significance of the decrease in lymphocyte count is not known. The decrease was not correlated with infection related adverse events. However, there are no long-term observations. This concern is listed in the risk management plan. A pharmacoepidemiology study is proposed to further evaluate changes in lymphocyte counts over time and potential association between low lymphocyte count and infections related to T-cell dysfunction (active tuberculosis and herpes zoster).

Saxagliptin did not have an effect on CRP, fibrinogen, or IL-6 values.

In a pooled analysis of 5 Phase 3 placebo-controlled studies, comparable reductions from baseline in mean platelet count were observed in all treatment groups, including placebo. The magnitude of the

decrease was approximately 2% from a baseline platelet count of 260,000 cells/µL (260.0 x 109 c/L). There is no evidence that there is an effect of saxagliptin treatment on platelet count that is of clinical importance.

There were no clinically meaningful differences in fasting lipid parameters and physical measurements in the observed long-term values compared to the week 24 data. The fact that very few subjects remained in the studies at week 102 makes the interpretation difficult. After completion of the long-term extension studies, the applicant will provide results as a post-authorisation follow up measure.

- Safety in special populations

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). No studies were done in pregnant subjects.

The Applicant compared AUC and C_{max} in patients with moderate hepatic impairment for saxagliptin to sitagliptin. This comparison is not considered to be the most appropriate as hepatic elimination has a larger influence on saxagliptin than on sitagliptin, and because saxagliptin also has an active metabolite. BMS-510849 was shown to be approximately 2-fold less potent than parent saxagliptin with respect to DPP-4, but is still considered to contribute to the DPP-4 inhibitory effect due to higher plasma concentrations than the mother substance.

The PK data available are based on an open-label single dose study including only 18 subjects with hepatic impairment (6 in each Child Pugh class), thus there is a high degree of uncertainty in the estimation of exposure. No subjects with hepatic impairment were included in the clinical studies (2b/3-program). Based on this limited experience saxagliptin should be used with caution in patients with moderate hepatic impairment and not recommended used in patients with severe hepatic impairment. This is reflected in SPC section 4.2, 4.4 and 5.3.

As the clinical data regarding moderate renal impairment is scarce and there are no data for subjects with severe renal impairment, saxagliptin cannot be recommended for these subjects. Until more data in this patient group is available, saxagliptin should not be recommended to patients with moderate and severe renal impairment. Further data will be submitted post-authorisation.

Immunological events

No studies on immunological events are presented, nor studies in immunocompromised subjects. According to Richter et al.[1], long-term data on safety are needed as the new DPP-4 inhibitors may influence the immune system. Together with complementary activities such as performing a descriptive analysis of all events occurring in immunocompromised patients for all pharmacoepidemiology studies, and analysing all adverse events (serious and non serious) related to potentially immunocompromised subjects in the planned large randomized clinical trial on CV outcomes, the Applicant will conduct 2 studies on severe hypersensitivity reactions and infections in hospitalized patients; this set of activities is considered sufficient to address immunological events.

- Safety related to drug-drug interactions and other interactions

14 of 15 subjects (93%) who received the combination of saxagliptin and ketoconazole, reduced transiently the lymphocyte count, and 33% experienced transient pyrexia, chills and lymphopenia (study CV181005). In study CV181022, again a transient reduction (mean -30.6%) in lymphocyte count was found in subjects who received the combination of saxagliptin and ketoconazole.

[1] Richter B, et al. D peptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2008; 2: CD006739

- Discontinuation due to adverse events

The frequency of AEs leading to discontinuation was low, most frequently lymphopenia, increased blood CK, increased blood creatinine, nausea and eye pain. The most common AEs leading to discontinuation in the metformin monotherapy were gastrointestinal disorders.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Gastrointestinal-related AEs	Routine PhV	4.8 Undesirable effects Vomiting is listed as a common adverse reaction with saxagliptin monotherapy, and in combination treatment with metformin, a sulphonylurea, and a thiazolidinedione.
Infections	Routine PhV with targeted questionnaires for spontaneous reports Supplemental case report forms to get more detailed information and assessment in clinical studies An epidemiology study (CV181P68, see Annex 5) will be performed to estimate and compare the incidence of hospitalizations for infections between patients with type 2 diabetes who are new users of saxagliptin and those who are new users of other oral antidiabetic treatments.	4.8 Undesirable effects Upper respiratory tract infection, urinary tract infection, gastroenteritis, and sinusitis are listed as common adverse reactions with saxagliptin monotherapy, and in combination treatment with metformin, a sulphonylurea, and a thiazolidinedione. Nasopharyngitis is listed as a common adverse reaction with saxagliptin given as initial combination treatment with metformin.
Important potential risks		
Skin lesions	Routine PhV with targeted questionnaires for spontaneous reports Supplemental case report forms for clinical studies	4.4 Special warnings and precautions for use Skin disorders Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies (see section 5.3). 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 Onglyza (section 4.8). Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended. 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 for 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 PhV with targeted questionnaires for spontaneous reports Supplemental case report forms for clinical studies An epidemiology study (CV181P69, see Annex 5) will be performed to identify risk factors for low lymphocyte count, defined as an absolute lymphocyte count <750 cells/µL, among patients with type 2 diabetes who are new users of saxagliptin and in patients who are new users of non-saxagliptin oral antidiabetic treatments.	4.8 Undesirable effects Laboratory tests Across clinical studies, the incidence of laboratory adverse events 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 PhV with targeted questionnaires for spontaneous reports Supplemental case report forms for clinical studies	None
Localized oedema	Routine PhV with targeted questionnaires for spontaneous reports Supplemental case report for clinical studies	4.8 Undesirable effects Peripheral oedema is listed as a common adverse reaction with saxagliptin combination treatment with a thiazolidinedione.

		It is noted that all of the reported adverse drug reactions of peripheral oedema were of mild to moderate intensity and none resulted in study drug discontinuation.
Hypoglycaemia	Routine PhV Supplemental case report forms for clinical studies	4.4 Special warnings and precautions for use Use with sulphonylureas Sulphonylureas are known to cause hypoglycaemia. Therefore, a lower dose of sulphonylurea may be required to reduce the risk of hypoglycaemia when used in combination with Onglyza. 4.8 Undesirable effects Hypoglycaemia is listed as a very common adverse reaction with saxagliptin combination treatment with a sulphonylurea. It is noted that there was no statistically significant difference compared to placebo. The incidence of confirmed hypoglycaemia was uncommon for Onglyza 5 mg (0.8%) and placebo (0.7%).
Important Missing / Limited Information		
Patient ≥ 75 years of age	Routine PhV	Warnings and precautions: Choose dose with care in elderly, based on renal function
Paediatric population	Routine PhV	4.2 Posology and method of administration Paediatric population Onglyza is not recommended for use in children and adolescents due to lack of data on safety and efficacy.
Patient with moderate and severe renal impairment including end-stage renal disease (ESRD) requiring haemodialysis, or undergoing peritoneal dialysis	Routine PhV A short-term 12-week, multicenter, randomized, parallel-group, double blind, placebo-controlled study to evaluate the treatment effect of saxagliptin compared with placebo in adult patients with type 2 diabetes and renal impairment with an additional 40-week long-term observational period has been initiated. The primary outcome measure includes absolute change from baseline in glucosylated hemoglobin A1c assessed after 12 and 52 weeks. A secondary outcome measure includes safety and tolerability assessed after 12 and 52 weeks. Enrolment of 168 subjects is completed. Study start	4.2 Posology and method of administration Renal impairment No dose adjustment is recommended for patients with mild renal impairment. Clinical study experience with Onglyza in patients with moderate to severe renal impairment is limited. Therefore, use of Onglyza is not recommended in this patient population (see sections 4.4 and 5.2). 4.4 Special warnings and precautions for use Renal impairment Clinical study experience with Onglyza in patients with moderate to severe renal impairment is limited. Therefore, use of Onglyza is not recommended in this

	date was January, 2008 and estimated study completion date is March, 2010. An epidemiology study (CV181P67, see Annex 5) will be performed to evaluate the relative risk of acute renal failure for patients with type 2 diabetes who are new users of saxagliptin compared with those who are new users of other oral antidiabetic treatments.	patient population (see sections 4.2 and 5.2). 5.2 Pharmacokinetic properties Renal impairment Special populations A single dose, open label study was conducted to evaluate the pharmacokinetics of a 10 mg oral dose of saxagliptin in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. 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).
Safety in patient with severe hepatic impairment	Routine PhV An epidemiology study (CV181P67, see Annex 5) will be performed to evaluate the relative risk of acute hepatic failure for patients with type 2 diabetes who are new users of saxagliptin compared with those who are new users of other oral antidiabetic treatments.	4.2 Posology and method of administration Hepatic impairment No dose adjustment is necessary for patients with mild or moderate hepatic impairment (see section 5.2). Saxagliptin should be used with caution in patients with moderate hepatic impairment, and is not recommended for use in patients with severe hepatic impairment (see section 4.4). 4.4 Special warnings and precautions for use Hepatic impairment Saxagliptin should be used with caution in patients with moderate hepatic impairment, and is not recommended for use in patients with severe hepatic impairment (see section 4.2). 5.2 Pharmacokinetic properties Hepatic impairment Special populations 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.
Safety in patient with cardiovascular disease and/or compromised cardiac function (CHF) III and IV	Routine PhV An epidemiology study in US and European databases (CV181P66, see Annex 5) will be performed to estimate and compare the incidence of major adverse cardiovascular events (MACE) among patients with type 2 diabetes who are new users of saxagliptin and those who are new users of other oral antidiabetic treatments. If an increased risk of MACE is noted among saxagliptin initiators, further analyses will be conducted to identify risk factors within the saxagliptin cohort. A multi-center, randomized, double-blind, placebo-controlled Phase 4 trial to evaluate the effect of saxagliptin on the incidence of major adverse cardiovascular events in patients with type 2 diabetes is planned. The proposed primary objective is to assess the time to first event for the composite endpoint of major adverse CV events (MACE, including CV death, non-fatal myocardial infarction and non-fatal stroke) during treatment with saxagliptin compared with placebo when added to current care, in patients with type 2 diabetes. Clinically identified MACE will be adjudicated by an independent Clinical Event Committee (CEC), using prospectively defined criteria without knowledge of treatment group assignment. In addition, standard safety assessment will be performed. Trial duration: 5 years. Planned study population: 15%-20% from Europe.	4.4 Special warnings and precautions for use Cardiac failure Experience in NYHA class I-II is limited, and there is no experience in clinical studies with saxagliptin in NYHA class III-IV.
Safety in patient with immunocompromised conditions	Routine PhV Descriptive analyses will be performed for events in patients with a history of immunocompromised status, in addition, analyses to explore	4.4 Special warnings and precautions for use Immunocompromised patients Immunocompromised patients, such as patients who have undergone organ

	possible differences in hazard ratios by patient characteristics, are planned for the five Epidemiology and Outcomes Research studies presented in Annex 5.	transplantation or patients diagnosed with human immunodeficiency syndrome, have not been studied in the Onglyza clinical program. Therefore, the efficacy and safety profile of saxagliptin in these patients has not been established.
Severe hypersensitivity reactions, including severe cutaneous adverse reaction	Routine PhV An epidemiology study (CV181P75, see Annex 5) will be performed estimate and compare the incidence of hospitalizations for anaphylaxis, angioedema, and other severe skin reactions between patients with type 2 diabetes who are new users of saxagliptin and those who are new users of other OADs.	None
Safety in pregnancy/lactation	Routine PhV Pregnancy outcome follow up as defined by internal procedures. This is done for female patients who got pregnant after taking the drug and male patients taking drug at the time that the spouse or significant other becomes pregnant. Cases are followed up until final pregnancy outcome is registered. Adverse events for the mother, father, foetus and offsping are captured per pharmacovigilance standards.	4.6 Pregnancy and lactation Pregnancy There are no data from the use of saxagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Onglyza should not be used during pregnancy unless clearly necessary. Lactation It is unknown whether saxagliptin is excreted in human breast milk. Animal studies have shown excretion of saxagliptin and/or metabolite in milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue therapy taking into account the benefit of breast feeding for the child and the benefit of therapy to the woman.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality
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. There are a number of quality issues that will be resolved as Follow-up Measures within an agreed timeframe. None of these issues is expected to have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology
The *in vitro* affinity for the DPP4 enzyme has been shown and maximal enzyme inhibition measured *ex vivo* in plasma is evident at low doses. The affinity for other DPP's is low. *In vivo* efficacy has been

demonstrated in animal models by several pharmacodynamic endpoints. Long-term efficacy has not been demonstrated in an animal model.

The main metabolite of saxagliptin, BMS-510849, also has high affinity for the DPP4 enzyme, but shows less pharmacodynamic effect in terms of lowering glucose levels than the parent compound. Only at doses in excess of those required to produce maximal DPP4 inhibition, a significant *in vivo* effect was shown. The contribution of the metabolite to the overall efficacy of saxagliptin has not been fully elucidated.

Saxagliptin was evaluated *in vitro* for the potential to antagonize the binding of appropriate radioligands to receptor and ion-channels or to inhibit different enzymes, with no significant effects observed. Cell surface DPP4 (also known as CD26) has been reported to function as a co-stimulatory signalling molecule in T lymphocyte activation. Inhibition of T-lymphocytes was shown at much higher concentrations of saxagliptin than is needed for DDP4 inhibition. Moreover, these concentrations exceed the C_{max} that is measured in humans after therapeutic doses. However, due to the large volume of distribution is cannot be excluded that the concentration required to inhibit T cell activation is reached within the T cells.

No significant findings were reported from safety pharmacology studies, and therefore no adverse effects on the cardiovascular, respiratory and central nervous system is anticipated in humans.
No non-clinical pharmacodynamic interaction studies were performed.

The pharmacokinetics of saxagliptin and BMS-510849, the active metabolite, have been adequately characterised.
Bioavailability following oral administration of saxagliptin was determined to be 70% in rat, 77% 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 and monkey (2.1-4.4 hr). When considering the toxicokinetic studies, the AUC increases linear with dose between 30 and 600 mg/kg for mouse, between 2 and 600 mg/kg for rat, between 0.2 and 25 mg/kg for dog, and for all doses investigated for monkey. No substantial accumulation of saxagliptin and BMS-510849 was observed after once-daily repeated dosing of saxagliptin.

The intrinsic membrane permeability of saxagliptin is very low. Both saxagliptin and BMS-510849 were not prominent substrates for P-gp or for cellular uptake transporters.
Protein binding of saxagliptin was not observed in dog and human, and low in mouse (27%), rat (18%) and monkey (20%). Protein binding of BMS-510849 was also very low in all species tested (up to 10%).
The highest concentrations (1-12 h) of saxagliptin related material were found in gastrointestinal tissues, liver, urinary bladder and kidney. Since radioactivity was below 1% of the dose at 24 h post-dose, accumulation is not expected. Saxagliptin and BMS-510849 levels were lowest in the brain. Saxagliptin-derived components cross the placenta in rats; as such Onglyza should not be used during pregnancy (see section 4.6 and 5.3 of the SPC).

The pathways for *in vivo* metabolism of saxagliptin in humans were qualitatively similar to those in mice, rats, dogs, and cynomolgus monkeys. BMS-510849 was the major metabolite identified in plasma, urine and/or faeces in all species. The metabolic profiles from *in vitro* studies in liver microsomes and hepatocytes from various species were also similar. Co-administration with ketoconazole and diltiazem, CYP3A4/5 inhibitors, resulted in a 2.5 and 2.1 fold increase of the AUC of saxagliptin. No animal studies have been conducted on the effects of CYP3A4 inducers on the exposure of saxagliptin.
Following an oral dose of [^{14}C]saxagliptin, almost the entire radioactivity administered was recovered in the urine and faeces of rats, dogs and monkeys. Approximately 75% of the dose in human was excreted in the urine. In humans, saxagliptin and BMS-510849 accounted for 33.6% and 28.2% of the dose in urine suggesting that both elimination of unchanged saxagliptin and metabolism to BMS-510849 plays a major role in the disposition of saxagliptin. [^{14}C]saxagliptin-derived radioactivity was

excreted in milk, with radioactivity detected at all time points through 24 hours post-dose (see section 4.6 of SPC).

Interaction with other drugs via protein binding is not expected, since saxagliptin and BMS-510849 are poorly bound to plasma proteins. Saxagliptin is unlikely to cause clinically relevant drug-drug interactions through either inhibition or induction of the major CYP isozymes.

The single and repeat dose toxicity of saxagliptin was adequately evaluated in rats, dogs and monkeys at exposures comparable to or markedly higher than the therapeutic exposure. In rats, the observed target organ changes were generally minimal splenic lymphoid hyperplasia, pulmonary histiocytosis, and mononuclear-cell infiltrates/inflammation in the ocular accessory gland and liver in short and long-term studies, and after 104 weeks of dosing, the lung, urinary bladder, and epididymis, but only at high doses. In dogs, the major finding was gastrointestinal toxicity characterized by bloody/mucoid feces at moderate doses, and enteropathy at high doses. The NOAEL is 1 mg/kg/day (4 times the human exposure based on AUC). In monkeys, major target organ changes included reversible erosive and/or ulcerative skin lesions with scab formation and reversible multi-tissue mononuclear-cell infiltrates at low doses. The AUC at the NOAEL (0.3 mg/kg/day) for these changes was 1 (female) to 3 (male) times the human dose.
No genotoxic or carcinogenic potential was demonstrated.
The exposures of the active metabolite BMS-510849 in non-clinical studies were sufficiently high to exclude any unexpected toxic effects in a clinical setting.
Effects seen in reproduction toxicology studies were mild and confined to high doses with sufficient safety margins. High doses caused reduced ossification in both rats and rabbits, and decreased foetal body weight in rats.
Saxagliptin was considered a skin sensitizer, able to induce allergic contact dermatitis.
An immunotoxic effect of saxagliptin cannot be excluded based on the data provided, and this is addressed in the risk management plan.
Two lines of investigation were conducted in monkeys and rats. In monkeys skin lesions were detected at low doses.. A possible relevance for humans cannot be excluded, and the potential of saxagliptin to induce skin lesions and gastro-intestinal effects is addressed in the risk management plan.

Saxagliptin is neither PBT nor vPvB. Risk to the surface water, groundwater, soil, and sewage treatment plant is acceptable.

Efficacy

Core studies of this application are 6 phase 3 studies, 2 monotherapy trials, 3 add-on combination studies and 1 initial combination therapy trial. Based on these trials a marketing authorisation for saxagliptin as add-on combination and initial combination therapy was initially sought. Additionally topline results for an active comparator trial were submitted during the procedure. The claim for initial combination therapy was withdrawn during the procedure (see below). Study duration, chosen endpoints, in- and exclusion criteria of the studies were generally adequate and in accordance with the current guideline.

Efficacy was assessed as **monotherapy** in placebo controlled studies, but comparative studies were not submitted. The results on HbA1c lowering as compared with placebo were not considered sufficient taking into account that there should be a clinically relevant difference from placebo and that only saxagliptin 10 mg dose in study CV181011 reached delta of -0.7%.
Furthermore, the choice of the 5mg dose as the optimal dose is not justified by these studies. A post hoc analysis provided showed that at 12 weeks 5 mg performed better than 2.5 mg. However, over a longer time period (50-102 weeks) no difference was found between both doses. From these studies it cannot be concluded with certainty that saxagliptin 5 mg per day is the optimal dose. At this moment the Applicant does not seek a monotherapy indication.

Efficacy was assessed in 3 **add-on combination placebo controlled studies**, with inclusion criteria of TZD failure, SU failure and metformin failure.

In these trials, all doses of saxagliptin, except saxagliptin 2.5 mg + TZD, induced a reduction in HbA1c that was superior to placebo:

- saxagliptin 2.5 mg **+ TZD**: -0.36% [-0.57%, -0.15%];
- saxagliptin 5 mg + **TZD**: -0.63% [-0.54%, -0.42%];

- saxagliptin 2.5 mg **+ gly**: -0.62% [-0.78%, -0.45%];
- saxagliptin 5 mg **+ gly**: -0.72% [-0.88%, -0.56%];

- saxagliptin 2.5 mg **+ met**: -0.73% [-0.92%, -0.53%];
- saxagliptin 5 mg **+ met**: -0.83% [-1.02%, -0.63%];
- saxagliptin 10 mg **+ met**: -0.72% [-0.91%, -0.52%]).

Reductions in HbA1c were observed for all doses. In the add-on combination placebo-controlled studies the 5 mg dose proved to be better as compared with the 2.5 mg dose both in the short and long term treatment.
With respect to the add-on to TZD trial the addition of saxagliptin to TZD was superior to placebo, and therefore the results are acceptable, albeit that the data suggest that patients in this study were not real TZD failures, and part of the effect might be due to the ongoing effect of the TZD.

An active comparator study is needed in the add-on studies; such a study was not originally submitted and this was a major objection. The initial combination study CV181039 did provide data to compare the safety and efficacy of saxagliptin 10 mg and metformin monotherapy. This study also showed that 10 mg is not more efficacious than 5 mg. However, it should be noted that the study population is different from the other core Phase 3 studies. A post-hoc analysis of treatment effects in subjects with a baseline HbA1c <10% was performed to demonstrate generalizability of the results from Study CV181039 to the expected treated population in clinical practice. Demographic data show a slightly higher mean age, higher body weight, and shorter duration of diabetes in this subgroup compared with the subgroup with HbA1c ≥10%. Results show that saxagliptin seems less effective than metformin, as is the case for other DPP-4 inhibitors. This post-hoc analysis provides useful knowledge about the efficacy and safety of saxagliptin compared to metformin, even though the subgroup population had a somewhat higher mean HbA1c (8.8-8.7 %) than the population included in the saxagliptin monotherapy studies (7.8-8.0%). Even though no direct comparison between saxagliptin and the other DPP-4 inhibitors was originally performed, results from the monotherapy studies suggest a similar reduction in HbA1c compared to vildagliptin and sitagliptin.

At the time of the initial assessment the Applicant had two ongoing active controlled trials, one comparing saxagliptin + metformin with sitagliptin + metformin and the other saxagliptin + metformin with SU + metformin. Based on the comparative results of the post-hoc analysis of the initial combination study it was considered acceptable to submit final results from these studies as follow-up measures Concerning the saxagliptin vs. sitagliptin study an abbreviated study report with topline results was submitted during the procedure. Data from this study indicate non-inferiority within the pre-defined non-inferiority margin of 0.3%. Final results of both comparative studies will be assessed further when the final results are submitted as a Follow-Up Measure.

Regarding the **Initial Combination Active Controlled Study** HbA1c mean changes from baseline (LOCF) during the ST + LT Treatment indicate that saxagliptin 5 mg + Met and saxagliptin 10 mg + Met are comparable over time and better than saxagliptin 10 mg or Metformin, whereas metformin is better than saxagliptin 10 mg. Although the difference in change in HbA1c was statistically significant compared to metformin, the 95% CI is wide [-0.73, -0.35] and hence the clinical relevance was considered questionable by the CHMP.
Initial combination therapy with saxagliptin and metformin however, is not in accordance with current European and American therapeutic guidelines (Diabetes Care, vol. 32, no.1, January 2009) that recommend starting with monotherapy. This claim could therefore not be granted and was withdrawn by the MAH.

Safety
Once-daily, orally-administered saxagliptin was safe and well-tolerated at doses of up to 400 mg QD for 2 weeks, 100 mg QD for 6 weeks, 40 mg QD for 12 weeks, and at 2.5, 5, and 10 mg QD for up to 102 weeks. Saxagliptin given at doses of 2.5 and 5 mg was associated with an overall clinical AE profile that was comparable to placebo.

Although no comparative add-on combination treatment data are currently available to address how saxagliptin compares to established medications in treating T2DM, the initial combination study CV181039 provided data to compare the safety and efficacy of saxagliptin 10 mg and metformin monotherapy. Overall, there were few differences between saxagliptin monotherapy and metformin monotherapy groups. The data of the ongoing comparative studies will provide further comparative data.

The overall profile of AEs associated with extended dosing of saxagliptin for up to 2 years was consistent with that seen at 24 weeks. However the number of long-term exposed subjects (>24 weeks) is limited. This point will be addressed post-authorisation as long-term data from the phase 3 core studies will be submitted as follow-up measures.

Specific events of interest were hypoglycaemia (combination with SU); skin lesions; selected infections (events related to herpes simplex virus or Mycobacterium tuberculosis); decreased lymphocyte counts; decreased platelet counts; events of localized oedema (combination with TZD); the evaluation of CV events, abnormalities in liver function tests, and hypersensitivity reactions. The safety profile for saxagliptin in doses of 2.5 and 5 mg was similar to the safety profile of placebo for these events, except for those related to lymphocyte counts. 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. No studies on immunological events are presented, nor studies in immunocompromised subjects. Long-term data on safety are needed as the new DPP-4 inhibitors may influence the immune system. To address this concern the Applicant will perform complementary activities together with 2 studies on severe hypersensitivity reactions and infections in hospitalized patients.

A study on saxagliptin in subjects with moderate or severe renal impairment is ongoing. At this point in time, as other treatment options are available for use in diabetic patients with renal impairment, saxagliptin is not recommended in patients with moderate or severe renal impairment.

No dose adjustment is needed in patients with mild or moderate hepatic impairment. However, in patients with severe hepatic impairment (Child-Pugh C) exposure to saxagliptin may be increased two-fold. Saxagliptin should be used with caution in patients with moderate hepatic impairment and not recommended used in severe hepatic impairment.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

A readability test was performed. There were two rounds of each ten participants and a pilot of 3 participants. There were 14 questions about the package leaflet and the participants were also asked to provide feedback in terms of their own impressions. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The test a criterion was that 81% of the participants must be able to answer correctly, i.e. must be able to find the information and act upon it. This test criterion has been met. The conclusions are clear, concise and clearly presented.

Risk-benefit assessment

Benefits
The pharmacokinetics of saxagliptin is rather uncomplicated.
Saxagliptin at doses of 2.5 mg daily and higher can reduce HbA1c in T2DM subjects. However, given as **monotherapy**, results were not convincing and less effective than metformin. Given as add-on treatment to metformin, SU or TZD, more relevant results were obtained: in the add-on trials all doses of saxagliptin, except saxagliptin 2.5 mg + TZD, induced a reduction in HbA1c which was superior to placebo.

At the time of the initial assessment two active controlled trials were ongoing, one comparing saxagliptin + metformin with sitagliptin + metformin and the other saxagliptin + metformin with SU + metformin Preliminary data of the comparative add-on study with saxagliptin that were submitted during the registration procedure indicate non-inferiority between saxagliptin and sitagliptin within the pre-defined non-inferiority margin of 0.3%. Final results of both comparative studies will be submitted as a post-authorisation measure.

Neither in the **initial combination study**, nor in any other, has it been shown that an initial combination treatment would be a better option than adding a second glucose-lowering agent when the first does not show the intended effect. Initial combination therapy with saxagliptin and metformin is not in accordance with current European and US therapeutic guidelines. The claim for initial combination therapy can not be granted and was subsequently withdrawn by the MAH.

Risks
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 overall profile of AEs associated with extended dosing of saxagliptin for up to 2 years was consistent with that seen at 24 weeks. However, the number of long-term exposed subjects is limited, a point which is addressed in the risk management plan.

As the clinical data regarding moderate renal impairment is scarce and there are no data for subjects with severe renal impairment, saxagliptin cannot be recommended for these subjects.

Data on immunological events and immunocompromised subjects is currently insufficient and will be collected through post-authorisation studies and complementary activities (see Safety section). Skin lesions are a concern for other DPP-4 inhibitors and there is limited experience in patients with diabetic skin complications treated with saxagliptin, therefore a warning has been included in section 4.4. 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.

The increased incidence of hypoglycaemia when saxaglipitin is administered in combination with SU, the increased incidence of peripheral oedema when saxagliptin is given in combination with TZD, and the observation of a decrease in lymphocyte count are described in the SPC.

The overall experience in patients with heart failure and other cardiac disorders is limited and information about the very limited experience in NYHA class I-II, and lack of experience in class III-IV is reflected in the SPC section 4.4. However, in a metaanalysis of Phase 2/3 clinical trials, saxagliptin was not associated with an increased risk of cardiovascular events.

Saxagliptin should be used with caution in patients with moderate hepatic impairment and not recommended in patients with severe hepatic impairment.

Balance
Efficacy of saxagliptin was shown when given as add-on treatment to metformin, SU and TZD; and saxagliptin was considered safe and well-tolerated. However the number of long-term exposed

subjects is limited in a product intended to be used in T2DM. Based on these results, the benefit-risk is considered acceptable for the currently claimed indications.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Onglyza in the treatment of adult patients with type 2 diabetes mellitus to improve glycaemic control:

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

was favourable and therefore recommended the granting of the marketing authorisation.